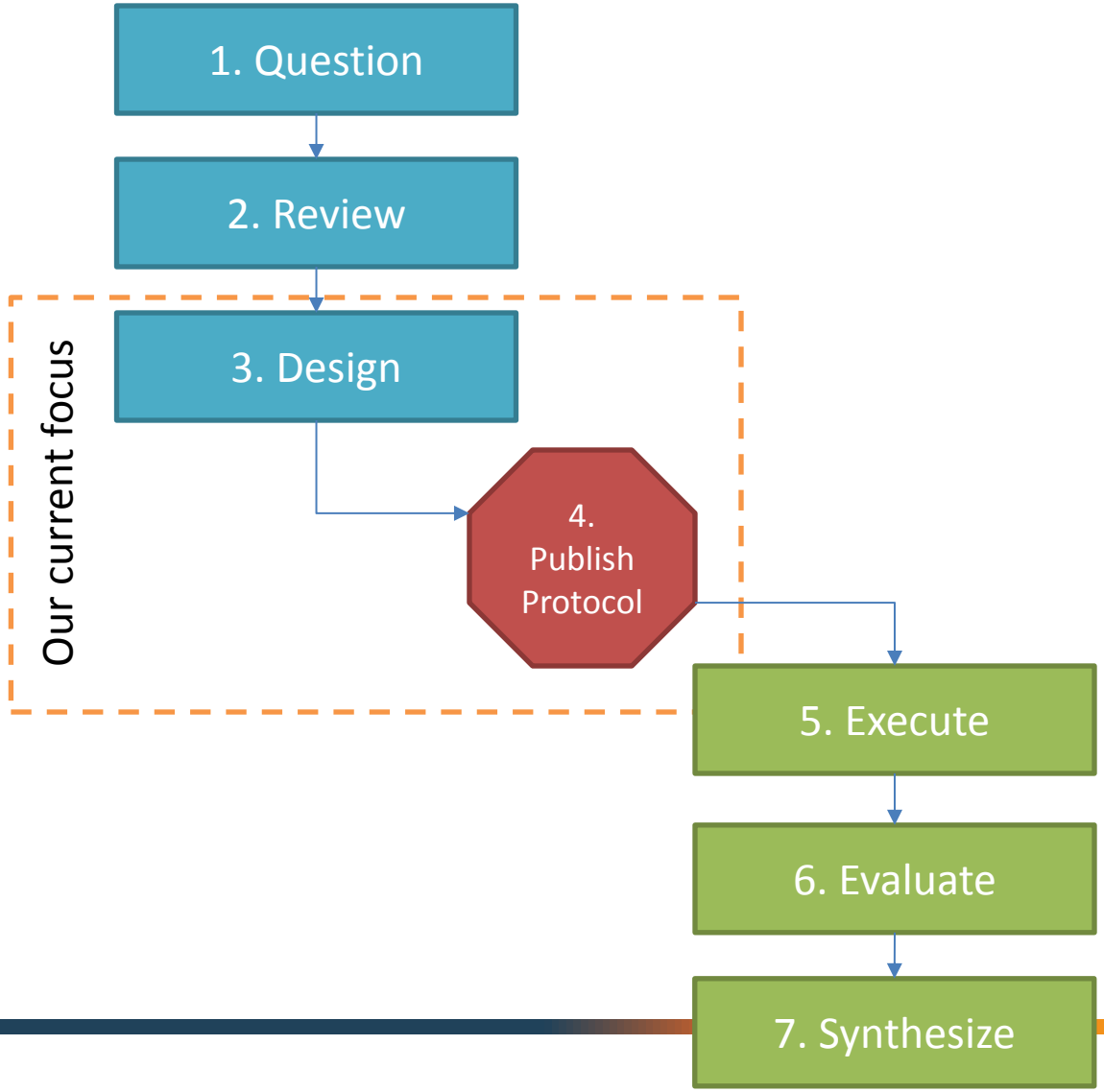
Study designer track: Deep dive into cohort study design using ATLAS

A standardized process for evidence generation and dissemination



What is a protocol?

"In the natural sciences a protocol is a **predefined written procedural method** in the design and implementation of experiments.

Protocols are written whenever it is desirable to standardize a laboratory method to **ensure successful replication of results** by others in the same laboratory or by other laboratories.

Detailed protocols also facilitate the assessment of results through peer review."

https://en.wikipedia.org/wiki/Protocol_(science)

What should a protocol be in epidemiology?

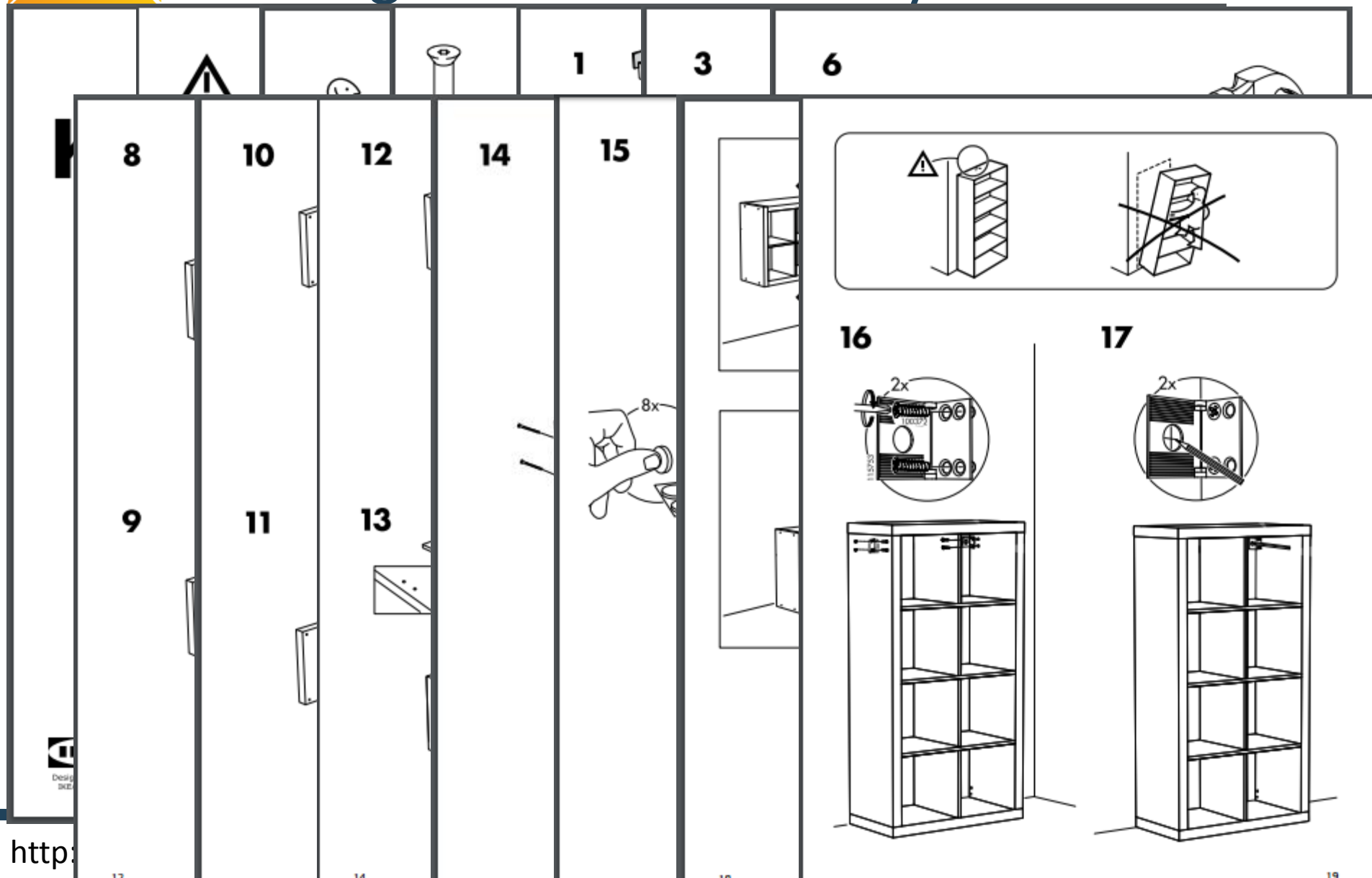
"The study protocol is a core document of a study. A protocol should be drafted as one of the first steps in any research project. The final version **must precisely describe everything being done in the study so that the study can be reproduced.** "

-ENCePP Guide on Methodological Standards in Pharmacoepidemiology

Analogy for a retrospective analysis of observational healthcare data

- Assembly Instructions:
  - Initial parts already exist
  - Defined step-by-step procedure can be followed
  - If followed correctly, you should always get the same output

Lessons from IKEA: making effective assembly instructions



http

Protocol / assembly instructions: initial warnings

ENGLISH
Important information
Read carefully.
Keep this information for further reference.

WARNING

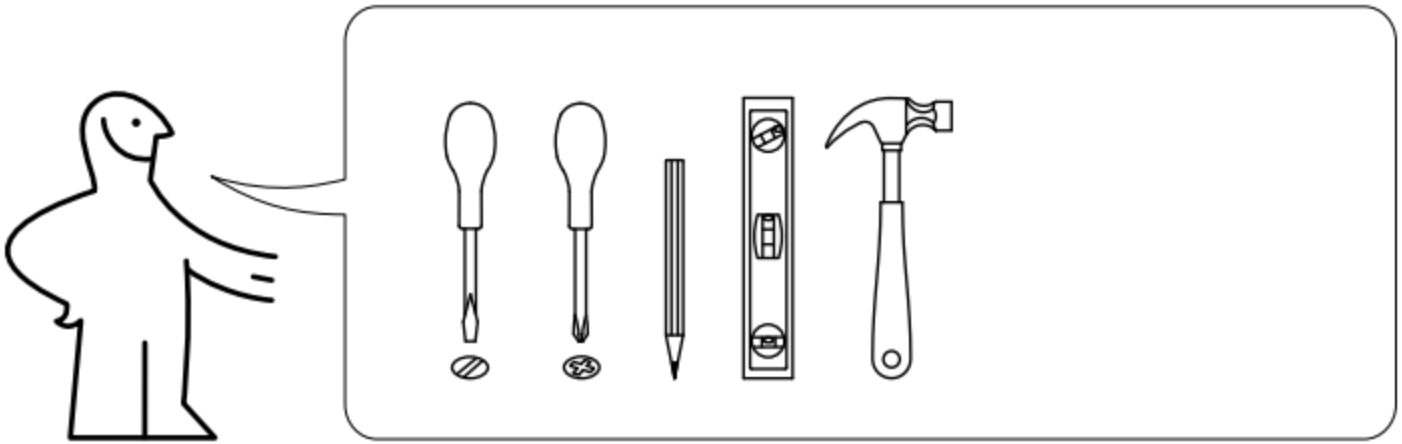
Serious or fatal crushing injuries can occur from furniture tip-over. To prevent this furniture from tipping over it must be permanently fixed to the wall.

Fixing devices for the wall are not included since different wall materials require different types of fixing devices. Use fixing devices suitable for the walls in your home. For advice on suitable fixing systems, contact your local specialized dealer.

- What warnings should communicated in your epidemiology protocol, prior to execution of the analysis?

http://www.ikea.com/us/en/assembly_instructions/kallax-shelf-unit__AA-1055145-3_pub.pdf

Protocol / assembly instructions: required tools



- What tools do you need to have access to in order to properly complete the analysis?

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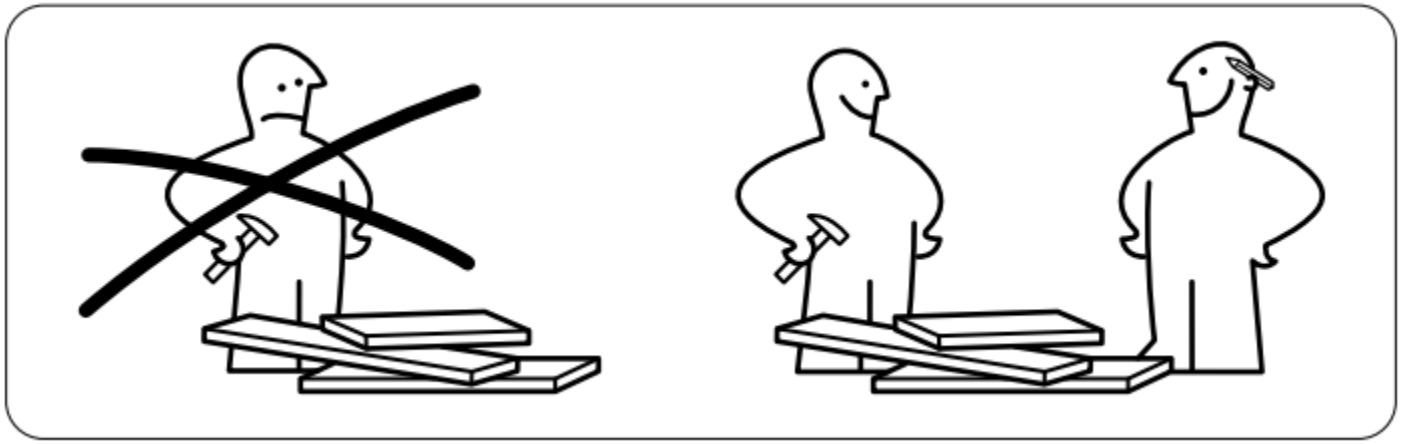
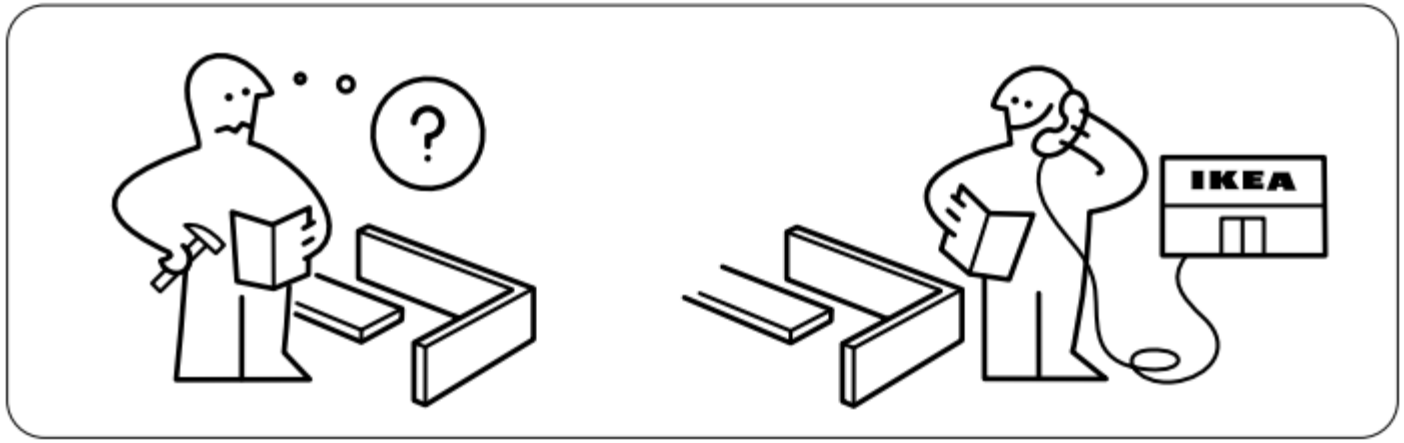
Protocol / assembly instructions: required expertise



- Study design should not be a one-person effort
- Anyone in any role can contribute an initial research question…
- …but it's unlikely that anyone has all of the necessary expertise to design and implement a study to answer that question
  - Therapeutic area and clinical domain knowledge
  - Understanding how the clinical phenomena manifests in the health care system and data capture processes
  - Working competency with the observational databases and source vocabularies
  - Expertise with standardized analytics tools to design and implement analyses
- Protocol development should be shared collaboration activity

http://www.ikea.com/us/en/assembly_instructions/kallax-shelf-unit__AA-1055145-3_pub.pdf

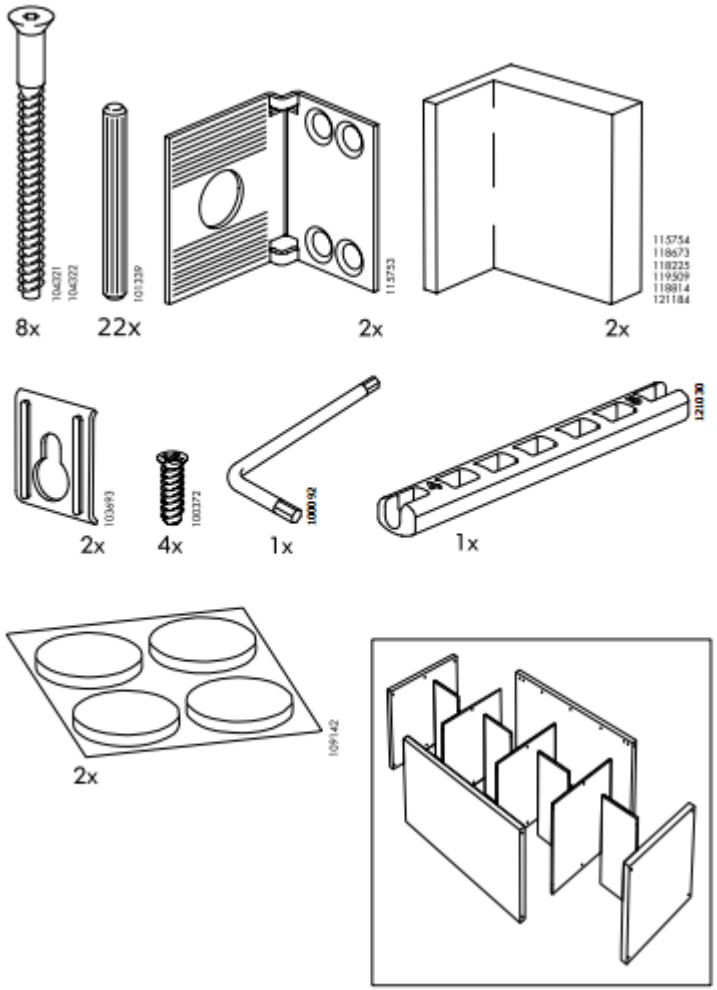
Protocol / assembly instructions: required expertise



- A protocol should be a complete specification of all procedures to be executed, which is pre-defined and documented prior to study execution
- There should be a pre-defined process for how to reconcile any ambiguities identified during implementation
- All resolutions should be documented as a protocol amendment

http://www.ikea.com/us/en/assembly_instructions/kallax-shelf-unit__AA-1055145-3_pub.pdf

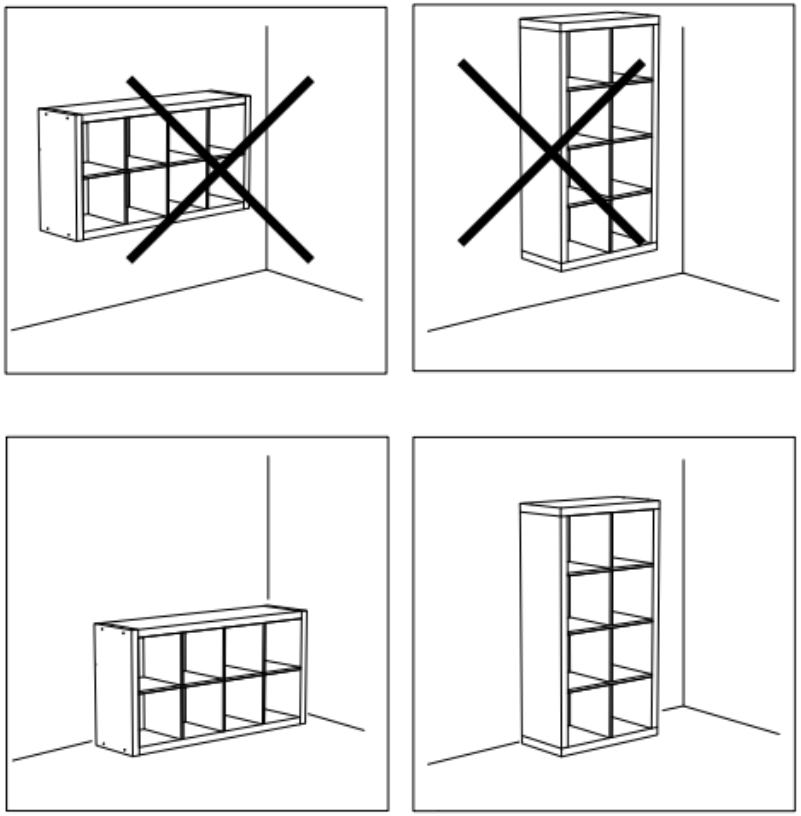
Protocol / assembly instructions: complete inventory of initial inputs



- IKEA doesn't just say: 'use some particle board and a few screws'….so we shouldn't just say: 'use an administrative claims database'
- Full specification requires documenting scope of source data used (release date, scope of calendar time and population), version of CDM and ETL process, version of vocabulary

http://www.ikea.com/us/en/assembly_instructions/kallax-shelf-unit__AA-1055145-3_pub.pdf

Protocol / assembly instructions: intended use for the final outputs



- It is important to decide upfront how the evidence generated it going to be used once completed
  - What decision is being made?
  - Who is the decision-maker?
  - How can the evidence this study generates inform the decision?

http://www.ikea.com/us/en/assembly_instructions/kallax-shelf-unit__AA-1055145-3_pub.pdf

Observational data analysis is a science, not an art

- If you want to generate reliable evidence from observational healthcare databases to meaningfully inform medical decision making, you must apply a consistent, reproducible, verifiable process that follows the scientific method
- If you are looking for 'artistic' opportunities:
  - Propose interesting and clinically relevant questions to answer
  - Discover new data capture processes and incorporate these elements into the OMOP common data model
  - Design novel visualizations to more effectively communicate the evidence generated

Replication of Garbe et al. using the OHDSI framework

Eur J Clin Pharmacol (2013) 69:549–557
DOI 10.1007/s00228-012-1334-2

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

High-dimensional versus conventional propensity scores in a comparative effectiveness study of coxibs and reduced upper gastrointestinal complications

E. Garbe · S. Kloss · M. Suling · I. Pigeot · S. Schneeweiss

Received: 28 February 2012 / Accepted: 6 June 2012 / Published online: 5 July 2012

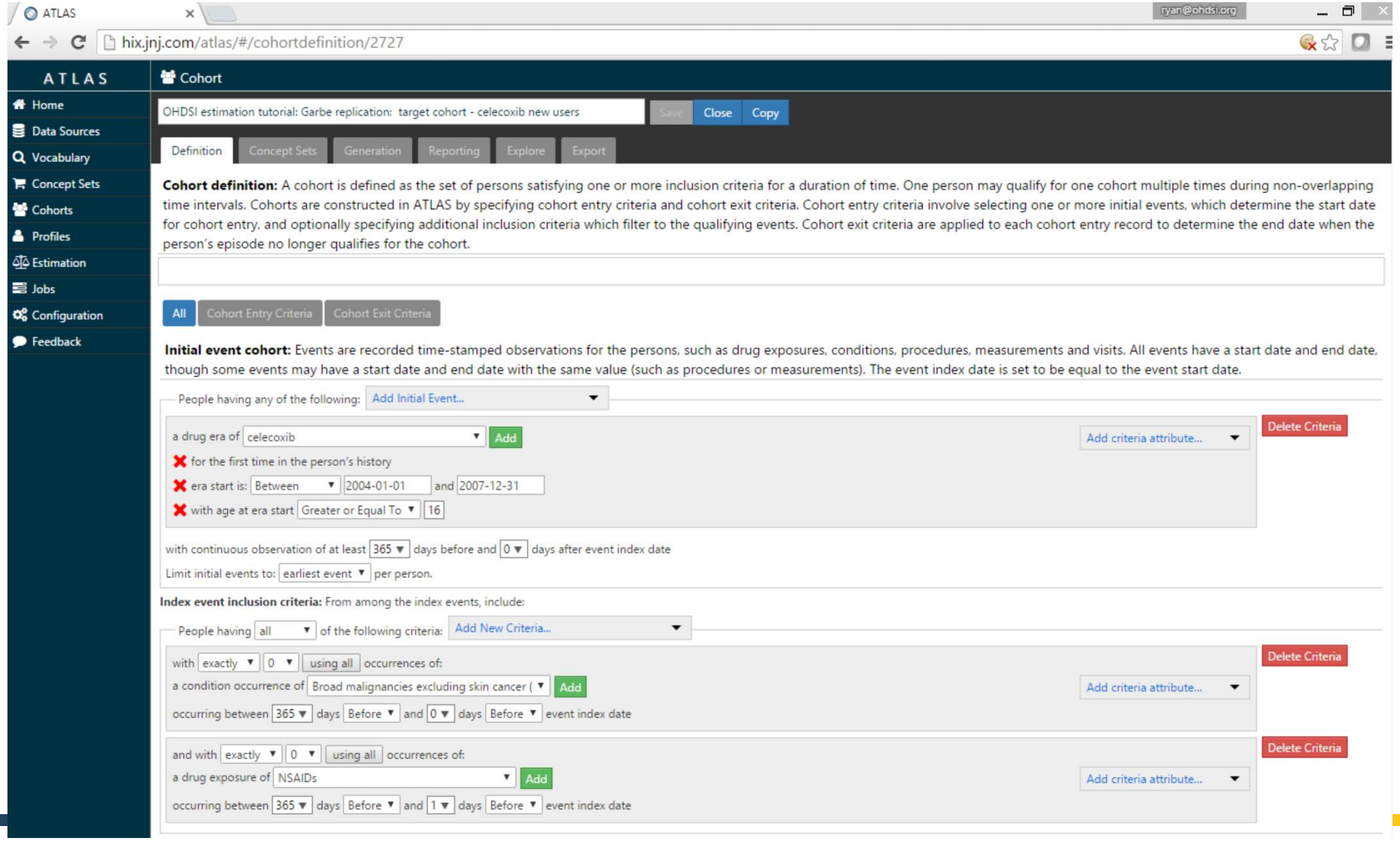
What is the design used by Garbe et al?

Input parameter	Design choice
Target cohort (T)	Celecoxib new users
Comparator cohort (C)	Traditional non-steroid antiflammatory drugs (NSAID) new users
Outcome cohort (O)	Upper gastrointestinal complications (UGIC)
Time-at-risk	cohort start → cohort end
Model specification	1:1 propensity score-matched multivariable conditional Poisson regression

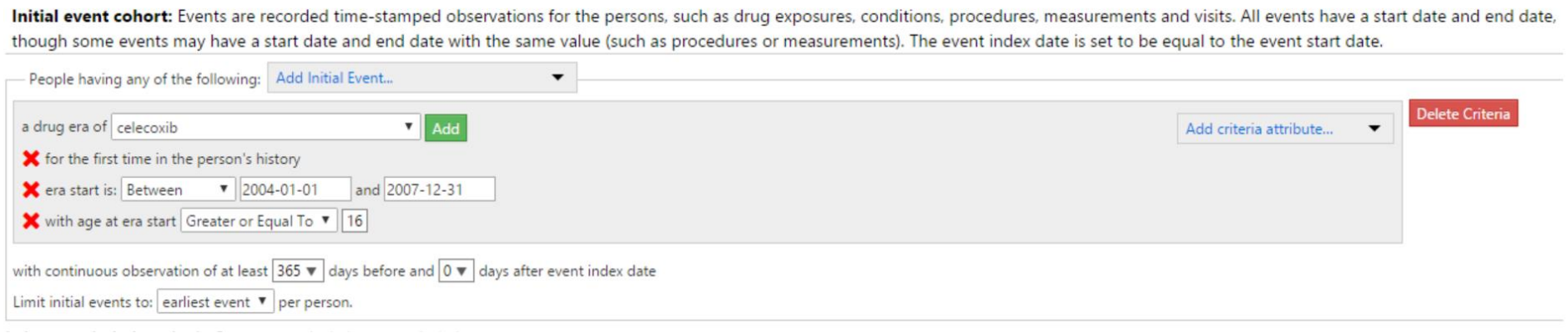
Garbe et al. description of cohort(s)

This was a cohort study in which a new user design was applied. The aim was to estimate the effect of tNSAIDs and coxibs on the risk of UGIC. New users of tNSAIDs or coxibs were defined as patients who were continuously enrolled in their SHI provider for at least 12 months without any notation of NSAID use, including coxibs, during this time period. Cohort entry was the first notation of a prescription for a tNSAID or a coxib. Cohort exit was defined as discontinuation or switch of the initial NSAID, disenrollment from the SHI provider, hospitalization for UGIC, hospital diagnosis of cancer, death, or the end of the study period, whichever came first. Patients were required to be at least 16 years of age at the time of first use and not to have a diagnosis of cancer in the 12 months preceding cohort entry.

Garbe et al. replication: Implementing the target cohort in ATLAS



Implementing the target cohort in ATLAS: Defining the initial event



Ambiguities from publication which require detailed specification in a complete protocol:

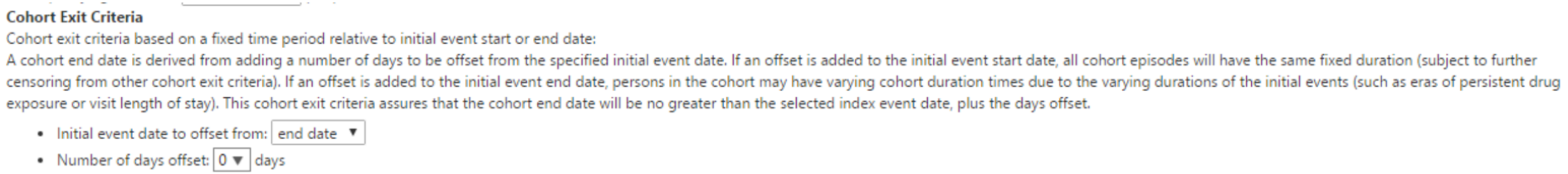
1) What is the time period for exposure?
2) Does exposure need to be first time in history, or only require 12 months prior with no exposure?

Implementing the target cohort in ATLAS: Specifying initial event inclusion criteria

Ambiguities from publication which require detailed specification in a complete protocol:

1) Does ‘at least 12 months without any notation of NSAID use…during this period’ mean no exposure any time in prior history or any time in last 12 months?
2) How do you define ‘diagnosis of cancer’?

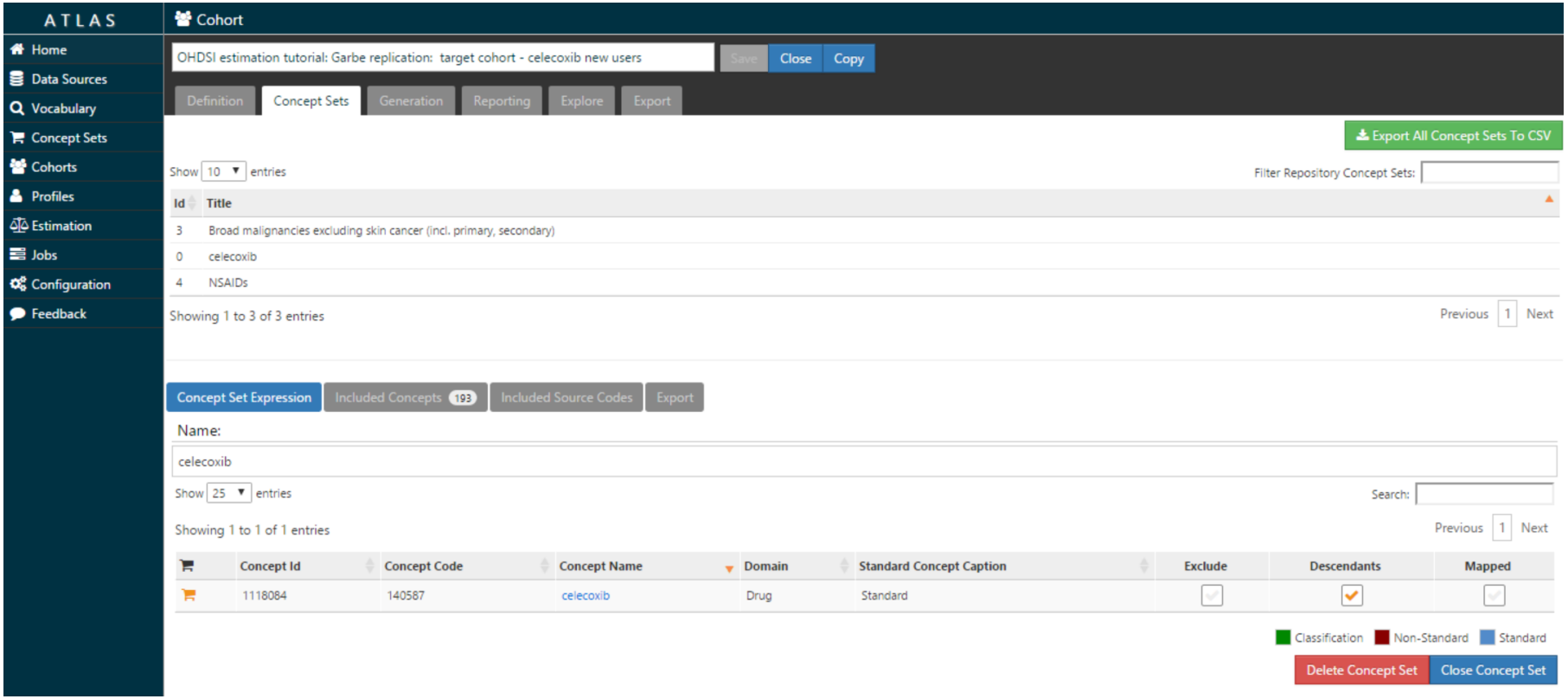
Implementing the target cohort in ATLAS: Select cohort exit criteria



Ambiguities from publication which require detailed specification in a complete protocol:

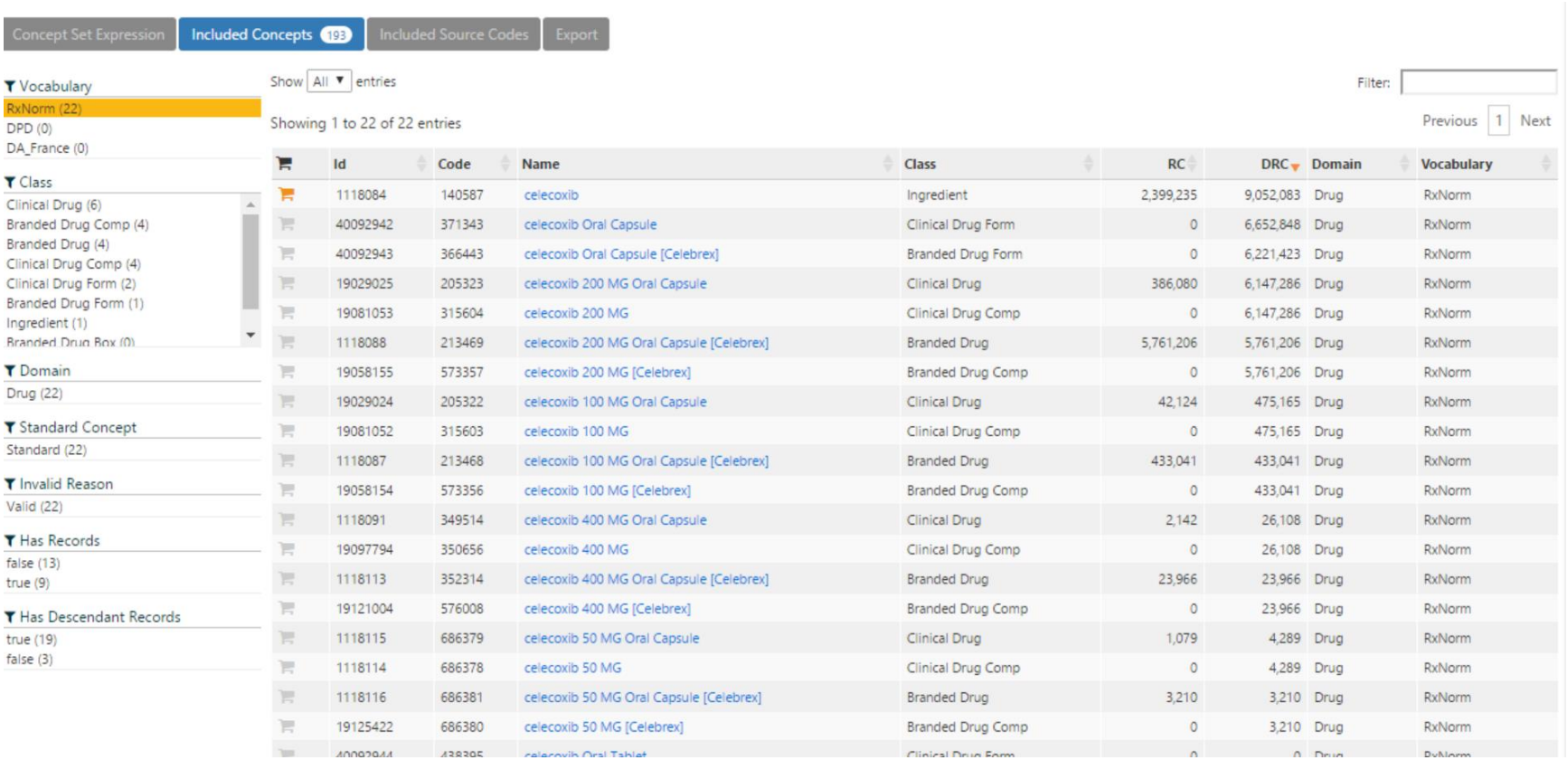
1) How is continuous exposure defined, such that one can determine a ‘discontinuation or switch’?
2) How do we differentiate between ‘potential time-at-risk’ vs. ‘realized time-at-risk’ to disentangle exposure cohort definition from analytic censoring strategy?

Implementing the target cohort in ATLAS: Define ‘celecoxib’ concept set



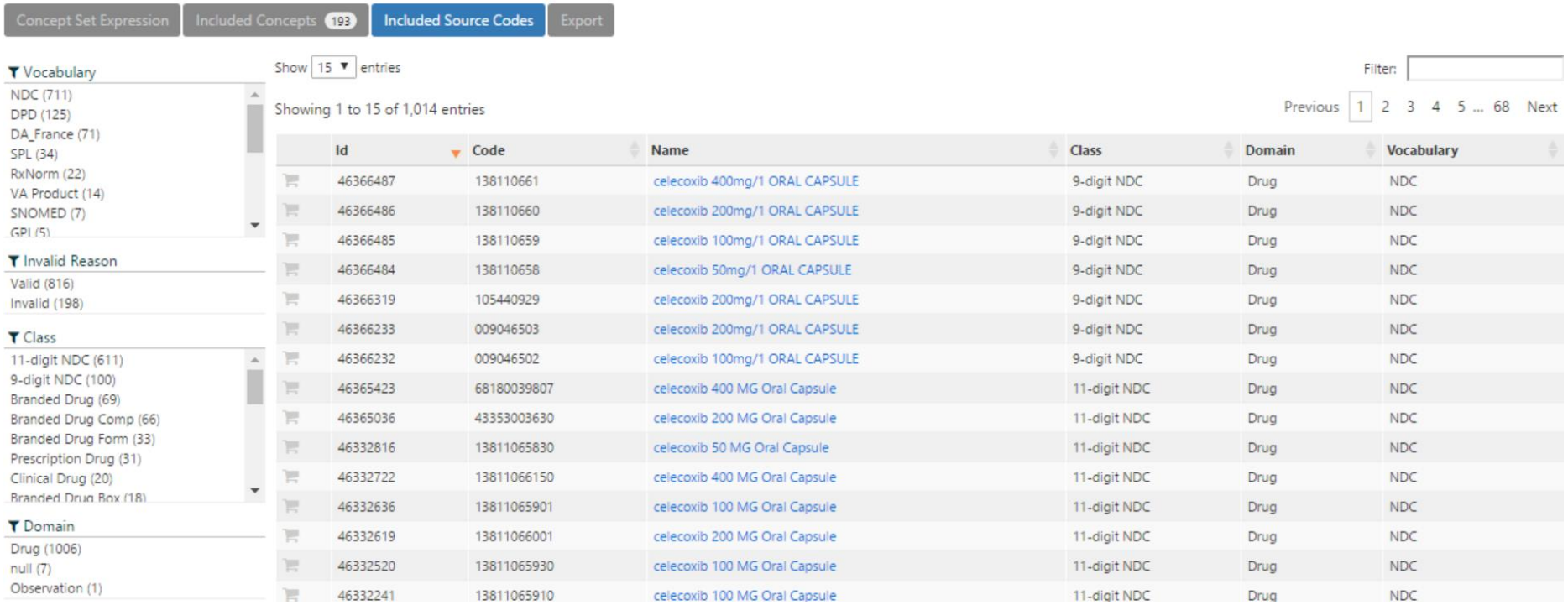
- Use of OHDSI standardized vocabularies enables efficient definition of concept sets, which can be fully expressed as all included concepts and included source codes
- Use of standardized vocabularies enables same definition to be applied across different databases, even if those databases use different source coding

Implementing the target cohort in ATLAS: Review ‘celecoxib’ included concepts



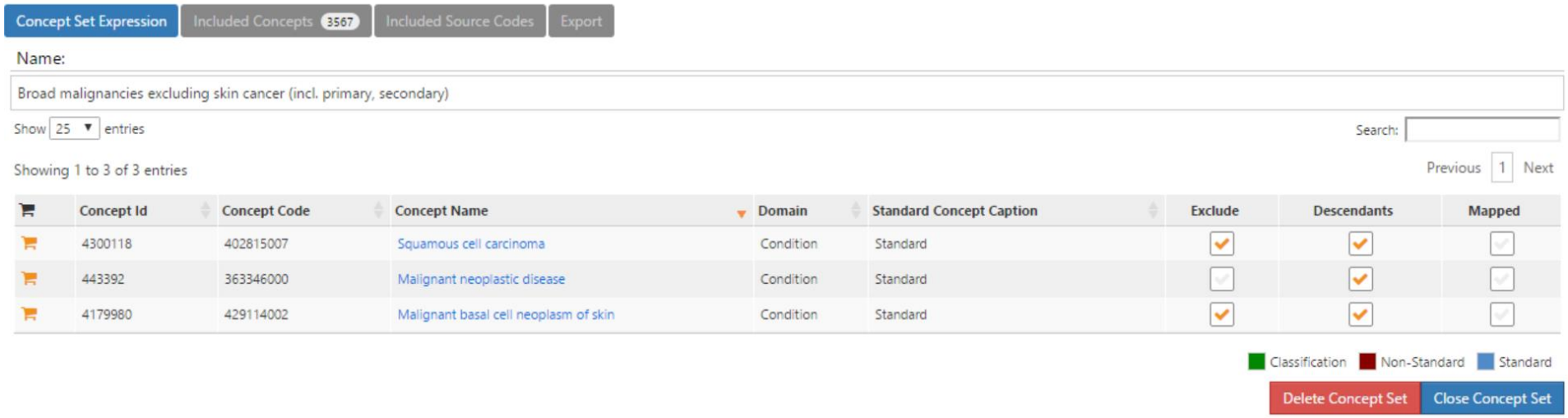
- RxNorm is a standard vocabulary to represent drugs
- Descendant concepts from RxNorm ingredient includes clinical drugs, branded drugs, clinical/brand drug forms, and clinical/branded drug component
- RC: ‘record count’ = how often that standard concept appeared directly in a database
- DRC: ‘descendant record count’ = how often that standard concept or any of its descendant concepts appeared in a database

Implementing the target cohort in ATLAS: Review ‘celecoxib’ included source codes



- Many different source vocabularies used across various health systems are mapped into one common reference standard used in OMOP Common Data Model (ex: NDC, DPD, DA France, VA Product, GPI all mapped into RxNorm)
- By defining a concept set as one standard concept and including all descendants, the definition includes 193 different standard concepts and 1,014 different source vocabulary terms.

Implementing the target cohort in ATLAS: Define ‘cancer’ concept set



- OHDSI standardized vocabularies allow for use of hierarchical structure contained within vocabularies to define large sets of concepts using a small number of concepts
- Example: to define ‘all malignancies except skin cancer’, we select all ‘malignant neoplastic disease’ with associated descendants, but exclude all descendants of both ‘squamous cell carcinoma’ and ‘malignant basal cell neoplasm of skin’
- Expansion of this expression defined by 3 concepts manifest as 3,567 distinct standard concepts and 10,810 included source codes

Hands-on Exercise

Create a cohort definition to replicate the comparator group used in Garbe et al.

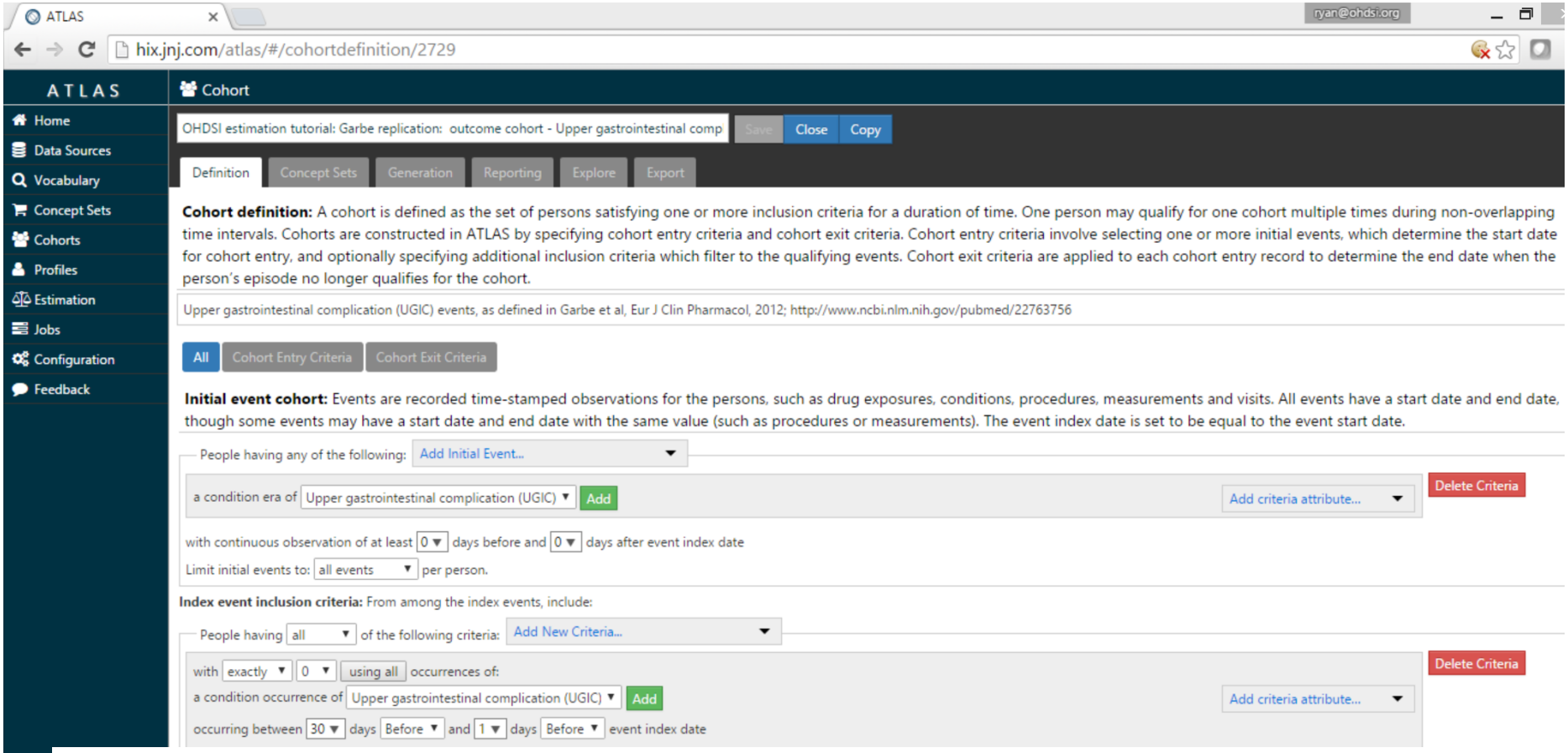
1. Go to: http://www.ohdsi.org/redshift/atlas
2. Click on 'Define a New Cohort' button
3. Give your cohort a new name (ex. "OHDSI tutorial Garbe comparator replication by Patrick Ryan")
4. On 'Definition' tab, define cohort entry criteria (initial events and all inclusion criteria) and cohort exit criteria
5. Hit 'Save' button beside the cohort definition name
6. Go to 'Generation' tab, and click 'Generate' button beside whichever database(s) you'd like to explore

Garbe et al. replication: Implementing the outcome in ATLAS

Definition of UGIC

Upper gastrointestinal complications were defined as hemorrhage, perforation, or obstruction located in the stomach, duodenum, or gastrojejunal part of the GI tract. The following ICD-10 codes included in the subdivisions hemorrhage and perforation were ascertained for the outcome: gastric ulcer (K25), duodenal ulcer (K26), peptic ulcer (K27), gastrojejunal ulcer (K28), hemorrhage of anus and rectum (K62.5), hematemesis (K92.0), melena (K92.1), and GI hemorrhage unspecified (K92.2). High positive predictive values of site- and lesion-specific codes (between 80 and 97 %) and somewhat lower predictive values of non-specific codes (between 57 and 70 %) have been reported for GI ulcers and complications in the ICD coding system in several studies [13, 14].

Garbe et al. replication: Implementing the outcome cohort in ATLAS



Ambiguities from publication which require detailed specification in a complete protocol:

1) How do we determine distinct events (and not misclassification continuation of care for prior episode as incident occurrence)?
2) How does 'validation' of ICD9 codes in Italy and Canada improve your confidence in accuracy of ICD10 codes in Germany?

Implementing the outcome cohort in ATLAS: Define 'UGIC' concept set

Concept Set Expression | Included Concepts 325 | Included Source Codes | Export

Name:

Upper gastrointestinal complication (UGIC)

Show 25 entries Search:

Showing 1 to 14 of 14 entries Previous 1 Next

Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	Exclude	Descendants	Mapped
46273478	1092881000119105	Rectal hemorrhage due to ulcerative colitis	Condition	Standard	☑	☑	☐
194158	48729005	Perinatal gastrointestinal hemorrhage	Condition	Standard	☑	☑	☐
4172869	276525003	Peptic ulcer of newborn	Condition	Standard	☑	☑	☐
4027663	13200003	Peptic ulcer	Condition	Standard	☐	☑	☐
4048286	206425006	Neonatal rectal hemorrhage	Condition	Standard	☑	☑	☐
4048608	206424005	Neonatal melena	Condition	Standard	☑	☑	☐
4071070	206423004	Neonatal hematemesis	Condition	Standard	☑	☑	☐
4103703	2901004	Melena	Condition	Standard	☐	☑	☐
316457	35265002	Mallory-Weiss syndrome	Condition	Standard	☑	☑	☐
4059178	16121001	Gastrojejunal ulcer	Condition	Standard	☐	☑	☐
192671	74474003	Gastrointestinal hemorrhage	Condition	Standard	☐	☑	☐
4265600	397825006	Gastric ulcer	Condition	Standard	☐	☑	☐
4198381	51868009	Duodenal ulcer disease	Condition	Standard	☐	☑	☐
26441	57748001	Bleeding ulcer of esophagus	Condition	Standard	☑	☑	☐

Classification Non-Standard Standard

Delete Concept Set Close Concept Set

- Standard concept set can be constructed that yields a specific set of source codes
- Standard concepts can then be applied to other databases that use different source codes

Implementing the outcome cohort in ATLAS: Define 'UGIC' concept set

Concept Set Expression | Included Concepts 325 | **Included Source Codes** | Export

Vocabulary
- ICD10CM (47)
- SNOMED (0)
- CIEL (0)
- Read (0)
- ICD9CM (0)
- ICD10 (0)
- OXMIS (0)
- MeSH (0)

Invalid Reason
- Valid (47)
- Invalid (0)

Class
- 4-char billing code (40)
- 3-char nonbill code (4)
- 5-char billing code (3)
- 4-dig nonbill code (0)
- OXMIS (0)
- Diagnosis (0)
- 5-dig billing code (0)
- 4-dig billing code (0)

Domain
- Condition (47)
- null (0)
- Observation (0)

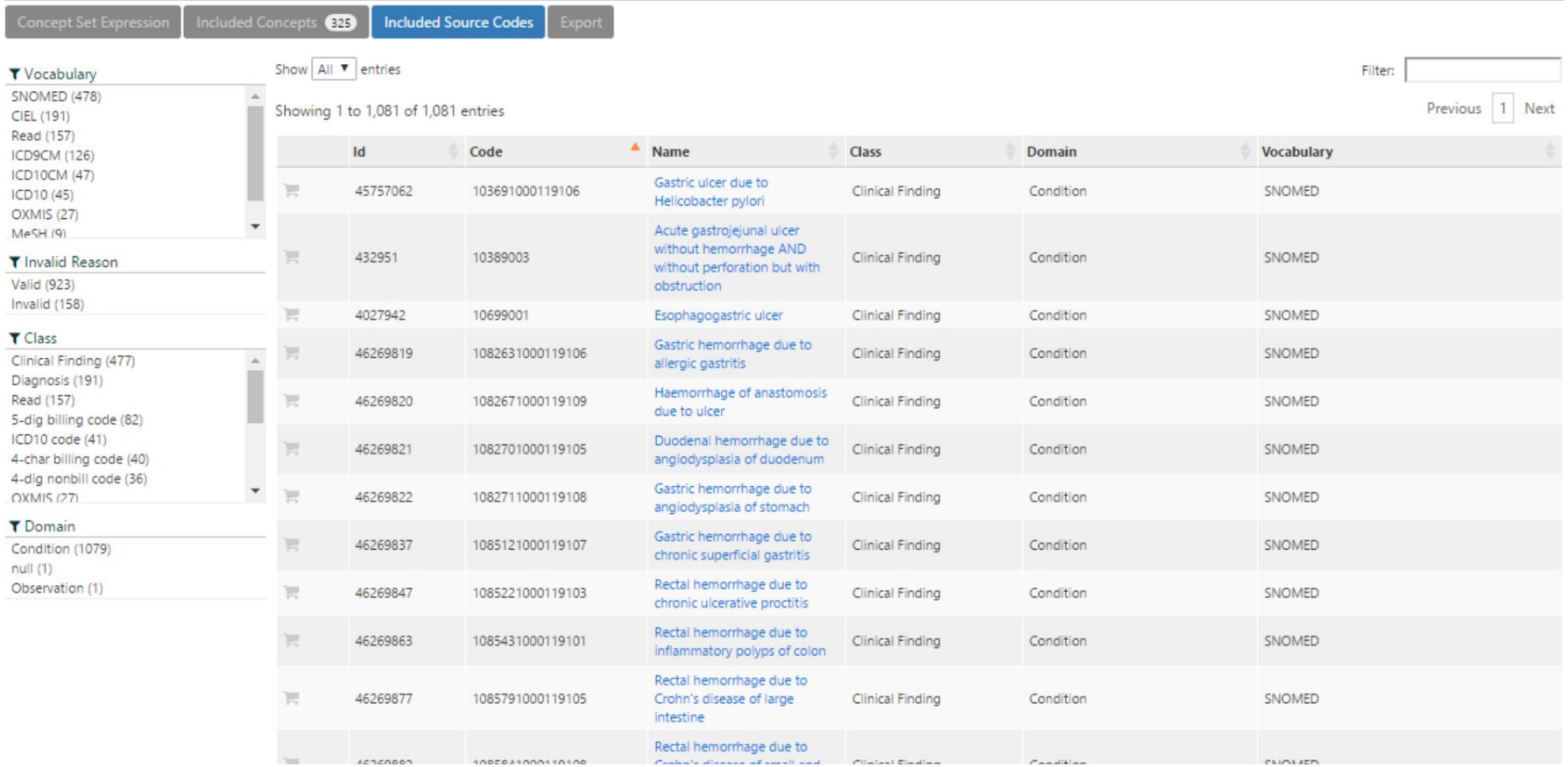
Show All entries Filter:

Showing 1 to 47 of 47 entries Previous 1 Next

Id	Code	Name	Class	Domain	Vocabulary
35208201	K25.0	Acute gastric ulcer with hemorrhage	4-char billing code	Condition	ICD10CM
1569562	K25	Gastric ulcer	3-char nonbill code	Condition	ICD10CM
35208202	K25.1	Acute gastric ulcer with perforation	4-char billing code	Condition	ICD10CM
35208203	K25.2	Acute gastric ulcer with both hemorrhage and perforation	4-char billing code	Condition	ICD10CM
35208204	K25.3	Acute gastric ulcer without hemorrhage or perforation	4-char billing code	Condition	ICD10CM
35208205	K25.4	Chronic or unspecified gastric ulcer with hemorrhage	4-char billing code	Condition	ICD10CM
35208206	K25.5	Chronic or unspecified gastric ulcer with perforation	4-char billing code	Condition	ICD10CM
35208207	K25.6	Chronic or unspecified gastric ulcer with both hemorrhage and perforation	4-char billing code	Condition	ICD10CM
35208208	K25.7	Chronic gastric ulcer without hemorrhage or perforation	4-char billing code	Condition	ICD10CM
35208209	K25.9	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation	4-char billing code	Condition	ICD10CM
35208210	K26.0	Acute duodenal ulcer with hemorrhage	4-char billing code	Condition	ICD10CM
1569563	K26	Duodenal ulcer	3-char nonbill code	Condition	ICD10CM
35208211	K26.1	Acute duodenal ulcer with perforation	4-char billing code	Condition	ICD10CM
35208212	K26.2	Acute duodenal ulcer with both hemorrhage and perforation	4-char billing code	Condition	ICD10CM

- 47 distinct ICD10CM codes map to standard concepts
- Complete listing required for full transparency, rather than assuming user knows subcodes within hierarchy (e.g. NEVER WRITE ICD9 ###.*)

Implementing the outcome cohort in ATLAS: Define 'UGIC' concept set



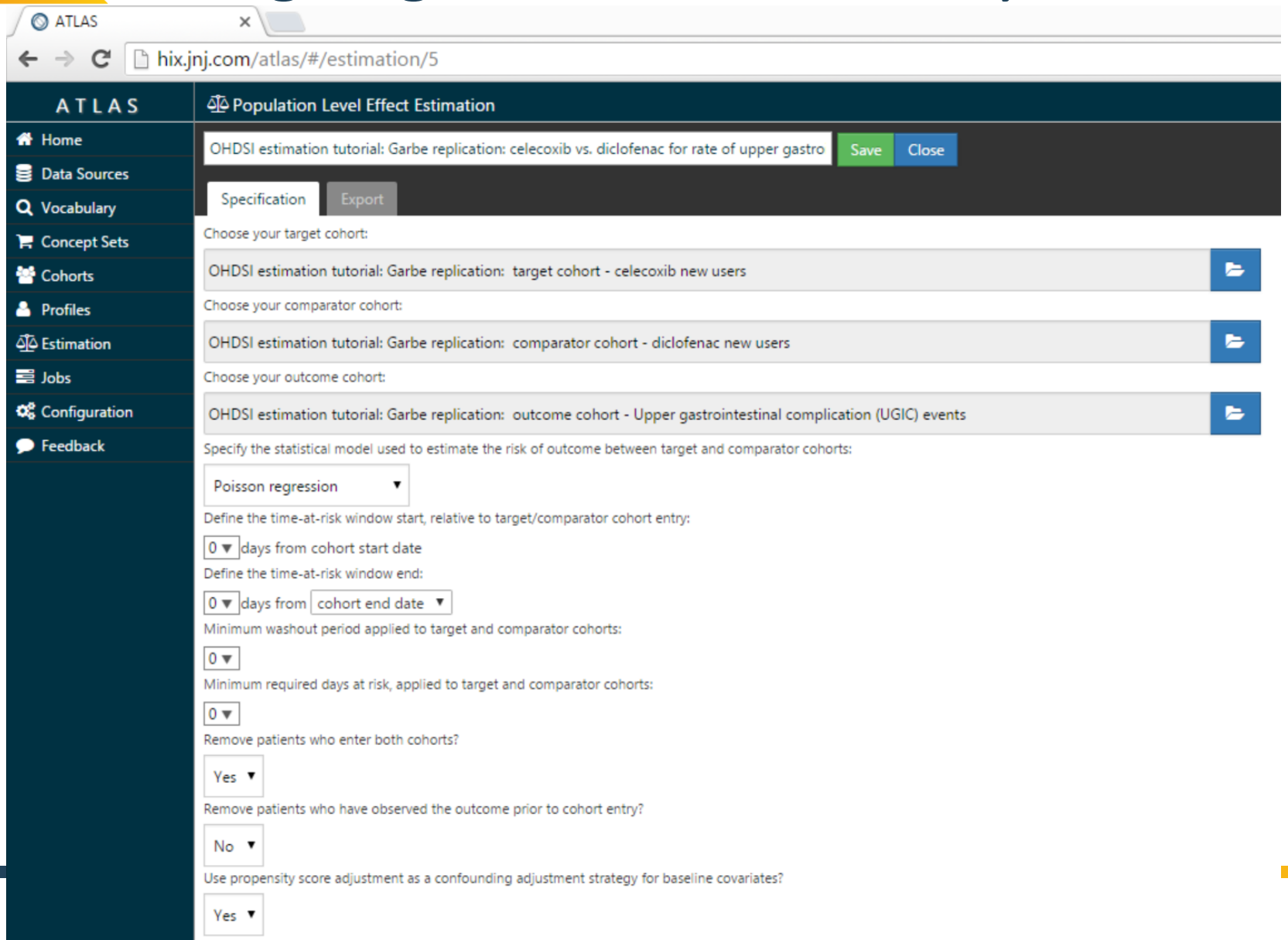
- 47 distinct ICD10CM codes map to standard concepts…
- …but so do 126 ICD9CM codes, 157 Read codes, 27 OXMIS codes, etc.
- Using one standard concept definition allows consistent application of clinical construct across different databases, even if they use different source vocabularies
- Cross-database analyses require review of standard concepts and mapped source codes

Garbe et al. replication: Designing the statistical analysis in ATLAS

Statistical analysis

We used a Poisson regression analysis to estimate the rate ratio (RR) of UGIC for coxib initiation versus tNSAID initiation and its 95 % confidence interval (CI). A conventional approach and the hd-PS approach were used to estimate the PS. The PS was estimated as the probability of initiating a coxib in a logistic regression model. In the conventional approach, the PS was estimated via a logistic regression model for coxib initiation that included all 79 pre-specified covariates described above, which were ascertained during the 6-month period before cohort entry.

Garbe et al. replication: Designing the statistical analysis in ATLAS



The choice of the outcome model defines your research question

	Logistic regression	Poisson regression	Cox proportional hazards
How the outcome cohort is used	Binary classifier of presence/ absence of outcome during the fixed time-at-risk period	Count the number of occurrences of outcomes during time-at-risk,	Compute time-to-event from time-at-risk start until earliest of first occurrence of outcome or time-at-risk end, and track the censoring event (outcome or no outcome)
'Risk' metric	Odds ratio	Rate ratio	Hazards ratio
Key model assumptions	Constant response in fixed window	Outcomes follow Poisson distribution	Proportionality – constant relative hazard

Cohort restriction decisions

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

Poisson regression

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

0 days from cohort start date

Define the time-at-risk window end:

0 days from cohort end date

Minimum washout period applied to target and comparator cohorts:

0

Minimum required days at risk, applied to target and comparator cohorts:

0

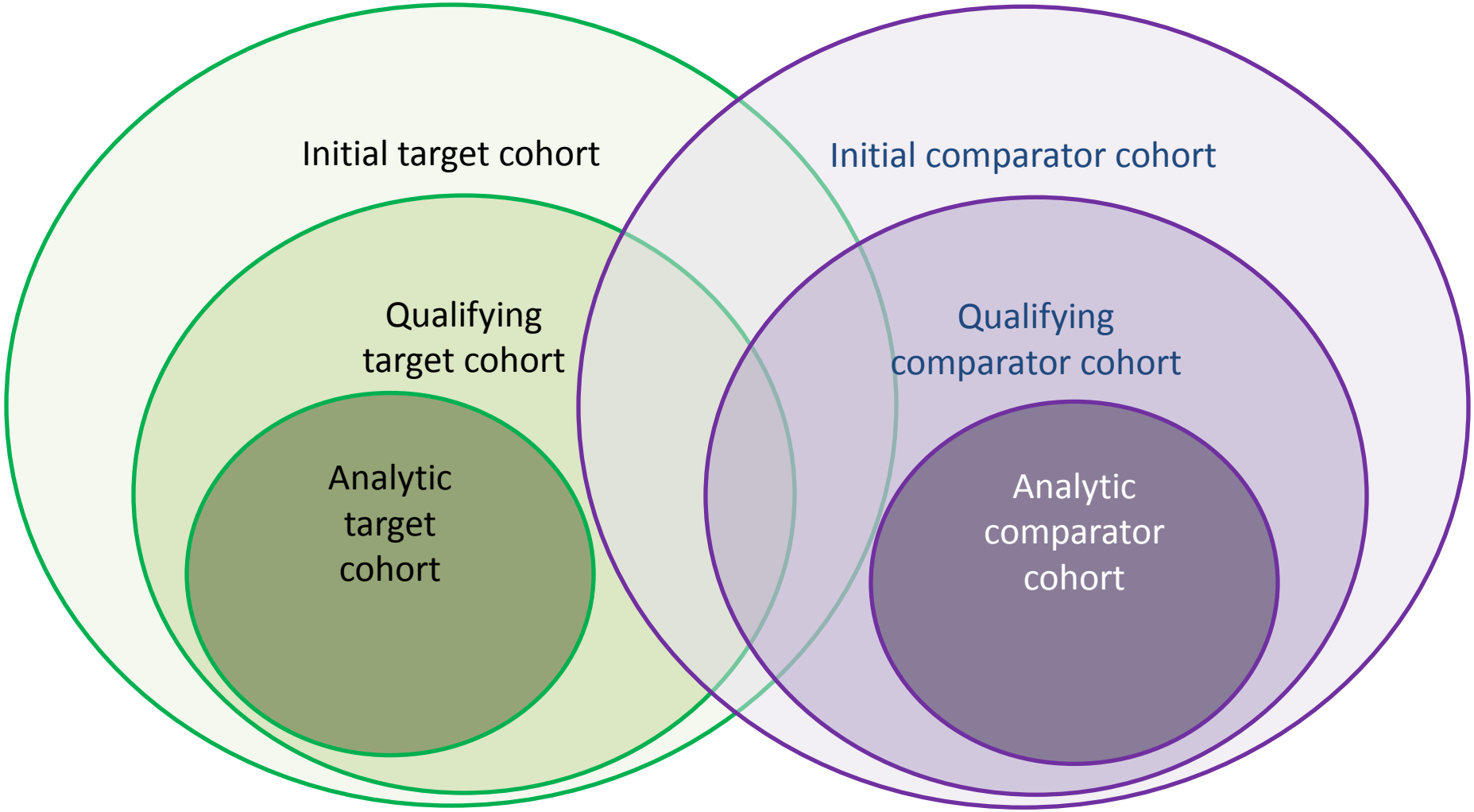
Remove patients who enter both cohorts?

Yes

Remove patients who have observed the outcome prior to cohort entry?

No

Cohort restriction in comparative cohort analyses



Two forms of attrition to consider as diagnostics

1. Initial cohort → Qualifying cohort: (independent from analysis)

How did additional inclusion criteria impact the proportion and composition of your cohort?

Graham replication: comparator cohort – warfarin new users

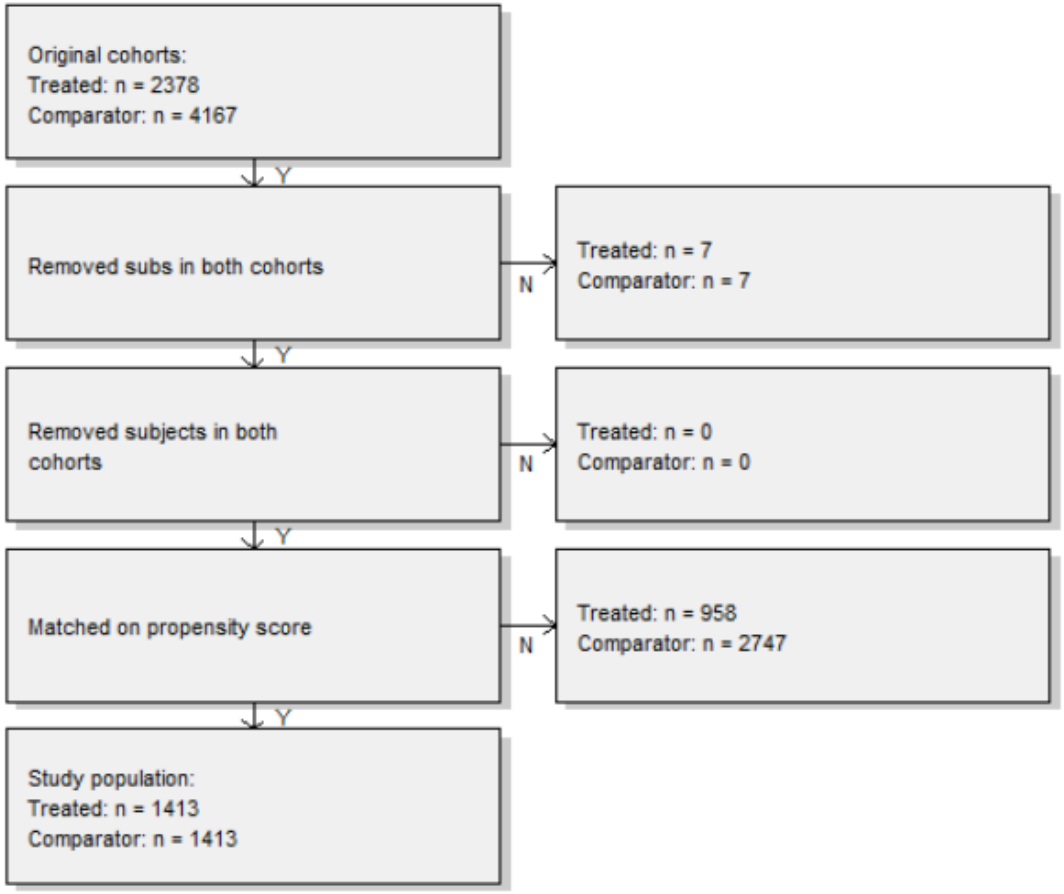
	Match Rate	Matches	Total
Summary Statistics:	31.52%	52,400	166,243

	Inclusion Rule	N	% Remain	% Diff
1.	Has prior atrial fibrillation of atrial flutter diagnosis	78,371	47.14%	52.86%
2.	Has no prior treatment with comparator drug (dabigatran)	74,931	45.07%	2.07%
3.	Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)	71,879	43.24%	1.84%
4.	Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date	71,834	43.21%	0.03%
5.	Not undergoing dialysis or kidney transplant recipient	70,148	42.20%	1.01%
6.	No mitral valve disease, heart valve repair, or replacement in the prior 6 months	64,580	38.85%	3.35%
7.	No deep vein thrombosis or pulmonary embolism in the prior 6 months	54,791	32.96%	5.89%
8.	No joint replacement surgery in the prior 6 months	52,400	31.52%	1.44%

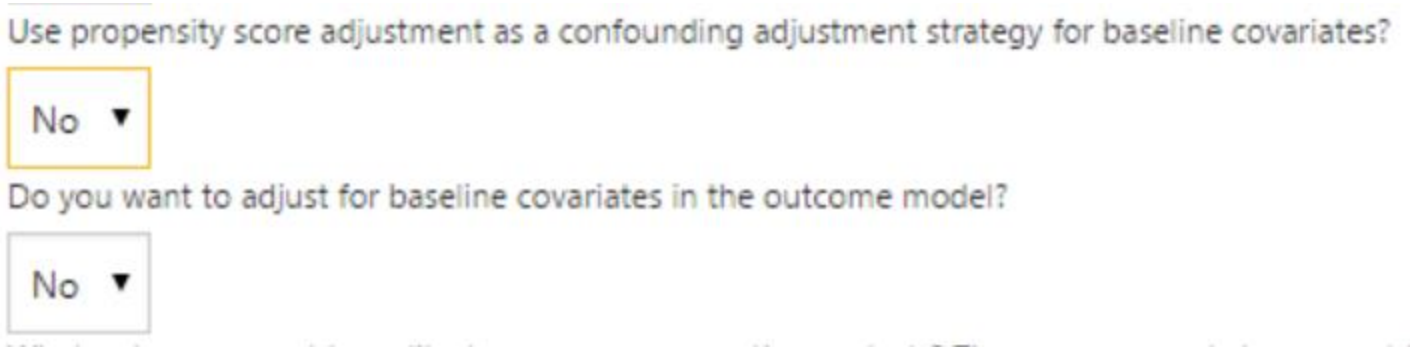
Two forms of attrition to consider as diagnostics

2. Qualifying cohort → Analytic cohort

How did analysis restrictions impact the proportion and composition of your cohort?



Covariate adjustment strategy

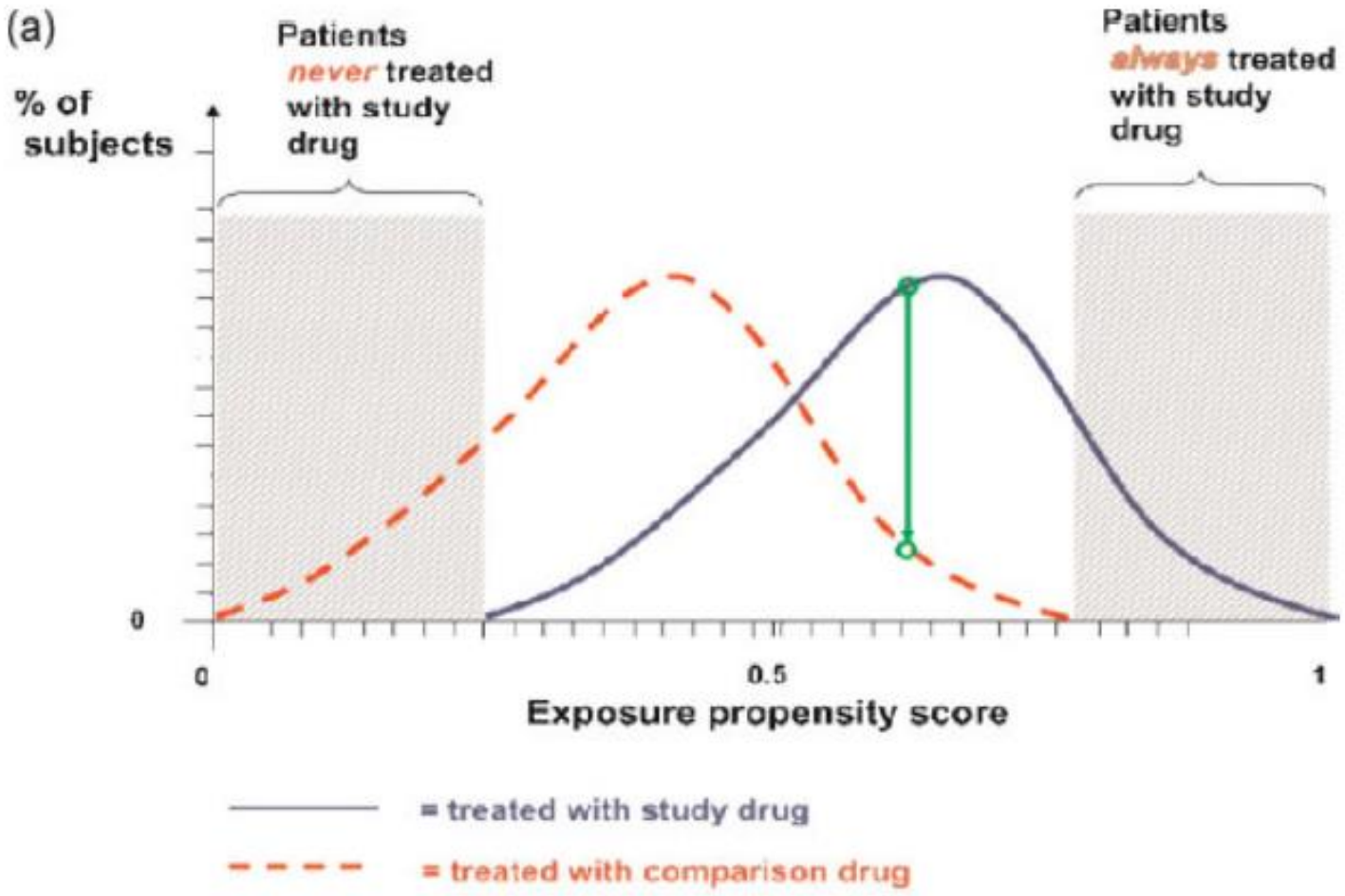


Propensity score introduction

- $e(x) = Pr(Z=1|x)$
  - Z is treatment assignment
  - x is a set of all covariates at the time of treatment assignment
- Propensity score = probability of belonging to the target cohort vs. the comparator cohort, given the baseline covariates
- Propensity score can be used as a 'balancing score': if the two cohorts have similar propensity score distribution, then the distribution of covariates should be the similar (need to perform diagnostic to check)

Rubin Biometrika 1983

Intuition around propensity score balance



Schneeweiss. PDS 2011

"Five reasons to use propensity score in pharmacoepidemiology"

- Theoretical advantages
  - Confounding by indication is the primary threat to validity, PS focuses directly on indications for use and non-use of drug under study
- Value of propensity scores for matching or trimming the population
  - Eliminate 'uncomparable' controls without assumptions of linear relationship between PS and outcome
- Improved estimation with few outcomes
  - PS allows matching on one scalar value rather than needing degrees of freedom for all covariates
- Propensity score by treatment interactions
  - PS enables exploration of patient-level heterogeneity in response
- Propensity score calibration to correct for measurement error

Glynn et al, BCPT 2006

Covariate selection in propensity score modeling

- What covariates should you include in propensity score model?
  - Variables that predict exposure status (Rubin Biometrika 1983)
  - Variables that are confounders, associated with both exposure and outcome (Schneeweiss Epidemiology 2009)
  - Variables that are associated with outcomes (Brookhart AJE 2006)
- Propensity score tends to balance distributions of covariates used in estimation
  - The method does NOTHING for unmeasured confounding or other covariates not entered into model

My perspective on covariate selection

- Choosing the ‘right’ variables in the model is an empirical question. It is the set of variables that yield the unbiased estimate of the effect of interest.

- The goal of fitting a propensity score is to predict treatment assignment, so a reasonable objective function is to maximize discrimination (AUC)

- Large-scale regression, using L1 regularization (LASSO), that uses a large set of potential covariates will often outperform a traditional regression that uses a small subset of those covariates
  - Regularization reduces risk of model overfitting, by only selecting the covariates that have an adequate information component
  - Covariates that aren’t used are effectively ‘unmeasured’

Covariate selection in ATLAS

Use propensity score adjustment as a confounding adjustment strategy for baseline covariates?

Yes

Which types of baseline covariates do you want to include in the propensity score model?

- [x] Demographics
  - [x] Gender
  - [x] Age group (5-year bands)
  - [x] Index year
  - [ ] Index month
  - [ ] Race
  - [ ] Ethnicity
- [x] Conditions
  - [ ] In prior 30d
  - [x] In prior 365d
  - [ ] In prior 180d within inpatient setting
  - [ ] All time prior
  - [ ] Overlapping index date
- [ ] Condition aggregation
  - [ ] SNOMED
  - [ ] MedDRA
- [x] Drugs
  - [ ] In prior 30d
  - [ ] In prior 365d
  - [ ] All time prior
  - [x] Overlapping index date
- [x] Drug aggregation
  - [ ] Clinical Drug
  - [x] Ingredient
  - [x] ATC Class
- [ ] Procedures
  - [ ] In prior 30d
  - [ ] In prior 365d
- [ ] Measurement
  - [ ] Existence in prior 30d
  - [ ] Existence in prior 365d
  - [ ] Count in prior 365d
  - [ ] Has latest prior numeric value below normal range
  - [ ] Has latest prior numeric value above normal range
- [ ] Risk scores
  - [ ] Charlson
  - [ ] CHADS2
  - [ ] DCSI
- [x] Concept counts (count of distinct conditions/procedures/visits in history)
- [ ] Interaction terms
  - [ ] By index year
  - [ ] By index month

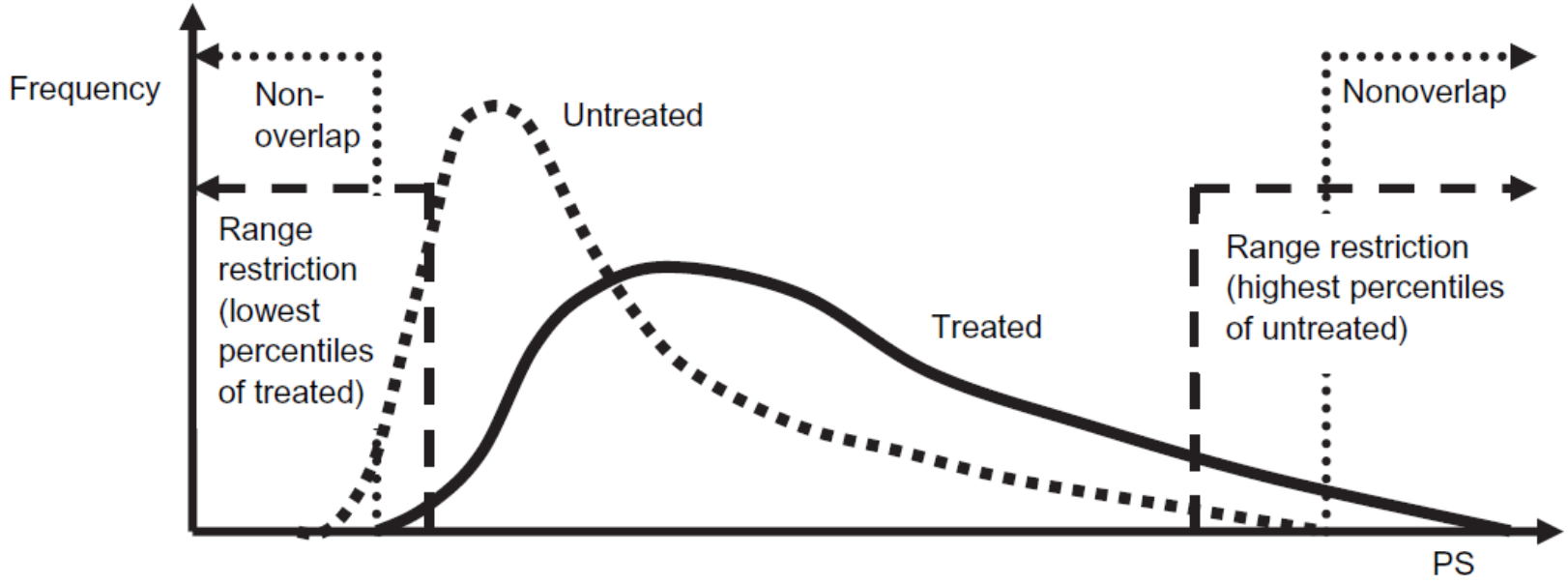
What concepts do you want to include in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

OHDSI estimation tutorial- Garbe replication: covariates to include in PS model

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

OHDSI estimation tutorial- Garbe replication: covariates to exclude in PS model

Design choice: propensity score trimming by percentile



- Simulation studies suggest PS trimming may eliminate confounding due to extreme patients with 'last resort treatment' or 'treatment withhold'
- The subpopulation you select may be systematically different from the overall population

Sturmer AJE 2010

Propensity score trimming by percentile in ATLAS

Design choice: propensity score trimming by equipoise

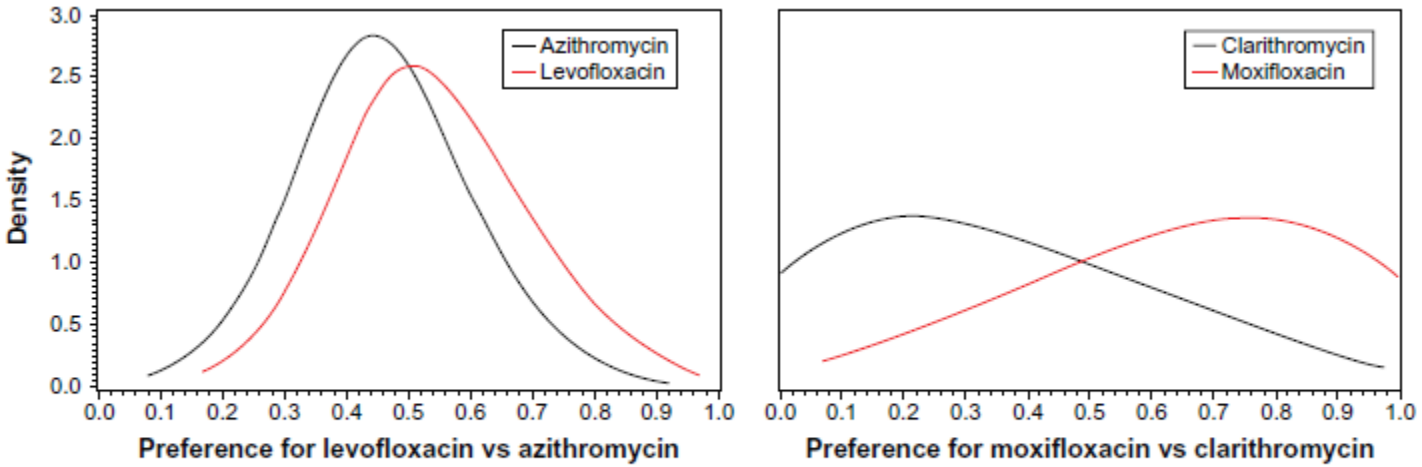
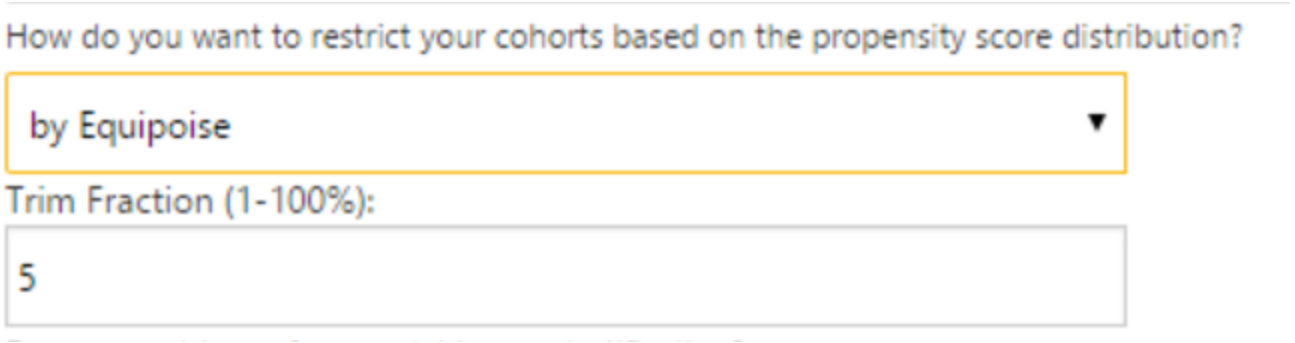


Figure 1 Preference score distributions.
Notes: Preference distributions for a pair of antibiotics given to very similar patients (left) and for a pair given to substantially different patient populations. (See Table 1 for salient differences).

- Preference score (PREF) = propensity score, weighted for the imbalance in the prevalence of the target vs. comparator cohort
- PREF= 0.5 means equally likely to belong to either cohort
- Trimming to PREF near 0.5 restricts to persons who had reasonable probability of assignment in both groups ('near clinical equipoise')

Idea derived from Walker CER 2013

Propensity score trimming by equipoise in ATLAS



Methods for confounding adjustment using a propensity score

Regression adjustment	The PS is used as a covariable in an outcome regression model to adjust the as… assun… same… relationship between propensity score and outcome is correctly specified.
Matching	The PS is used to match exposed subjects to unexposed subjects with similar values of the PS. This method assumes that within the matched sample, exposed and unexposed subjects have a similar distribution of baseline characteristics.
Stratification	The PS is used to stratify subjects into (often quintiles or deciles) strata. Treatment effects are estimated separately within each stratum and then combined into an overall estimate of treatment effect. This method assumes that within each stratum, exposed and unexposed subjects have a similar distribution of baseline characteristics.
Inverse Probability Weighting	The PS is used to create weights based on the inverse probability which is defined as: E*/PS + (1-E)/(1-PS). This assumes that baseline characteristics are similar in the exposed and unexposed group.

* E: exposure

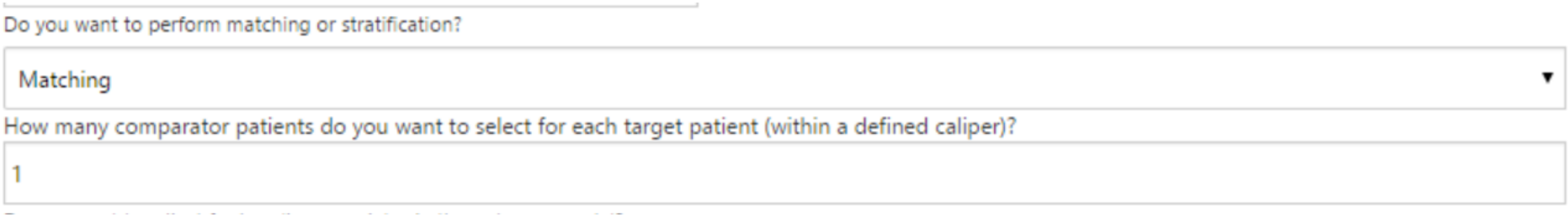
Not generally recommended

Fully implemented in OHDSI CohortMethod R package

Garbe et al, Eur J Clin Pharmacol 2013, http://www.ncbi.nlm.nih.gov/pubmed/22763756

Propensity score adjustment in ATLAS

Matching:



Stratification:

Outcome model covariate adjustment

- Final outcome model can be univariate (estimate effect of cohort class on outcome alone) or multivariate (estimate effect of cohort class on outcome, adjusting for other baseline covariates)
- If propensity score matching or stratification is used, outcome model should be conditional regression (estimate effect of cohort class on outcome within each matched set)
- Outcome model typically bounded by degrees of freedom; can only include additional covariates if sufficient number of outcomes (rule of thumb: 10 outcomes per extra covariate)

Outcome model covariate adjustment in ATLAS

Do you want to adjust for baseline covariates in the outcome model?

Yes ▾

Which types of baseline covariates do you want to include in the outcome model?

- ☐ Demographics
  - ☐ Gender
  - ☐ Age group (5-year bands)
  - ☐ Index year
  - ☐ Index month
  - ☐ Race
  - ☐ Ethnicity
- ☐ Conditions
  - ☐ In prior 30d
  - ☐ In prior 365d
  - ☐ In prior 180d within inpatient setting
  - ☐ All time prior
  - ☐ Overlapping index date
- ☐ Condition aggregation
  - ☐ SNOMED
  - ☐ MedDRA
- ☐ Drugs
  - ☐ In prior 30d
  - ☐ In prior 365d
  - ☐ All time prior
  - ☐ Overlapping index date
- ☐ Drug aggregation
  - ☐ Clinical Drug
  - ☐ Ingredient
  - ☐ ATC Class
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  - ☐ Has latest prior numeric value below normal range
  - ☐ Has latest prior numeric value above normal range
- ☐ Risk scores
  - ☐ Charlson
  - ☐ CHADS2
  - ☐ DCSI
- ☐ Concept counts (count of distinct conditions/procedures/visits in history)
- ☐ Interaction terms
  - ☐ By index year
  - ☐ By index month

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

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

Negative control outcomes for empirical calibration

- Observational data analyses may have residual bias, so it's important to perform diagnostics to quantify the extent of this potential issue
- Bias = expected value of the error distribution (random + systematic)
- Negative control outcomes can be used efficiently in cohort analyses
  - Outcomes which have no evidence about association with either target cohort or outcome cohort, therefore 'true RR' assumed to equal 1 and any difference between effect estimate and 'true RR' can be classified as systematic error
  - Convention: find outcomes there 'absence of evidence' can be inferred to be 'evidence of absence':
    1. not listed on target/comparator product labels
    2. not co-occurring with target/comparators in published literature (Medline)
    3. don't have increased signal score from spontaneous adverse event reporting (FAERS)
    4. do appear with adequate prevalence in the observational database so that an effect could have been previously observable had it existed
- Sample of negative control outcomes (n>20) can be used to estimate 'empirical null' distribution, which can then be used to empirically calibrate p-value for unknown outcome of interest

Pleasure reading to motivate use of negative controls

Research Article

Statistics in Medicine

Received 12 November 2012, Accepted 3 July 2013 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5925

Interpreting observational studies: why empirical calibration is needed to correct *p*-values

Martijn J. Schuemie,[a,b*†] Patrick B. Ryan,[b,c] William DuMouchel,[b,d] Marc A. Suchard[b,e] and David Madigan[b,f]

http://onlinelibrary.wiley.com/doi/10.1002/sim.5925/full

Negative control selection in ATLAS

What outcomes would you like to use as your negative controls? These are concepts known not to be associated with either the target or comparator group, such that we can assume the true relative risk should equal 1. These negative control outcomes will be used for empirical calibration.

OHDSI estimation tutorial: Garbe et al. replication, negative controls

Concept Set

OHDSI estimation tutorial: Garbe et al. replication, negative controls | Save | Close

Concept Set Expression | Included Concepts 34 | Included Source Codes | Export

Vocabulary
SNOMED (34)

Class
Clinical Finding (34)

Domain
Condition (34)

Standard Concept
Standard (34)

Invalid Reason
Valid (34)

Has Records
true (34)

Has Descendant Records
true (34)

Show All entries Filter:

Showing 1 to 34 of 34 entries Previous 1 Next

Id	Code	Name	Class	RC	DRC	Domain	Vocabulary
257007	61582004	Allergic rhinitis	Clinical Finding	35,111,076	55,582,634	Condition	SNOMED
255573	13645005	Chronic obstructive lung disease	Clinical Finding	22,235,402	28,534,157	Condition	SNOMED
319843	11851006	Mitral valve disorder	Clinical Finding	4,805,521	6,232,915	Condition	SNOMED
141932	398838000	Seborrheic keratosis	Clinical Finding	4,758,455	4,758,455	Condition	SNOMED
380094	57406009	Carpal tunnel syndrome	Clinical Finding	4,713,600	4,713,600	Condition	SNOMED
313459	73430006	Sleep apnea	Clinical Finding	4,280,415	17,180,747	Condition	SNOMED
436665	13746004	Bipolar disorder	Clinical Finding	3,472,356	7,920,853	Condition	SNOMED
443800	14302001	Amenorrhea	Clinical Finding	3,221,577	3,257,684	Condition	SNOMED
197236	95315005	Uterine leiomyoma	Clinical Finding	3,021,864	3,898,566	Condition	SNOMED
321596	20696009	Peripheral venous insufficiency	Clinical Finding	2,950,514	3,004,234	Condition	SNOMED
436676	47505003	Posttraumatic stress disorder	Clinical Finding	2,933,195	2,978,063	Condition	SNOMED
139099	400097005	Ingrowing nail	Clinical Finding	2,928,631	2,928,631	Condition	SNOMED
314658	8186001	Cardiomegaly	Clinical Finding	2,651,255	2,651,255	Condition	SNOMED
433753	15167005	Alcohol abuse	Clinical Finding	1,758,133	2,013,798	Condition	SNOMED
440374	191736004	Obsessive-compulsive disorder	Clinical Finding	1,666,847	1,666,981	Condition	SNOMED

Putting it all together…

ATLAS print friendly – the start of your team's protocol

Population Level Effect Estimation

OHDSI estimation tutorial: Garbe replication: celecoxib vs. diclofenac for rate of upper gastro | Save | Close

Specification | Export

Print Friendly | R Code

Research question

To compare the risk of **OHDSI estimation tutorial: Garbe replication: outcome cohort - Upper gastrointestinal complication (UGIC) events** between **OHDSI estimation tutorial: Garbe replication: target cohort - celecoxib new users** and **OHDSI estimation tutorial: Garbe replication: comparator cohort - diclofenac new users**, we will estimate the population-level effect of exposure on the rate of the outcome during the period from 0 days from cohort start date to 0 days from cohort end date.

Study Design:

This study will follow a retrospective, observational, comparative cohort design. We define 'retrospective' to mean the study will be conducted using data already collected prior to the start of the study. We define 'observational' to mean there is no intervention or treatment assignment imposed by the study. We define 'cohort' to mean a set of patients satisfying a one or more inclusion criteria for a duration of time. We define 'comparative cohort design' to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry.

In this study, we compare **OHDSI estimation tutorial: Garbe replication: target cohort - celecoxib new users** with **OHDSI estimation tutorial: Garbe replication: comparator cohort - diclofenac new users** for the rate of **OHDSI estimation tutorial: Garbe replication: outcome cohort - Upper gastrointestinal complication (UGIC) events** from 0 days from cohort start date to 0 days from cohort end date.

The overall study population could be considered to be patients who entered either the target cohort or comparator cohort. Patients were excluded from consideration is they qualified for both the target cohort and comparator cohort at any time in their record.

The rate of outcomes among patients in the target and comparator cohorts is determined by counting the number of outcome occurrences of **OHDSI estimation tutorial: Garbe replication: outcome cohort - Upper gastrointestinal complication (UGIC) events** during the time-at-risk of 0 days from cohort start date to 0 days from cohort end date.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7.

The types of baseline covariates used to fit the propensity score model will be:

- Demographics
  - Gender
  - Age group (5-year bands)
  - Index year
- Conditions
  - In prior 365d

ATLAS R code – the start of your team's implementation

Population Level Effect Estimation

OHDSI estimation tutorial: Garbe replication: celecoxib vs. diclofenac for rate of upper gastro | Save | Close

Specification | Export

Print Friendly | R Code

```
#######################################################
# Study: OHDSI estimation tutorial: Garbe replication: celecoxib vs. diclofenac for rate of upper gastrointestinal complications (UGIC)
#######################################################

#######################################################
# Cohort Method Installation & Load
#######################################################

# Uncomment to install Cohort Method
# install.packages("drat")
# drat::addRepo(c("OHDSI","cloudyr"))
# install.packages("CohortMethod")

# Load the Cohort Method library
library(CohortMethod)
library(SqlRender)

#######################################################
# Data extraction
#######################################################

# TODO: Insert your connection details here
connectionDetails <- createConnectionDetails(dbms = "postgresql",
                                             server = "localhost/ohdsi",
                                             user = "joe",
                                             password = "supersecret")
cdmDatabaseSchema <- "my_cdm_data"
resultsDatabaseSchema <- "my_results"
exposureTable <- "exposure_table"
outcomeTable <- "outcome_table"
cdmVersion <- "5"
```

Hands-on exercise

- Design your study!
  - What's your target cohort?
  - What's your compactor cohort?
  - What's your outcome cohort?
  - What's your time-at-risk?
  - What's your model specification?
  - What's your covariate adjustment strategy?

- Save your progress in ATLAS