# The Book of OHDSI

*Observational Health Data Science and Informatics*

*2019-06-06*

# Contents

# Preface

This is a book about OHDSI, and is currently very much under development.

The book is written in RMarkdown with bookdown. It is automatically rebuilt from source by travis.

## Goals of this book

This book aims to be a central knowledge repository for OHDSI, and focuses on describing the OHDSI community, data standards, and tools. It is intended both for those new to OHDSI and veterans alike, and aims to be practical, providing the necessary theory and subsequent instructions on how to do things. After reading this book you will understand what OHDSI is, and how you can join the journey. You will learn what the common data model and standard vocabularies are, and how they can be used to standard an observational healthcare database. You will learn there are three main uses cases for these data: characterization, population-level estimation, and patient-level prediction, and that all three activities are supported by OHDSI's open source tools, and how to use them. You will learn how to establish the quality of the generated evidence through data quality, clinical validity, software validity, and method validity. Lastly, you will learn how these tools can be used to execute these studies in a distributed research network.

## Structure of the book

This book is organizes in five major sections: (I) The OHDSI Community, (II) Uniform data representation, (III) Data Analytics, (IV) Evidence Quality, and (V) OHDSI Studies. Each section has multiple chapters, and each chapter aims to follow the following main outline: Introduction, Theory, Practice, Excercises.

# Part I

# The OHDSI Community

# Chapter 1

# Mission, vision, values

## 1.1 Our Mission

To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

## 1.2 Our Vision

A world in which observational research produces a comprehensive understanding of health and disease.

## 1.3 Our Objectives

- **Innovation**: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.
- **Reproducibility**: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
- **Community**: Everyone is welcome to actively participate in OHDSI, whether you are a patient, a health professional, a researcher, or someone who simply believes in our cause.
- **Collaboration**: We work collectively to prioritize and address the real world needs of our community's participants.

- **Openness**: We strive to make all our community's proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
- **Beneficence**: We seek to protect the rights of individuals and organizations within our community at all times.

# Chapter 2

# Collaborators

History of OHDSI

Map of collaborators Forums Wiki Workgroups and chapters Symposia and hack-a-thons

Governance at local sites

# Chapter 3

# Open Science

Mention FAIR principles?

# Chapter 4

# Where to begin

This chapter will discuss where to begin if one is new in OHDSI. For various activities, we can describe how one might get started.

For example, if interested in doing a network study, these are the steps. Same for interests in methods research, grant writing, etc.

Add a diagram that shows what tools are used for which steps?

# Part II

# Uniform Data Representation

# Chapter 5

# The Common Data Model

*Chapter leads: Clair Blacketer & Mui VanZandt*

No single observational data source provides a comprehensive view of the clinical data a patient accumulates while receiving healthcare, and therefore none can be sufficient to meet all expected outcome analysis needs. This explains the need for assessing and analyzing multiple data sources concurrently using a common data standard. This standard is provided by the OMOP Common Data Model (CDM).

The CDM is designed to support the conduct of research to identify and evaluate associations between interventions (drug exposure, procedures, healthcare policy changes etc.) and outcomes caused by these interventions (condition occurrences, procedures, drug exposure etc.). Outcomes can be efficacious (benefit) or adverse (safety risk). Often times, specific patient cohorts (e.g., those taking a certain drug or suffering from a certain disease) may be defined for treatments or outcomes, using clinical events (diagnoses, observations, procedures, etc.) that occur in predefined temporal relationships to each other. The CDM, combined with its standardized content (via the Standardized Vocabularies), will ensure that research methods can be systematically applied to produce meaningfully comparable and reproducible results.

## 5.1 Design Principles

The CDM is designed to include all observational health data elements (experiences of the patient receiving health care) that are relevant for analysis use cases to support the generation of reliable scientific evidence about disease natural history, healthcare delivery, effects of medical interventions, the identification of demographic information, health care interventions and outcomes.

Therefore, the CDM is designed to store observational data to allow for research, under the following principles:

- **Suitability for purpose**: The CDM aims to provide data organized in a way optimal for analysis, rather than for the purpose of addressing the operational needs of health care providers or payers.
- **Data protection**: All data that might jeopardize the identity and protection of patients, such as names, precise birthdays etc. are limited. Exceptions are possible where the research expressly requires more detailed information, such as precise birth dates for the study of infants.
- **Design of domains**: The domains are modeled in a person-centric relational data model, where for each record the identity of the person and a date is captured as a minimum.
- **Rationale for domains**: Domains are identified and separately defined in an entity-relationship model if they have an analysis use case and the domain has specific attributes that are not otherwise applicable. All other data can be preserved as an observation in an entity-attribute-value structure.
- **Standardized Vocabularies**: To standardize the content of those records, the CDM relies on the Standardized Vocabularies containing all necessary and appropriate corresponding standard healthcare concepts.
- **Reuse of existing vocabularies**: If possible, these concepts are leveraged from national or industry standardization or vocabulary definition organizations or initiatives, such as the National Library of Medicine, the Department of Veterans' Affairs, the Center of Disease Control and Prevention, etc.
- **Maintaining source codes**: Even though all codes are mapped to the Standardized Vocabularies, the model also stores the original source code to ensure no information is lost.
- **Technology neutrality**: The CDM does not require a specific technology. It can be realized in any relational database, such as Oracle, SQL Server etc., or as SAS analytical datasets.
- **Scalability**: The CDM is optimized for data processing and computational analysis to accommodate data sources that vary in size, including databases with up to hundreds of millions of persons and billions of clinical observations.
- **Backwards compatibility**: All changes from previous CDMs are clearly delineated in the github repository (https://github.com/OHDSI/CommonDataModel). Older versions of the CDM can be easily created from the CDMv5, and no information is lost that was present previously.

## 5.2 Data Model Conventions

There are a number of implicit and explicit conventions that have been adopted in the CDM. Developers of methods that run against the CDM need to understand these conventions.

### 5.2.1 General conventions of the model

The OMOP CDM is considered a "person-centric" model, meaning that the people (or patients) drive the event and observation tables. At a minimum, the tables have a foreign key into the PERSON table and a date. This allows for a longitudinal view on all healthcare-relevant events by person. The exceptions from this rule are the standardized health system data tables, which are linked directly to events of the various domains.

### 5.2.2 General conventions of schemas

New to CDM v6.0 is the concept of schemas. This allows for more separation between read-only and writeable tables. The clinical data, event, and vocabulary tables are in the 'CDM' schema and are considered read-only to the end user. This means that the tables can be queried but no information can be accidentally removed or written over except by the database administrator. Tables that need to be manipulated by web-based tools or end users have moved to the 'Results' schema. Currently the only two tables in the 'Results' schema are COHORT and COHORT_DEFINITON, **Todo: add a sentence explaining that these tables describe groups of interest that the user might define, put in links to the later sections** though likely more will be added over the course of v6.0 point releases. These tables can be written to, meaning that a cohort created in ATLAS or by a user can be stored in the COHORT table and accessed at a later date. This does mean that cohorts in the COHORT table can be manipulated by anyone so it is always recommended that the SQL code used to create the cohort be saved along with the project or analysis in the event it needs to be regenerated.

### 5.2.3 General conventions of data tables

The CDM is platform-independent. Data types are defined generically using ANSI SQL data types (VARCHAR, INTEGER, FLOAT, DATE, DATETIME, CLOB). Precision is provided only for VARCHAR. It reflects the minimal required string length and can be expanded within a CDM instantiation. The CDM does not prescribe the date and datetime format. Standard queries against CDM may vary for local instantiations and date/datetime configurations.

In most cases, the first field in each table ends in '_ID', containing a record identifier that can be used as a foreign key in another table. For example, the CONDITION_OCCURRENCE table contains the field VISIT_OCCURRENCE_ID which is a foreign key to the VISIT_OCCURRENCE table where VISIT_OCCURRENCE_ID is the primary key.

### 5.2.4 General conventions of fields

Variable names across all tables follow one convention:

| Notation | Description |
|---|---|
| [entity]_SOURCE_VALUE | Verbatim information from the source data, typically used in ETL to map to CONCEPT_ID, and not to be used by any standard analytics. For example, CONDITION_SOURCE_VALUE = '787.02' was the ICD-9 code captured as a diagnosis from the administrative claim. |
| [entity]_ID | Unique identifiers for key entities, which can serve as foreign keys to establish relationships across entities. For example, PERSON_ID uniquely identifies each individual. VISIT_OCCURRENCE_ID uniquely identifies a PERSON encounter at a point of care. |
| [entity]_CONCEPT_ID | Foreign key into the Standardized Vocabularies (i.e. the standard concept attribute for the corresponding term is true), which serves as the primary basis for all standardized analytics. For example, CONDITION_CONCEPT_ID = 31967 contains the reference value for the SNOMED concept of 'Nausea' |
| [entity]_SOURCE_CONCEPT_ID | Foreign key into the Standardized Vocabularies representing the concept and terminology used in the source data, when applicable. For example, CONDITION_SOURCE_CONCEPT_ID = 45431665 denotes the concept of 'Nausea' in the Read terminology; the analogous CONDITION_CONCEPT_ID might be 31967, since SNOMED-CT is the Standardized Vocabulary for most clinical diagnoses and findings. |
| [entity]_TYPE_CONCEPT_ID | Delineates the origin of the source information, standardized within the Standardized Vocabularies. For example, DRUG_TYPE_CONCEPT_ID can allow analysts to discriminate between 'Pharmacy dispensing' and 'Prescription written' |

### 5.2.5 Representation of content through Concepts

In CDM data tables the content of each record is represented using Concepts. Concepts are stored in event tables with their CONCEPT_IDs as foreign keys to the CONCEPT table, which contains Concepts necessary to describe the healthcare experience of a patient. If a Standard Concept does not exist or cannot be identified, the the CONCEPT_ID 0 is used, representing a non-existing concept or un-mappable source value.

Records in the CONCEPT table contain detailed information about each concept (name, domain, class etc.). Concepts, Concept Relationships, Concept Ancestors and other information relating to Concepts is contained in the tables of the Standardized Vocabularies.

### 5.2.6 Difference between Concept IDs and Source Values

Many tables contain equivalent information in multiple places: As a Source Value, a Source Concept and as a Standard Concept.

- **Source Values** contain the codes from public code systems such as ICD-9-CM, NDC, CPT-4, READ etc. or locally controlled vocabularies (such as F for female and M for male) copied from the source data. Source Values are stored in the [entity]_SOURCE_VALUE fields in the data tables.
- **Concepts** are CDM-specific entities that represent the meaning of a clinical fact. Most concepts are based on code systems used in healthcare (called Source Concepts), while others were created de-novo (CONCEPT_CODE = 'OMOP generated'). Concepts have unique IDs across all domains.
- **Source Concepts** are the concepts that represent the code used in the source. Source Concepts are only used for common healthcare code systems, not for OMOP-generated Concepts. Source Concepts are stored in the [entity]_SOURCE_CONCEPT_ID field in the data tables.
- **Standard Concepts** are those concepts that are used to define the unique meaning of a clinical entity. For each entity there is one Standard Concept. Standard Concepts are typically drawn from existing public vocabulary sources. Concepts that have the equivalent meaning to a Standard Concept are mapped to the Standard Concept. Standard Concepts are referred to in the [entity]_CONCEPT_ID field of the data tables.

Source Values are only provided for convenience and quality assurance (QA) purposes. Source Values and Source Concepts are optional, while **Standard Concepts are mandatory**. Source Values may contain information that is only meaningful in the context of a specific data source. This mandatory use of Standard Concepts is what allows all OHDSI collaborators to speak the same language. For example, let's look at the condition 'Pulmonary Tuberculosis' (TB). Figure 5.1 shows that the ICD9CM code for TB is 011.

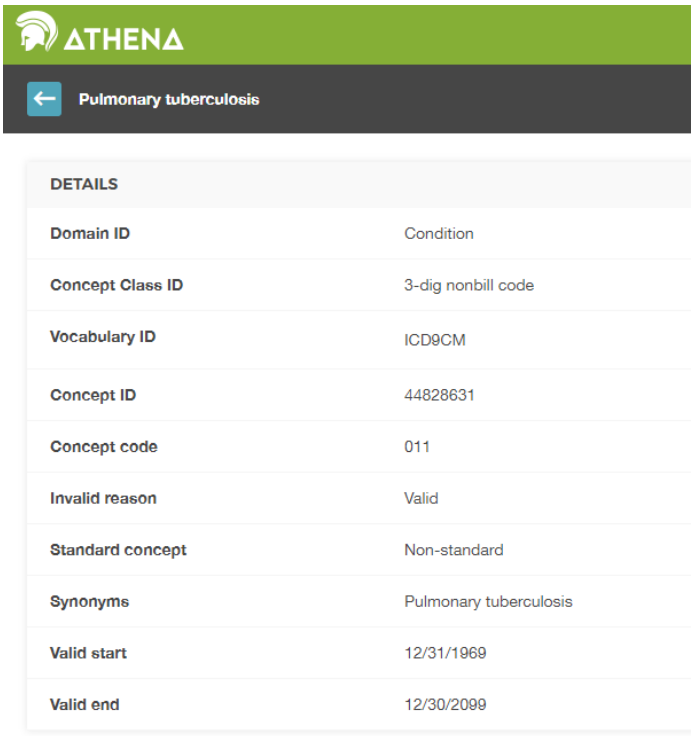
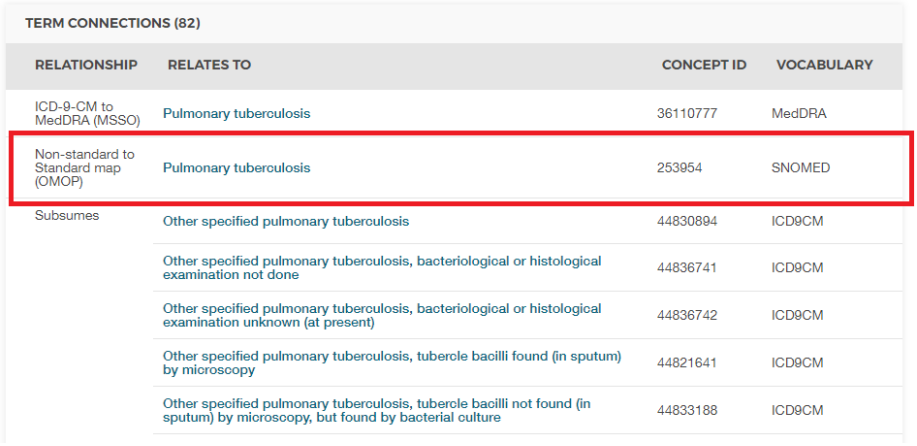



Figure 5.1: ICD9CM code for Pulmonary Tuberculosis



TERM CONNECTIONS (82)

| RELATIONSHIP | RELATES TO | CONCEPT ID | VOCABULARY |
|---|---|---|---|
| ICD-9-CM to MedDRA (MSSO) | Pulmonary tuberculosis | 36110777 | MedDRA |
| Non-standard to Standard map (OMOP) | Pulmonary tuberculosis | 253954 | SNOMED |
| Subsumes | Other specified pulmonary tuberculosis | 44830894 | ICD9CM |
| | Other specified pulmonary tuberculosis, bacteriological or histological examination not done | 44836741 | ICD9CM |
| | Other specified pulmonary tuberculosis, bacteriological or histological examination unknown (at present) | 44836742 | ICD9CM |
| | Other specified pulmonary tuberculosis, tubercle bacilli found (in sputum) by microscopy | 44821641 | ICD9CM |
| | Other specified pulmonary tuberculosis, tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture | 44833188 | ICD9CM |

Figure 5.2: SNOMED code for Pulmonary Tuberculosis

Without the use of a standard way to represent TB the code 011 could be interpreted as 'Hospital Inpatient (Including Medicare Part A)' in the UB04 vocabulary, or as 'Nervous System Neoplasms without Complications, Comorbidities' in the DRG vocabulary. This is where Concept IDs, both Source and Standard, are valuable. The Concept ID that represents the 011 ICD9CM code is 44828631. This differentiates the ICD9CM from the UBO4 and from the DRG. The Standard Concept that ICD9CM code maps to is 253954 as shown in figure 5.2 by the relationship 'Non-standard to Standard map (OMOP)'. This same mapping relationship exists between Read, ICD10, CIEL, and MeSH codes, among others, so that any research that references the standard SNOMED concept is sure to include all supported source codes.

An example of how this relationship is depicted in the tables is shown in Table 5.7.

## 5.3 OMOP CDM Standardized Tables

The OMOP CDM contains 16 Clinical data tables, 10 Vocabulary tables, 2 Metadata tables, 4 Health System data tables, 2 Health Economics data tables, 3 standardized derived elements, and 2 results schema tables. These tables are fully specified in the CDM Wiki: https://github.com/OHDSI/CommonDataModel/wiki.

To illustrate how these tables are used in practice the data of one person will be used as a common thread throughout the rest of the chapter. While part of the CDM the Vocabulary tables are not covered here, rather, they are detailed in depth in Chapter 6.

### 5.3.1 Running Example: Endometriosis

Endometriosis is a painful condition whereby cells normally found in the lining of a woman's uterus occur elsewhere in the body. Severe cases can lead to infertility, bowel, and bladder problems. The following sections will detail one patient's experience with this disease and how her clinical experience might be represented in the Common Data Model.

> Every step of this painfull journey I had to convince everyone how much pain I was in.

Lauren had been experiencing endometriosis symptoms for many year; however, it took a ruptured cyst in her ovary before she was diagnosed. You can read more about Lauren at https://www.endometriosis-uk.org/laurens-story.

### 5.3.2 PERSON table

As the Common Data Model is a person-centric model (see section 5.2.1) let's start with how she would be represented in the PERSON table.

**What do we know about Lauren?**

- She is a 36-year-old woman
- Her birthday is 12-March-1982
- She is white
- She is english

With that in mind, her PERSON table might look something like this:

Table 5.2: The PERSON table.

| Column Name | Value | Explanation |
|---|---|---|
| PERSON_ID | 1 | PERSON_ID should be an integer, either directly from the source or generated as part of the build process. |

| Column Name | Value | Explanation |
|---|---|---|
| GENDER_CONCEPT_ID | 8532 | The concept ID referring to female gender is 8532. |
| YEAR_OF_BIRTH | 1982 | |
| MONTH_OF_BIRTH | 3 | |
| DAY_OF_BIRTH | 12 | |
| BIRTH_DATETIME | 1982-03-12 00:00:00 | When the time is not known midnight is used. |
| DEATH_DATETIME | | |
| RACE_CONCEPT_ID | 8527 | The concept ID referring to white race is 8527. |
| ETHNICITY_CONCEPT_ID | 38003564 | Typically hispanic status is stored for ethnicity. The concept ID 38003564 refers to 'Not hispanic'. |
| LOCATION_ID | | Her address is not known. |
| PROVIDER_ID | | Her primary care provider is not known. |
| CARE_SITE_ID | | Her primary care site is not known. |
| PERSON_SOURCE_VALUE | E | Typically this would be her identifier in the source data, though often is it the same as the PERSON_ID. |
| GENDER_SOURCE_VALUE | F | The gender value as it appears in the source is stored here. |
| GENDER_SOURCE_ CONCEPT_ID | 0 | If the gender value in the source was coded using a vocabulary recognized by OHDSI, that concept ID would go here. For example, if her gender was 'Sex-F' in the source and it was stated to be in the PCORNet vocabulary concept ID 44814665 would go in this field. |
| RACE_SOURCE_VALUE | white | The race value as it appears in the source is stored here. |
| RACE_SOURCE_CONCEPT_ID | 0 | Same principle as GENDER_SOURCE_CONCEPT_ID. |
| ETHNICITY_SOURCE_VALUE | English | The ethnicity value as it appears in the source is stored here. |
| ETHNICITY_SOURCE_ CONCEPT_ID | 0 | Same principle as GENDER_SOURCE_CONCEPT_ID. |

### 5.3.3 OBSERVATION_PERIOD table

The OBSERVATION_PERIOD table is designed to define the amount of time for which a patient's clinical events are recorded in the source system. For US healthcare insurance claims this is typically the enrollment period of the patient. When working with data from electronic health records (EHR) often the first record in the system is considered the OBSERVATION_PERIOD_START_DATE and the latest record is considered the OBSERVATION_PERIOD_END_DATE with the understanding that only the clinical events that happened within that particular system were recorded.

**How can we determine Lauren's observation period?**

Lauren's information is most similar to EHR data in that we only have records of her encounters from which to determine her observation period.

| Encounter_ID | Start_Date | Stop_Date | EncounterClass |
|---|---|---|---|
| 70 | 2010-01-06 | 2010-01-06 | outpatient |
| 80 | 2011-01-06 | 2011-01-06 | outpatient |
| 90 | 2012-01-06 | 2012-01-06 | outpatient |
| 100 | 2013-01-07 | 2013-01-07 | outpatient |
| 101 | 2013-01-14 | 2013-01-14 | ambulatory |
| 102 | 2013-01-17 | 2013-01-24 | inpatient |

Based on the encounter records her OBSERVATION_PERIOD table might look something like this:

Table 5.4: The OBSERVATION_PERIOD table.

| Column Name | Value | Explanation |
|---|---|---|
| OBSERVATION_PERIOD_ID | 1 | This is typically an autogenerated field that creates a unique id number for each record in the table. |
| PERSON_ID | 1 | This comes from the PERSON table and links PERSON and OBSERVATION_PERIOD. |
| OBSERVATION_PERIOD_START_DATE | 2010-01-06 | This is the start date of her earliest encounter on record. |
| OBSERVATION_PERIOD_END_DATE | 2013-01-24 | This is the end date of her latest encounter on record. |

| Column Name | Value | Explanation |
|---|---|---|
| PERIOD_TYPE_CONCEPT_ID | 44814725 | The best option in the Vocabulary with the concept class 'Obs Period Type' is 44814724, which stands for 'Period covering healthcare encounters'. |

### 5.3.4 VISIT_OCCURRENCE

The VISIT_OCCURRENCE table houses information about a patient's encounters with the health care system. Within the OHDSI vernacular these are referred to as visits and are considered to be discreet events. There are 12 categories of visits though the most common are inpatient, outpatient, emergency and long term care.

**How do we represent Lauren's encounters as visits?**

Revisting the encounters we used to determine her observation period:

| Encounter_ID | Start_Date | Stop_Date | EncounterClass |
|---|---|---|---|
| 70 | 2010-01-06 | 2010-01-06 | outpatient |
| 80 | 2011-01-06 | 2011-01-06 | outpatient |
| 90 | 2012-01-06 | 2012-01-06 | outpatient |
| 100 | 2013-01-07 | 2013-01-07 | outpatient |
| 101 | 2013-01-14 | 2013-01-14 | ambulatory |
| **102** | **2013-01-17** | **2013-01-24** | **inpatient** |

As an example let's represent the inpatient encounter as a record in the VISIT_OCCURRENCE table.

Table 5.6: The VISIT_OCCURRENCE table.

| Column Name | Value | Explanation |
|---|---|---|
| VISIT_OCCURRENCE_ID | 314 | This is typically an autogenerated field that creates a unique id number for each visit on the person's record in the converted CDM database. |
| PERSON_ID | 1 | This comes from the PERSON table and links PERSON and VISIT_OCCURRENCE. |
| VISIT_CONCEPT_ID | 9201 | The concept ID referring to an inpatient visit is 9201. |

| Column Name | Value | Explanation |
|---|---|---|
| VISIT_START_DATE | 2013-01-17 | The start date of the visit. |
| VISIT_START_DATETIME | 2013-01-17 00:00:00 | The date and time of the visit started. When time is unknown midnight is used. |
| VISIT_END_DATE | 2013-01-24 | The end date of the visit. If this is a one-day visit the end date should match the start date. |
| VISIT_END_DATETIME | 2013-01-24 00:00:00 | The date and time of the visit end. If time is unknown midnight is used. |
| VISIT_TYPE_CONCEPT_ID | 32034 | This column is intended to provide information about the provenance of the visit record, i.e. does it come from an insurance claim, hospital billing record, EHR record, etc. For this example the concept ID 32035 is used as the encounters are similar to electronic health records |
| PROVIDER_ID* | NULL | If the encounter record has a provider associated, the id for that provider goes in this field. This should be the PROVIDER_ID from the PROVIDER table that represents the provider on the encounter. |
| CARE_SITE_ID | NULL | If the encounter record has a care site associated, the id for that care site goes in this field. This should be the CARE_SITE_ID from the CARE_SITE table that codes for the care site on the encounter. |
| VISIT_SOURCE_VALUE | Inpatient | The visit value as it appears in the source goes here. In this context 'visit' means outpatient, inpatient, emergency, etc. |
| VISIT_SOURCE_CONCEPT_ID | 0 | If the visit value from the source is coded using a vocabulary that is recognized by OHDSI, the concept ID that represents the visit source value would go here. |

| Column Name | Value | Explanation |
|---|---|---|
| ADMITTED_FROM_CONCEPT_ID | 0 | If known, this is the concept ID that represents where the patient was admitted from. This concept should have the concept class 'Place of Service' and the domain 'Visit'. For example, if a patient was admitted to the hospital from home, the concept ID would be 8536. |
| ADMITTED_FROM_SOURCE_VALUE | NULL | This is the value from the source that represents where the patient was admitted from. Using the above example, this would be 'home'. |
| DISCHARGE_TO_CONCEPT_ID | 0 | If known, this is the concept ID that represents where the patient was discharged to. This concept should have the concept class 'Place of Service' and the domain 'Visit'. For example, if a patient was released to an assisted living facility, the concept ID would be 8615. |
| DISCHARGE_TO_SOURCE_VALUE | 0 | This is the value from the source that represents where the patient was discharged to. Using the above example, this would be 'assisted living facility'. |
| PRECEDING_VISIT_OCCURRENCE_ID | NULL | The VISIT_OCCURRENCE_ID for the visit immediately preceding the current one in time for the patient. |

*A patient may interact with multiple health care providers during one visit, as is often the case with inpatient stays. These interactions can be recorded in the VISIT_DETAIL table. While not covered in depth in this chapter, you can read more about the VISIT_DETAIL table on the CDM wiki.

### 5.3.5 CONDITION_OCCURRENCE

Records in the CONDITION_OCCURRENCE table are diagnoses, signs, or symptoms of a condition either observed by a Provider or reported by the patient.

**What are Lauren's conditions?**

Revisiting her account she says:

> About 3 years ago I noticed my periods, which had also been painful, were getting increasingly more painful. I started becoming aware of a sharp jabbing pain right by my colon and feeling tender and bloated around my tailbone and lower pelvis area. My periods had become so painful that I was missing 1-2 days of work a month. Painkillers sometimes dulled the pain, but usually they didn't do much.

The SNOMED code for painful menstruation cramps, otherwise known as dysmenorrhea, is 266599000. Table 5.7 shows how that would be represented in the CONDITION_OCCURRENCE table:

Table 5.7: The CONDITION_OCCURRENCE table.

| Column | Value | Explanation |
|---|---|---|
| CONDITION_OCCURRENCE_ID | 961 | This is typically an autogenerated field that creates a unique id number for each condition on the person's record in the converted CDM database. |
| PERSON_ID | 1 | This comes from the PERSON table and links PERSON and CONDITION_OCCURRENCE. |
| CONDITION_CONCEPT_ID | 194696 | The concept ID that represents the SNOMED code 266599000 is 194696 |
| CONDITION_START_DATE | 2010-01-06 | The date when the instance of the Condition is recorded. |
| CONDITION_START_DATETIME | 2010-01-06 00:00:00 | The date and time when the instance of the Condition is recorded. Midnight is used when the time is unknown |
| CONDITION_END_DATE | NULL | If known, this is the date when the instance of the Condition is considered to have ended. |
| CONDITION_END_DATETIME | NULL | If known, this is the date and time when the instance of the Condition is considered to have ended. |
| CONDITION_TYPE_CONCEPT_ID | 32020 | This column is intended to provide information about the provenance of the condition, i.e. does it come from an insurance claim, hospital billing record, EHR record, etc. For this example the concept ID 32020 is used as the encounters are similar to electronic health records. Concept IDs in this field should be in the 'Condition Type' vocabulary. |

| Column | Value | Explanation |
|---|---|---|
| CONDITION_STATUS_CONCEPT_ID | 0 | If known, the CONDITION_STATUS_CONCEPT_ID represents when and/or how the condition was diagnosed. For example, a condition could be an admitting diagnosis, in which case the concept ID 4203942 would be used. |
| STOP_REASON | NULL | If known, the reason that the Condition was no longer present, as indicated in the source data. |
| PROVIDER_ID | NULL | If the condition record has a diagnosing provider listed, the id for that provider goes in this field. This should be the PROVIDER_ID from the PROVIDER table that represents the provider on the encounter. |
| VISIT_OCCURRENCE_ID | 5091 | If known, this is the visit (represented as VISIT_OCCURRENCE_ID taken from the VISIT_OCCURRENCE table) during which the condition was diagnosed. |
| VISIT_DETAIL_ID | NULL | If known, this is the visit detail encounter (represented as VISIT_DETAIL_ID from the VISIT_DETAIL table) during which the condition was diagnosed. |
| CONDITION_SOURCE_VALUE | 266569009 | This is the value from the source that represents the condition. In Lauren's case of dysmenorrhea the SNOMED code for that condition is stored here and the standard concept ID mapped from that code is stored in CONDITION_CONCEPT_ID. |

| Column | Value | Explanation |
|---|---|---|
| CONDITION_SOURCE_CONCEPT_ID | 194696 | If the condition value from the source is coded using a vocabulary that is recognized by OHDSI, the concept ID that represents that value would go here. In the example of dysmennorhea the source value is a SNOMED code so the concept ID that represents that code is 194696. In this case it is the same as the CONDITION_CONCEPT_ID since the SNOMED vocabulary is the standard condition vocabulary |
| CONDITION_STATUS_SOURCE_VALUE | 0 | If the condition status value from the source is coded using a vocabulary that is recognized by OHDSI, the concept ID that represents that source value would go here. |

### 5.3.6 DRUG_EXPOSURE

The DRUG_EXPOSURE captures records about the utilization of a Drug when ingested or otherwise introduced into the body. Drugs include prescription and over-the-counter medicines, vaccines, and large-molecule biologic therapies. Radiological devices ingested or applied locally do not count as Drugs.

Drug Exposure is inferred from clinical events associated with orders, prescriptions written, pharmacy dispensings, procedural administrations, and other patient-reported information.

**What are Lauren's drug exposures?**

We know that Lauren was given 60 acetaminophen 325mg oral tablets for 30 days (NDC code 69842087651) at her visit on 2010-01-06 to help with her dysmenorrhea pain. Here's how that might look in the DRUG_EXPOSURE table:

Table 5.8: The DRUG_EXPOSURE table.

| Column | Value | Explanation |
|---|---|---|
| DRUG_EXPOSURE_ID | 1001 | This is typically an autogenerated field that creates a unique id number for each drug exposure on the person's record in the converted CDM database. |

| Column | Value | Explanation |
|---|---|---|
| PERSON_ID | 1 | This comes from the PERSON table and links PERSON and DRUG_EXPOSURE. |
| DRUG_CONCEPT_ID | 1127433 | The NDC code for acetaminophen maps to the RxNorm code 313782 which is represented by the concept ID 1127433. |
| DRUG_EXPOSURE_START_DATE | 2010-01-06 | The start date of the drug exposure |
| DRUG_EXPOSURE_START_DATETIME | 2010-01-06 00:00:00 | The start date and time of the drug exposure. Midnight is used when the time is not known. |
| DRUG_EXPOSURE_END_DATE | 2010-02-05 | The end date of the drug exposure. Depending on different sources, it could be a known or an inferred date and denotes the last day at which the patient was still exposed to the drug. In this case the end is inferred since we know Lauren had a 30 days supply. |
| DRUG_EXPOSURE_END_DATETIME | 2010-02-05 00:00:00 | The end date and time of the drug exposure. Similar rules apply as to DRUG_EXPOSURE_END_DATE. Midnight is used when time is unknown |
| VERBATIM_END_DATE | NULL | If the source provides an end date rather than just days supply that date goes here. |
| DRUG_TYPE_CONCEPT_ID | 38000177 | This column is intended to provide information about the provenance of the drug, i.e. does it come from an insurance claim, prescription record, etc. For this example the concept ID 38000177 is used as the drug record is from a written prescription. Concept IDs in this field should be in the 'Drug Type' vocabulary. |
| STOP_REASON | NULL | The reason the Drug was stopped. Reasons include regimen completed, changed, removed, etc. |

| Column | Value | Explanation |
|---|---|---|
| REFILLS | NULL | The number of refills after the initial prescription. The initial prescription is not counted, values start with null. In the case of Lauren's acetaminophen she did not have any refills so the value is NULL. |
| QUANTITY | 60 | The quantity of drug as recorded in the original prescription or dispensing record. |
| DAYS_SUPPLY | 30 | The number of days of supply of the medication as prescribed. |
| SIG | NULL | The directions ('signetur') on the Drug prescription as recorded in the original prescription (and printed on the container) or dispensing record. |
| ROUTE_CONCEPT_ID | 4132161 | This concept is meant to represent the route of the drug the patient was was exposed to. Lauren took her acetaminophen orally so the concept ID 4132161 is used. |
| LOT_NUMBER | NULL | An identifier assigned to a particular quantity or lot of Drug product from the manufacturer. |
| PROVIDER_ID | NULL | If the drug record has a prescribing provider listed, the id for that provider goes in this field. This should be the PROVIDER_ID from the PROVIDER table that represents the provider on the encounter. |
| VISIT_OCCURRENCE_ID | 5109 | If known, this is the visit (represented as VISIT_OCCURRENCE_ID taken from the VISIT_OCCURRENCE table) during which the drug was prescribed. |
| VISIT_DETAIL_ID | NULL | If known, this is the visit detail (represented as VISIT_DETAIL_ID taken from the VISIT_DETAIL table) during which the drug was prescribed. |

| Column | Value | Explanation |
|---|---|---|
| DRUG_SOURCE_VALUE | 69842087651 | This is the source code for the Drug as it appears in the source data. In Lauren's case she was prescribed acetaminophen and the NDC code is stored here. |
| DRUG_SOURCE_ CONCEPT_ID | 750264 | This is the concept ID that represents the drug source value. In this example the concept ID is 750264. |
| ROUTE_SOURCE_VALUE | NULL | The information about the route of administration as detailed in the source. |
| DOSE_UNIT_ SOURCE_VALUE | NULL | The information about the dose unit as detailed in the source. |

### 5.3.7 PROCEDURE_OCCURRENCE

The PROCEDURE_OCCURRENCE table contains records of activities or processes ordered by, or carried out by, a healthcare provider on the patient to have a diagnostic or therapeutic purpose. Procedures are present in various data sources in different forms with varying levels of standardization. For example:

- Medical Claims include procedure codes that are submitted as part of a claim for health services rendered, including procedures performed.
- Electronic Health Records that capture procedures as orders.

**What procedures did Lauren have?** From her description we know she had a ultrasound of her left ovary on 2013-01-14 that showed a 4x5cm cyst. Here's how that would look in the PROCEDURE_OCCURRENCE table:

Table 5.9: The PROCEDURE_OCCURRENCE table.

| Column | Value | Explanation |
|---|---|---|
| PROCEDURE_OCCURRENCE_ID | 1277 | This is typically an autogenerated field that creates a unique id number for each procedure occurrence on the person's record in the converted CDM database. |
| PERSON_ID | 1 | This comes from the PERSON table and links PERSON and PROCEDURE_OCCURRENCE |

| Column | Value | Explanation |
|---|---|---|
| PROCEDURE_CONCEPT_ID | 4127451 | The SNOMED procedure code for a pelvic ultrasound is 304435002 which is represented by the concept ID 4127451. |
| PROCEDURE_DATE | 2013-01-14 | The date on which the procedure was performed. |
| PROCEDURE_DATETIME | 2013-01-14 00:00:00 | The date and time on which the procedure was performed. Midnight is used when time is unknown. |
| PROCEDURE_TYPE_CONCEPT_ID | 38000275 | This column is intended to provide information about the provenance of the procedure, i.e. does it come from an insurance claim, EHR order, etc. For this example the concept ID 38000275 is used as the procedure record is from an EHR record. Concept IDs in this field should be in the 'Procedure Type' vocabulary. |
| MODIFIER_CONCEPT_ID | | This is meant for a concept ID representing the modifier on the procedure. For example, if the record indicated that a CPT4 procedure was performed bilaterally then the concept ID 42739579 would be used. |
| QUANTITY | 0 | The quantity of procedures ordered or administered. |
| PROVIDER_ID | NULL | If the procedure record has a provider listed, the id for that provider goes in this field. This should be the PROVIDER_ID from the PROVIDER table that represents the provider on the encounter. |
| VISIT_OCCURRENCE_ID | 740 | If known, this is the visit (represented as VISIT_OCCURRENCE_ID taken from the VISIT_OCCURRENCE table) during which the procedure was performed. |

| Column | Value | Explanation |
|---|---|---|
| VISIT_DETAIL_ID | NULL | If known, this is the visit detail (represented as VISIT_DETAIL_ID taken from the VISIT_DETAIL table) during which the procedure was performed. |
| PROCEDURE_SOURCE_VALUE | 3044350 | The source code for the Procedure as it appears in the source data. This code is mapped to a standard procedure Concept in the Standardized Vocabularies and the original code is, stored here for reference. |
| PROCEDURE_SOURCE_CONCEPT_ID | 4127451 | This is the concept ID that represents the procedure source value. |
| MODIFIER_SOURCE_VALUE | NULL | The source code for the modifier as it appears in the source data. |

# Chapter 6

# Standardized Vocabularies

The OMOP Standardized Vocabulary: Christian's (almost) finished paper + http://www.ohdsi.org/web/wiki/doku.php?id=documentation:vocabulary

# Chapter 7

# Extract Transform Load

Leads: Mui van Zandt & Clair Blacketer

Business Rules and Conventions: From the CDM Wiki + Themis

Conversion to OMOP CDM (ETL - Extract, Transform, Load): http://www.ohdsi.org/web/wiki/doku.php?id=documentation:etl_best_practices

- WhiteRabbit and Rabbit-in-a-Hat: http://www.ohdsi.org/web/wiki/doku.php?id=documentation:software:whiterabbit
- Usagi: http://www.ohdsi.org/web/wiki/doku.php?id=documentation:software:usagi
- Achilles: http://www.ohdsi.org/web/wiki/doku.php?id=documentation:software:achilles
- Athena: http://www.ohdsi.org/web/wiki/doku.php?id=documentation:vocabulary_etl

Mapping and QA of codes to Standard Concepts

- Mapping codes locally versus through the OHDSI Standard Vocabularies
- Usagi
- Systematic mapping of Drug codes
- Systematic mapping of Condition codes
- Systematic mapping of Procedure codes
- Systematic mapping of other codes

# Part III

# Data Analytics

# Chapter 8

# Data Analytics Use Cases

- Introduction

The OHDSI collaboration focuses on generating reliable evidence from real-world healthcare data, typically in the form of claims databases or electronic health record databases. The use cases that OHDSI focuses on fall into three major buckets and we describe these below. Note, for all the use cases, the evidence we generate inherits the limitations of the data; we discuss these limitations at length in Chapters X, Y, and Z.

- Theory

1. Population characterization

We can use the data to provide answers to questions about the charateristics of the patients in each database, the practice of healthcare, and study how these things change over time.

The data can provide answers to questions like: - for patients newly diagnosed with atrial fibrillation, how many receive a prescription for warfarin? - what is the average age of patients who undergo hip arthoplasty?

2. Population-level estimation

To a limited extent, the data can support causal inferences about the effects of healthcare interventions.

The data can provide answers to questions like: - for patients newly diagnosed with atrial fibrillation, in the first year after therapy initiation, does warfarin cause more major bleeds than dabigatran? - Does the causal effect of metformin on diarrhea vary by age?

3. Patient-Level prediction

Based on the collected patient health histories in the database, we can make patient-level predictions about future health events. - for a specific patient newly diagnosed with atrial fibrillation, in the first year after therapy initiation with warfarin, what is the probability the patient suffers an ischemic stroke?

These tasks overlap to a certain extent. For example, an important use-case for prediction is to predict an outcome for a specific patient had drug A been prescribed and also predict the same outcome had drug B been prescribed. Let's assume that in reality only one of these drugs is prescribed (say drug A) so we get to see whether the outcome following treatment with A actually occurs. Since drug B was not prescribed, the outcome following treatment B, while predictable, is "counterfactual" since it is not ever observed. Each of these prediction tasks falls under patient-level prediction. However, the difference between (or ratio of) the two outcomes is a unit-level *causal* effect.

There are many important healthcare questions for which OHDSI databases cannot provide answers. These include:

- Causal effects of interventions compared to placebo. Sometimes it is possible to consider the causal effect of a treatment as compared with non-treatment but not placebo tretamernt.
- Anything related to over-the-counter medications
- Many outcomes are sparsely recorded if at all. These include mortality, behavioral outcomes, lifestyle, and socioeconmic status.
- Since patients tend to encounter the healthcare system when they are unwell, measurement of the benefits of treatments can prove elusive.

Missingness in OHDSI databases presents subtle challenges. A health event (e.g., prescription, laboratory value, etc.) that should be recorded in a database, but isn't, is "missing." The statistics literature distinguishes between types of missingness such as "missing completely at random," "missing at random," and "missing not at random" and methods of increasing complexity attempt to address these types. Perkins et al. (2017) provide a use introduction to this topic.

What use cases are often observed? Drug safety, Drug utilization, etc.

- Practice

# Chapter 9

# OHDSI Analytics Tools

ATLAS: http://www.ohdsi.org/web/wiki/doku.php?id=documentation:software:atlas

ARACHNE: Network Research

Methods Library: https://ohdsi.github.io/MethodsLibrary/

Best practices enforced in all OHDSI methods.

Ethical consideration: e.g. should always communicate uncertainty. Prespecification of research questions, etc.

Analytic use cases

What is the difference between characterization, population-level estimation, patient-level prediction?

Case study: Perhaps on how to install the tools?

# Chapter 10

# SQL and R

*Chapter lead: Martijn Schuemie*

The Common Data Model is a relational database model, which means that the data will be stored in a relational database using a software platform like PostgreSQL, Oracle, or Microsoft SQL Server. The various OHDSI tools such as ATLAS and the Methods Library work by querying the database behind the scene, but we can also query the database directly ourselves if we have appropriate access rights. The main reason to do this is to perform analyses that currently are not supported by any existing tool. However, directly querying the database also comes with risks, as the OHDSI tools are often designed to help guide the user to approriate analysis of the data, and direct queries do not provide such guidance.

The standard language for querying relational databases is SQL (Structured Query Language), which can be used both to query the database as well as to make changes to the data. Although the basic commands in SQL are indeed standard, meaning the same across software platforms, each platform has its own dialect, with subtle changes. For example, to retrieve the top 10 rows of the person table on SQL Server one would type:

```
SELECT TOP 10 * FROM person;
```

Whereas the same query on PostgreSQL would be:

```
SELECT * FROM person LIMIT 10;
```

In OHDSI, we would like to be agnostic to the specific dialect a platform uses; We would like to 'speak' the same SQL language across all OHDSI databases. For this reason OHDSI developed the SqlRender package, an R package that can translate from one standard dialect to any of the supprted dialects that will be discussed later in this chapter. This standard dialect - **OHDSI SQL** - is

mainly a subset of the SQL Server SQL dialect. The example SQL statements provided throughout this chapter will all use OHDSI SQL.

Each database platform also comes with its own software tools for querying the database using SQL. In OHDSI we developed the DatabaseConnector package, a single R package that can connect to a wide range of database platforms. DatabaseConnector will also be discussed later in this chapter.

So although one can query a database that conforms to the CDM without using any OHDSI tools, the recommended path is to use the DatabaseConnector and SqlRender packages. This allows queries that are developed at one site to be used at any other site without modification. R itself also immediately provides features to further analyse the data extracted from the database, such as performing statistical analyses and generating (interactive) plots.

The SqlRender and DatabaseConnector packages are both available on CRAN (the Comprehensive R Archive Network), and can therefore be installed using:

```
install.packages(c("SqlRender", "DatabaseConnector"))
```

Both packages support a wide array of technical platforms including traditional database systems (PostgreSQL, Microsoft SQL Server, SQLite, and Oracle), parallel data warehouses (Microsoft APS, IBM Netezza, and Amazon RedShift), as well as Big Data platforms (Hadoop through Impala, and Google BigQuery). Both packages come with package manuals and vignettes that explore the full functionality. Here we describre some of the main features.

## 10.1 SqlRender

### 10.1.1 SQL parameterization

One of the functions of the package is to support parameterization of SQL. Often, small variations of SQL need to be generated based on some parameters. SqlRender offers a simple markup syntax inside the SQL code to allow parameterization. Rendering the SQL based on parameter values is done using the `render()` function.

#### Substituting parameter values

The `@` character can be used to indicate parameter names that need to be exchange for actual parameter values when rendering. In the following example, a variable called `a` is mentioned in the SQL. In the call to the render function the value of this parameter is defined:

```
sql <- "SELECT * FROM concept WHERE concept_id = @a;"
render(sql, a = 123)
```

```
## [1] "SELECT * FROM concept WHERE concept_id = 123;"
```

Note that, unlike the parameterization offered by most database management systems, it is just as easy to parameterize table or field names as values:

```
sql <- "SELECT * FROM @x WHERE person_id = @a;"
render(sql, x = "observation", a = 123)
```

```
## [1] "SELECT * FROM observation WHERE person_id = 123;"
```

The parameter values can be numbers, strings, booleans, as well as vectors, which are converted to comma-delimited lists:

```
sql <- "SELECT * FROM concept WHERE concept_id IN (@a);"
render(sql, a = c(123, 234, 345))
```

```
## [1] "SELECT * FROM concept WHERE concept_id IN (123,234,345);"
```

### If-then-else

Sometimes blocks of codes need to be turned on or off based on the values of one or more parameters. This is done using the `{Condition} ? {if true} : {if false}` syntax. If the *condition* evaluates to true or 1, the *if true* block is used, else the *if false* block is shown (if present).

```
sql <- "SELECT * FROM cohort {@x} ? {WHERE subject_id = 1}"
render(sql, x = FALSE)
```

```
## [1] "SELECT * FROM cohort "
```

```
render(sql, x = TRUE)
```

```
## [1] "SELECT * FROM cohort WHERE subject_id = 1"
```

Simple comparisons are also supported:

```
sql <- "SELECT * FROM cohort {@x == 1} ? {WHERE subject_id = 1};"
render(sql,x = 1)
```

```
## [1] "SELECT * FROM cohort WHERE subject_id = 1;"
```

```
render(sql,x = 2)
```

```
## [1] "SELECT * FROM cohort ;"
```

As well as the `IN` operator:

```
sql <- "SELECT * FROM cohort {@x IN (1,2,3)} ? {WHERE subject_id = 1};"
render(sql,x = 2)
```

```
## [1] "SELECT * FROM cohort WHERE subject_id = 1;"
```

### 10.1.2 Translation to other SQL dialects

Another function of the SqlRender package is to translate from OHDSI SQL to other SQL dialects. For example:

```
sql <- "SELECT TOP 10 * FROM person;"
translate(sql, targetDialect = "postgresql")
```

```
## [1] "SELECT  * FROM person LIMIT 10;"
```

The `targetDialect` parameter can have the following values: "oracle", "postgresql", "pdw", "redshift", "impala", "netezza", "bigquery", "sqlite", and "sql server".

There are limits to what SQL functions and constructs can be translated properly, both because only a limited set of translation rules have been implemented in the package, but also some SQL features do not have an equivalent in all dialects.

**Functions and structures supported by translate**

These SQL Server functions have been tested and were found to be translated correctly to the various dialects:

Table 10.1: Functions supported by translate.

| Function | Function | Function |
|---|---|---|
| ABS | EXP | RAND |
| ACOS | FLOOR | RANK |
| ASIN | GETDATE | RIGHT |
| ATAN | HASHBYTES* | ROUND |
| AVG | ISNULL | ROW_NUMBER |
| CAST | ISNUMERIC | RTRIM |
| CEILING | LEFT | SIN |
| CHARINDEX | LEN | SQRT |
| CONCAT | LOG | SQUARE |
| COS | LOG10 | STDEV |
| COUNT | LOWER | SUM |
| COUNT_BIG | LTRIM | TAN |
| DATEADD | MAX | UPPER |
| DATEDIFF | MIN | VAR |
| DATEFROMPARTS | MONTH | YEAR |
| DATETIMEFROMPARTS | NEWID | |
| DAY | PI | |
| EOMONTH | POWER | |

- Requires special priviliges on Oracle. Has no equivalent on SQLite.

Similarly, many SQL syntax structures are supported. Here is a non-exhaustive lists of things that we know will translate well:

```
-- Simple selects:
SELECT * FROM table;

-- Selects with joins:
SELECT * FROM table_1 INNER JOIN table_2 ON a = b;

-- Nested queries:
SELECT * FROM (SELECT * FROM table_1) tmp WHERE a = b;

-- Limiting to top rows:
SELECT TOP 10 * FROM table;

-- Selecting into a new table:
SELECT * INTO new_table FROM table;

-- Creating tables:
CREATE TABLE table (field INT);

-- Inserting verbatim values:
INSERT INTO other_table (field_1) VALUES (1);

-- Inserting from SELECT:
INSERT INTO other_table (field_1) SELECT value FROM table;

-- Simple drop commands:
DROP TABLE table;

-- Drop table if it exists:
IF OBJECT_ID('ACHILLES_analysis', 'U') IS NOT NULL
  DROP TABLE ACHILLES_analysis;

-- Drop temp table if it exists:
IF OBJECT_ID('tempdb..#cohorts', 'U') IS NOT NULL
  DROP TABLE #cohorts;

-- Common table expressions:
WITH cte AS (SELECT * FROM table) SELECT * FROM cte;

-- OVER clauses:
SELECT ROW_NUMBER() OVER (PARTITION BY a ORDER BY b)
  AS "Row Number" FROM table;

-- CASE WHEN clauses:
```

```
SELECT CASE WHEN a=1 THEN a ELSE 0 END AS value FROM table;

-- UNIONs:
SELECT * FROM a UNION SELECT * FROM b;

-- INTERSECTIONs:
SELECT * FROM a INTERSECT SELECT * FROM b;

-- EXCEPT:
SELECT * FROM a EXCEPT SELECT * FROM b;
```

### String concatenation

String concatenation is one area where SQL Server is less specific than other dialects. In SQL Server, one would write `SELECT first_name + ' ' + last_name AS full_name FROM table`, but this should be `SELECT first_name || ' ' || last_name AS full_name FROM table` in PostgreSQL and Oracle. SqlRender tries to guess when values that are being concatenated are strings. In the example above, because we have an explicit string (the space surrounded by single quotation marks), the translation will be correct. However, if the query had been `SELECT first_name + last_name AS full_name FROM table`, SqlRender would have had no clue the two fields were strings, and would incorrectly leave the plus sign. Another clue that a value is a string is an explicit cast to VARCHAR, so `SELECT last_name + CAST(age AS VARCHAR(3)) AS full_name FROM table` would also be translated correctly. To avoid ambiguity altogether, it is probable best to use the `CONCAT()` function to concatenate two or more strings.

### Table aliases and the AS keyword

Many SQL dialects allow the use of the `AS` keyword when defining a table alias, but will also work fine without the keyword. For example, both these SQL statements are fine for SQL Server, PostgreSQL, RedShift, etc.:

```
-- Using AS keyword
SELECT *
FROM my_table AS table_1
INNER JOIN (
  SELECT * FROM other_table
) AS table_2
ON table_1.person_id = table_2.person_id;

-- Not using AS keyword
SELECT *
FROM my_table table_1
INNER JOIN (
  SELECT * FROM other_table
```

```
) table_2
ON table_1.person_id = table_2.person_id;
```

However, Oracle will throw an error when the `AS` keyword is used. In the above example, the first query will fail. It is therefore recommended to not use the `AS` keyword when aliasing tables. (Note: we can't make SqlRender handle this, because it can't easily distinguish between table aliases where Oracle doesn't allow `AS` to be used, and field aliases, where Oracle requires `AS` to be used.)

### Temp tables

Temp tables can be very useful to store intermediate results, and when used correctly can be used to dramatically improve performance of queries. On most database platforms temp tables have very nice properties: they're only visible to the current user, are automatically dropped when the session ends, and can be created even when the user has no write access. Unfortunately, in Oracle temp tables are basically permanent tables, with the only difference that the data inside the table is only visible to the current user. This is why, in Oracle, SqlRender will try to emulate temp tables by

1. Adding a random string to the table name so tables from different users will not conflict.
2. Allowing the user to specify the schema where the temp tables will be created.

For example:

```
sql <- "SELECT * FROM #children;"
translate(sql, targetDialect = "oracle", oracleTempSchema = "temp_schema")
```

```
## [1] "SELECT * FROM temp_schema.nxpditeichildren ;"
```

Note that the user will need to have write privileges on `temp_schema`.

Also note that because Oracle has a limit on table names of 30 characters, **temp table names are only allowed to be at most 22 characters long** because else the name will become too long after appending the session ID.

Futhermore, remember that temp tables are not automatically dropped on Oracle, so you will need to explicitly `TRUNCATE` and `DROP` all temp tables once you're done with them to prevent orphan tables accumulating in the Oracle temp schema.

### Implicit casts

One of the few points where SQL Server is less explicit than other dialects is that it allows implicit casts. For example, this code will work on SQL Server:

```
CREATE TABLE #temp (txt VARCHAR);

INSERT INTO #temp
```

```
SELECT '1';

SELECT * FROM #temp WHERE txt = 1;
```

Even though `txt` is a VARCHAR field and we are comparing it with an integer, SQL Server will automatically cast one of the two to the correct type to allow the comparison. In contrast, other dialects such as PosgreSQL will throw an error when trying to compare a VARCHAR with an INT.

You should therefore always make casts explicit. In the above example, the last statement should be replaced with either

```
SELECT * FROM #temp WHERE txt = CAST(1 AS VARCHAR);
```

or

```
SELECT * FROM #temp WHERE CAST(txt AS INT) = 1;
```

### Case sensitivity in string comparisons

Some DBMS platforms such as SQL Server always perform string comparisons in a case-insensitive way, while others such as PostgreSQL are always case sensitive. It is therefore recommended to always assume case-sensitive comparisons, and to explicitly make comparisons case-insensitive when unsure about the case. For example, instead of

```
SELECT * FROM concept WHERE concep_class_id = 'Clinical Finding'
```

it is preferred to use

```
SELECT * FROM concept WHERE LOWER(concep_class_id) = 'clinical finding'
```

### Schemas and databases

In SQL Server, tables are located in a schema, and schemas reside in a database. For example, `cdm_data.dbo.person` refers to the `person` table in the `dbo` schema in the `cdm_data` database. In other dialects, even though a similar hierarchy often exists they are used very differently. In SQL Server, there is typically one schema per database (often called `dbo`), and users can easily use data in different databases. On other platforms, for example in PostgreSQL, it is not possible to use data across databases in a single session, but there are often many schemas in a database. In PostgreSQL one could say that the equivalent of SQL Server's database is the schema.

We therefore recommend concatenating SQL Server's database and schema into a single parameter, which we typically call `@databaseSchema`. For example, we could have the parameterized SQL

```
SELECT * FROM @databaseSchema.person
```

where on SQL Server we can include both database and schema names in

the value: `databaseSchema = "cdm_data.dbo"`. On other platforms, we can use the same code, but now only specify the schema as the parameter value: `databaseSchema = "cdm_data"`.

The one situation where this will fail is the `USE` command, since `USE cdm_data.dbo;` will throw an error. It is therefore preferred not to use the `USE` command, but always specify the database / schema where a table is located.

**Debugging parameterized SQL**

Debugging parameterized SQL can be a bit complicated; Only the rendered SQL can be tested against a database server, but changes to the code should be made in the parameterized (pre-rendered) SQL.

A Shiny app is included in the SqlRender package for interactively editing source SQL and generating rendered and translated SQL. The app can be started using:

```
launchSqlRenderDeveloper()
```

Which will open the default browser with the app.

## 10.2 DatabaseConnector

DatabaseConnector is an R package for connecting to various database platforms using Java's JDBC drivers. The package already contins most drivers, but because of licensing reasons the drivers for BigQuery, Netezza and Impala are not included but must be obtained by the user. Type `?jdbcDrivers` for instructions on how to download these drivers. Once downloaded, you can use the `pathToDriver` argument of the `connect`, `dbConnect`, and `createConnectionDetails` functions.

### 10.2.1 Creating a connection

To connect to a database a number of details need to be specified, such as the database platform, the location of the server, the user name, and password. We can call the `connect` function and specify these details directly:

```
conn <- connect(dbms = "postgresql",
                server = "localhost/postgres",
                user = "joe",
                password = "secret",
                schema = "cdm")
```

```
## Connecting using PostgreSQL driver
```

See `?connect` for information on which details are required for each platform. Don't forget to close any connection afterwards:

```
disconnect(conn)
```

Note that, instead of providing the server name, it is also possible to provide the JDBC connection string if this is more convenient:

```
conn <- connect(dbms = "postgresql",
                connectionString = "jdbc:postgresql://localhost:5432/postgres",
                user = "joe",
                password = "secret",
                schema = "cdm")
```

```
## Connecting using PostgreSQL driver
```

Sometimes we may want to first specify the connection details, and defer connecting until later. This may be convenient for example when the connection is established inside a function, and the details need to be passed as an argument. We can use the `createConnectionDetails` function for this purpose:

```
details <- createConnectionDetails(dbms = "postgresql",
                                   server = "localhost/postgres",
                                   user = "joe",
                                   password = "secret",
                                   schema = "cdm")
conn <- connect(details)
```

```
## Connecting using PostgreSQL driver
```

### 10.2.2 Querying

The main functions for querying database are the `querySql` and `executeSql` functions. The difference between these functions is that `querySql` expects data to be returned by the database, and can handle only one SQL statement at a time. In contrast, `executeSql` does not expect data to be returned, and accepts multiple SQL statments in a single SQL string.

Some examples:

```
querySql(conn, "SELECT TOP 3 * FROM person")
```

```
##   PERSON_ID GENDER_CONCEPT_ID YEAR_OF_BIRTH
## 1         1              8507          1975
## 2         2              8507          1976
## 3         3              8507          1977
```

```
executeSql(conn, "TRUNCATE TABLE foo; DROP TABLE foo; CREATE TABLE foo (bar INT);")
```

Both function provide extensive error reporting: When an error is thrown by the server, the error message and the offending piece of SQL are written to a text file to allow better debugging. The `executeSql` function also by default

shows a progress bar, indicating the percentage of SQL statements that has been executed. If those attributes are not desired, the package also offers the `lowLevelQuerySql` and `lowLevelExecuteSql` functions.

### 10.2.3 Querying using ffdf objects

Sometimes the data to be fetched from the database is too large to fit into memory. In this case one can use the `ff` package to store R data objects on file, and use them as if they are available in memory. `DatabaseConnector` can download data directly into ffdf objects:

```
x <- querySql.ffdf(conn, "SELECT * FROM person")
```

Where x is now an ffdf object.

### 10.2.4 Querying different platforms using the same SQL

The following convenience functions are available that first call the `render` and `translate` functions in the SqlRender package: `renderTranslateExecuteSql`, `renderTranslateQuerySql`, `renderTranslateQuerySql.ffdf`. For example:

```
x <- renderTranslatequerySql(conn,
                             sql = "SELECT TOP 10 * FROM @schema.person",
                             schema = "cdm_synpuf")
```

Note that the SQL Server-specific 'TOP 10' syntax will be translated to for example 'LIMIT 10' on PostgreSQL, and that the SQL parameter `@schema` will be instantiated with the provided value 'cdm_synpuf'.

### 10.2.5 Inserting tables

Although it is also possible to insert data in the database by sending SQL statements using the `executeSql` function, it is often convenient and faster to use the `insertTable` function:

```
data(mtcars)
insertTable(conn, "mtcars", mtcars, createTable = TRUE)
```

In this example, we're uploading the mtcars data frame to a table called 'mtcars' on the server, that will be automatically created.

## 10.3 Querying the CDM

Querying the CDM

Probably borrow heavily from https://github.com/OHDSI/QueryLibrary

## 10.4 Querying the vocabulary

## 10.5 Using the vocabulary when querying

# Chapter 11

# Building the building blocks: cohorts

Introduction: a cohort is a group of people that meet a set of criteria for a particular span of time etc. Cohorts are used throughout OHDSIs analytical tools as the primary building blocks.

Using ATLAS: use material from Patrick's tutorial on cohort building

Using SQL: For advanced users, explain how cohorts can be created programmatically.

Probabilistic cohorts: Aphrodite?

Case study: some example cohort definitions

# Chapter 12

# Characterization

ATLAS' incidence rate calculator + cohort characterization tool

FeatureExtraction package: https://github.com/OHDSI/FeatureExtraction

Case study: characteristics + IRs of some cohorts

Example .. http://www.pnas.org/content/113/27/7329

# Chapter 13

# Population-level estimation

*Chapter leads: Martijn Schuemie, David Madigan & Marc Suchard*

Observational healthcare data, such as administrative claims and electronic health records, offer opportunities to generate real-world evidence about the effect of treatments that can meaningfully improve the lives of patients. In this chapter we focus on population-level effect estimation, that is, the estimation of average causal effects of medical interventions on specific health outcomes of interest. In what follows, we consider two different estimation tasks:

- **Direct effect estimation**: estimating the effect of an exposure on the risk of an outcome, as compared to no exposure.
- **Comparative effect estimation**: estimation the effect of one exposure (the target exposure) on the risk of an outcome, as compared to another exposure (the comparator exposure).

In both cases, the patient-level causal effect contrasts a factual outcome, i.e., what happened to the exposed patient, with a counterfactual outcome, i.e., what would have happened had the exposure not occurred (direct) or had a different exposure occurred (comparative). Since any one patient reveals only the factual outcome (the fundamental problem of causal inference), the various effect estimation methods employ analytic devices to shed light on the counterfactual outcomes.

Use-cases for population-level effect estimation include treatment selection, safety surveillance, and comparative effectiveness. Methods can test specific hypotheses one-at-a-time (e.g. 'signal evaluation') or explore multiple-hypotheses-at-once (e.g. 'signal detection'). In all cases, the objective remains the same: to produce a high-quality estimate of the causal effect.

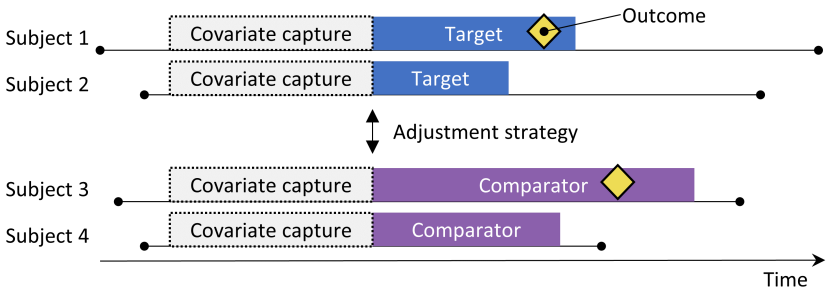



Figure 13.1: The new-user cohort design. Subjects observed to initiate the target treatment are compared to those initiating the comparator treatment. To adjust for differences between the two treatment groups several adjustment strategies can be used, such as stratification, matching, or weighting by the propensity score, or by adding baseline characateristcs to the outcome model. The chararacteristics included in the propensity model or outcome model are captured prior to treatment initiation.

## 13.1 Study designs

Several different study designs can be used to estimate treatment effects. The main difference between these is how they construct the (unobserved) counterfactual. Below is a brief discussion of the most commonly used designs, all of which are implemented as R packages in the OHDSI Methods Library.

### 13.1.1 Cohort method

The new-user cohort method attempts to emulate a randomized clinical trial (Hernan and Robins, 2016). Subjects that are observed to initiate one treatment (the target) are compared to subjects initiating another treatment (the comparator) and are followed for a specific amount of time following treatment initiation, for example the time they stay on the treatment. We can specify the questions we wish to answer in a cohort study by making the five choices highlighted in Table 13.1.

Table 13.1: Main design choices in a comparative cohort design.

| Choice | Description |
|---|---|
| Target cohort | A cohort representing the target treatment |
| Comparator cohort | A cohort representing the comparator treatment |
| Outcome cohort | A cohort representing the outcome of interest |

| Choice | Description |
|---|---|
| Time-at-risk | At what time (often relative to the target and comparator cohort start and end dates) do we consider the risk of the outcome? |
| Model | The model used to estimate the effect while adjusting for differences between the target and comparator |

The choice of model specifies, amongst others, the type of model. For example, we could use a logistic regression, which evaluates whether or not the outcome has occurred, and produces an odds ratio. A logistic regression assumes the time-at-risk is of the same length for both target and comparator, or irrelevant. Alternatively, we could choose a Poisson regression which estimates the incidence rate ratio, assuming a constant incidence rate. Often a Cox regression is used which considers time to first outcome to estimate the hazard ratio, assuming proportional hazards.

One crucial difference with a randomized trial is that there is no randomization, and therefore there might be systematic differences between the target and comparator populations. Without adjusting for these differences, estimates are likely to be confounded. A popular mechanism for adjusting for confounding is the use of Propensity Scores (PS). The PS is the probability of a subject receiving one treatment instead of the other, conditional on baseline characteristics. (Rosenbaum and Rubin, 1983) First, a model – typically a logistic regression – is fitted using the observed treatment assignments (target or comparator), then the model is used to produce the PS for each subject. In the past, PS were computed based on manually selected characteristics, and although the CohortMethod package can support such practices, we prefer the use of large-scale regularized regression using many generic characteristics. (Tian et al., 2018) These characteristics include demographics, as well as all diagnoses, drug exposures, measurement, and medical procedures observed prior to treatment initiation, and exclude the target and comparator treatment. A model typically involves 10,000 to 100,000 unique characteristics. The PS can be used in several ways, for example by stratifying the study population based on the PS, by matching target subjects to comparator subjects with similar PS, or by weighting subjects using Inverse Probability of Treatment Weighting (IPTW) derived from the PS. Another strategy for adjusting for differences between the two groups is to include additional variables in the outcome model. One major limitation of this approach is that whereas there often is a wealth of data to fit a propensity model, with thousands of people in both treatment groups, the outcomes we study tend to be somewhat rare, causing a paucity of data when trying to fit elaborate models with the outcome as dependent variable. One approach is to use both a PS and add the same variables that were used in the propensity model in the outcome model, thus adjusting for the same variables twice, but in different ways. The new-user cohort method inherently is a method for comparative effect estimation, comparing one treatment to another.

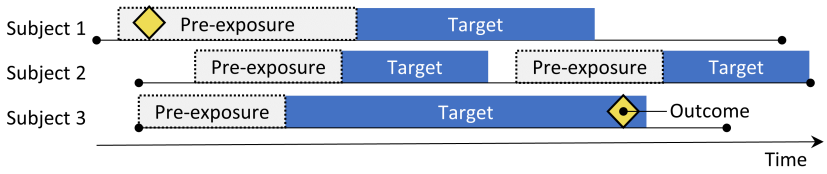



Figure 13.2: The self-controlled cohort design. The rate of outcomes during exposure to the target is compared to the rate of outcomes in the time pre-exposure.

It is difficult to use this method to compare a treatment against no treatment, since it is hard to define a group of unexposed people that is comparable with the exposed group. If one wants to use this design for direct effect estimation, the preferred way is to select a comparator treatment for the same indication as the exposure of interest, where the comparator treatment is believed to have no effect on the outcome. Unfortunately, such a comparator might not always be available.

### 13.1.2 Self-controlled cohort

The self-controlled cohort (SCC) design (Ryan et al., 2013) compares the rate of outcomes during exposure to the rate of outcomes in the time just prior to the exposure. The four choices shown in Table 13.2 define a self-controlled cohort question.

Table 13.2: Main design choices in a self-controlled cohort design.

| Choice | Description |
|---|---|
| Target cohort | A cohort representing the treatment |
| Outcome cohort | A cohort representing the outcome of interest |
| Time-at-risk | At what time (often relative to the target cohort start and end dates) do we consider the risk of the outcome? |
| Control time | The time period used as the control time |

Because the same subject that make up the exposed group are also used as the control group, no adjustment for between-person differences need to be made. However, the method is vulnerable to other differences, such as differences between different time periods.

### 13.1.3 Case-control

Case-control (Vandenbroucke and Pearce, 2012) studies consider the question "are persons with a specific disease outcome exposed more frequently to a specific agent than those without the disease?" Thus, the central idea is to compare "cases", i.e., subjects that experience the outcome of interest with "controls", i.e., subjects that did not experience the outcome of interest. The choices in Table 13.3 define a case-control question.

Table 13.3: Main design choices in a case-control design.

| Choice | Description |
|---|---|

| Choice | Description |
|---|---|
| Control selection | A strategy for selecting controls and their index date |
| Target cohort | A cohort representing the treatment |
| [Nesting cohort] | Optionally, a cohort defining the subpopulation from which cases and controls are drawn |
| Time-at-risk | At what time (often relative to the index date) do we consider exposure status? |

Often, one matches controls to cases based on characteristics such as age and sex to make them more comparable. Another widespread practice is to nest the analysis within a specific subgroup of people, for example people that have all been diagnosed with one of the indications of the exposure of interest.

### 13.1.4 Case-crossover

The case-crossover (Maclure, 1991) design evaluates whether the rate of exposure is different at the time of the outcome than at some predefined number of days prior to the outcome. It is trying to determine whether there is something special about the day the outcome occurred. Table 13.4 shows the choices that define a case-crosover question:

Table 13.4: Main design choices in a case-crossover design.

| Choice | Description |
|---|---|
| Outcome cohort | A cohort representing the cases (the outcome of interest) |
| Target cohort | A cohort representing the treatment |
| Time-at-risk | At what time (often relative to the index date) do we consider exposure status? |
| Control time | The time period used as the control time |

Since cases serve as their own control, it is a self-controlled design, and should therefore be robust to confounding due to between-person differences. One concern is that, because the outcome date is always later than the control date, the method will be positively biased if the overall frequency of exposure increases over time (or negatively biased if there is a decrease). To address this, the case-time-control design (Suissa, 1995) was developed, which adds matched controls to the case-crossover design to adjust for exposure trends.

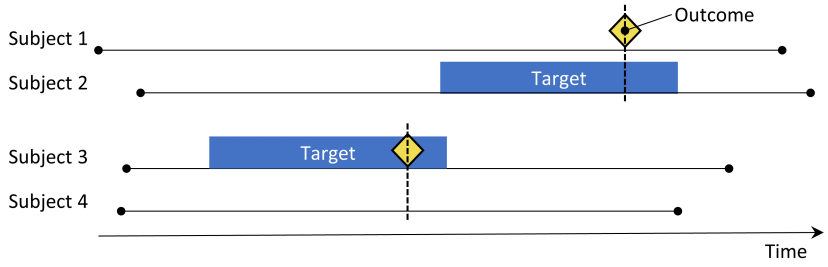



Figure 13.3: The case-control design. Subjects with the outcome ('cases') are compared to subjects without the outcome ('controls') in terms of their exposure status. Often, cases and controls are matched on various characteristics such as age and sex.

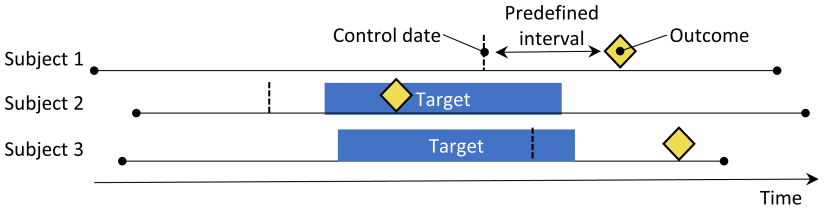



Figure 13.4: The case-crossover design. The time around the outcome is compared to a control date set at a predefined interval prior to the outcome date.

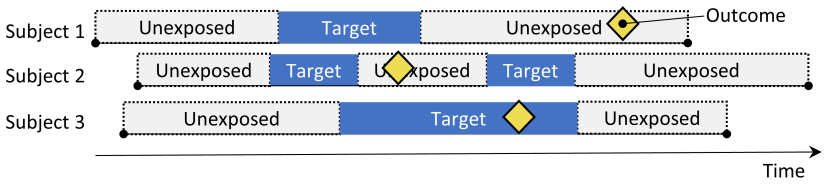



Figure 13.5: The Self-Controlled Case Series design. The rate of outcomes during exposure is compared to the rate of outcomes when not exposed.

### 13.1.5 Self-controlled case series

The Self-Controlled Case Series (SCCS) design (Farrington, 1995, whitaker_2006) compares the rate of outcomes during exposure to the rate of outcomes during all unexposed time, both before, between, and after exposures. It is a Poisson regression that is conditioned on the person. Thus, it seeks to answer the question: "Given that a patient has the outcome, is the outcome more likely during exposed time compared to non-exposed time?". The choices in Table 13.5 define an SCCS question.

Table 13.5: Main design choices in a self-controlled case series design.

| Choice | Description |
|---|---|
| Target cohort | A cohort representing the treatment |
| Outcome cohort | A cohort representing the outcome of interest |
| Time-at-risk | At what time (often relative to the target cohort start and end dates) do we consider the risk of the outcome? |
| Model | The model to estimate the effect, including any adjustments for time-varying confounders |

Like other self-controlled designs, the SCCS is robust to confounding due to between-person differences, but vulnerable to confounding due to time-varying effects. Several adjustments are possible to attempt to account for these, for example by including age and season. A special variant of the SCCS includes not just the exposure of interest, but all other exposures to drugs recorded in the database (Simpson et al., 2013), potentially adding thousands of additional variables to the model. L1-regularization using cross-validation to select the regularization hyperparameter is applied to the coefficients of all exposures except the exposure of interest.

One important assumption underlying the SCCS is that the observation period end is independent of the date of the outcome. Because for some outcomes, especially ones that can be fatal such as stroke, this assumption can be violated an extension to the SCCS has been developed that corrects for any such dependency. (Farrington et al., 2011)

## 13.2 Designing a hypertension study

### 13.2.1 Problem definition

ACE inhibitors are widely used in patients with hypertension or ischemic heart disease, especially those with other comorbidities such as congestive heart failure,

diabetes mellitus, or chronic kidney disease (Zaman et al., 2002). Angioedema, a serious and sometimes life-threatening adverse event that usually manifests as swelling of the lips, tongue, mouth, larynx, pharynx, or periorbital region, has been linked to the use of these medications (Sabroe and Black, 1997). However, limited information is available about the absolute and relative risks for angioedema associated with the use of these medications. Existing evidence is primarily based on investigations of specific cohorts (eg, predominantly male veterans or Medicaid beneficiaries), whose findings may not be generalizable to other populations, or based on investigations with few events, which provide unstable risk estimates (Powers et al., 2012). Several observational studies compare ACE inhibitors to beta-blockers for the risk of angioedema (Magid et al., 2010; Toh et al., 2012), but beta-blockers are no longer recommend as first-line treatment of hypertension (Whelton et al., 2018). A viable alternative treatment could be thiazides or thiazide-like diuretics, which could be just as effective in managing hypertension and its associated risks such as acute myocardial infarction.

We will apply our population-level estimation framework to observational healthcare data to address the following comparative estimation question:

> What is the risk of angioedema and acute myocaridal infarction in new users of ACE inhibitors compared to new users of thiazide and thiazide-like diuretics?

### 13.2.2 Target and comparator

Focus on first-line mono-therapy

### 13.2.3 Outcome

Angioedema and AMI

### 13.2.4 Time-at-risk

### 13.2.5 Model

### 13.2.6 Study summary

Table 13.6: Main design choices four our comparative cohort study.

| Choice | Value |
|---|---|
| Target cohort | |
| Comparator cohort | |

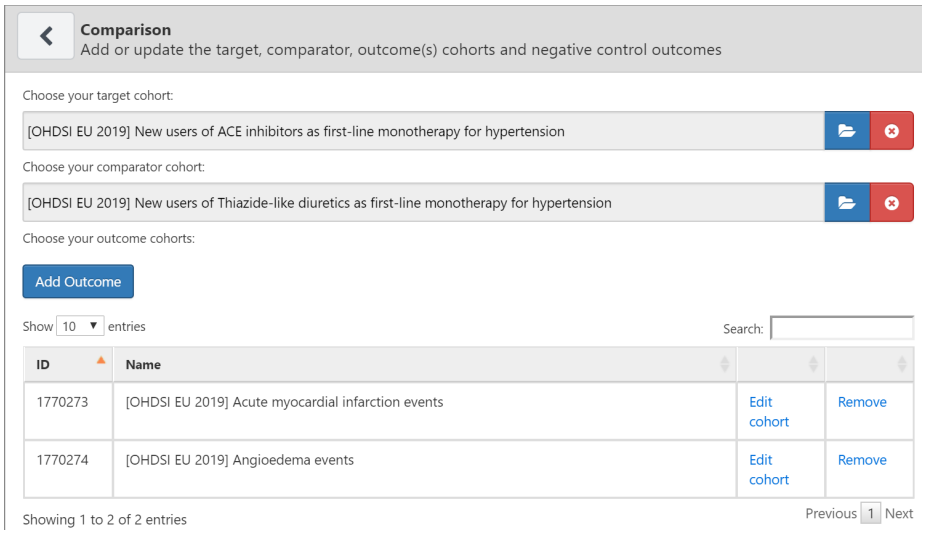



Figure 13.6: The comparison window.

| Choice | Value |
|---|---|
| Outcome cohort | |
| Time-at-risk | |
| Model | |

## 13.3 Implementation the study using ATLAS

SPECIFICATION

Comparative Cohort Settings

### 13.3.1 Specifying the comparisons

> Comparative Cohort Settings
>
> +Add Comparison

Click on + Add Comparison. The window in Figure 13.6 should appear. Then click on to add cohorts to target, comparator and outcome cohort.

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

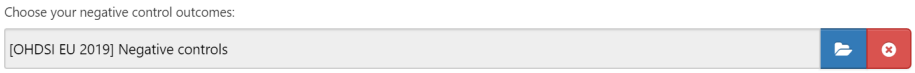



Figure 13.7: Negative control outcomes selection window.

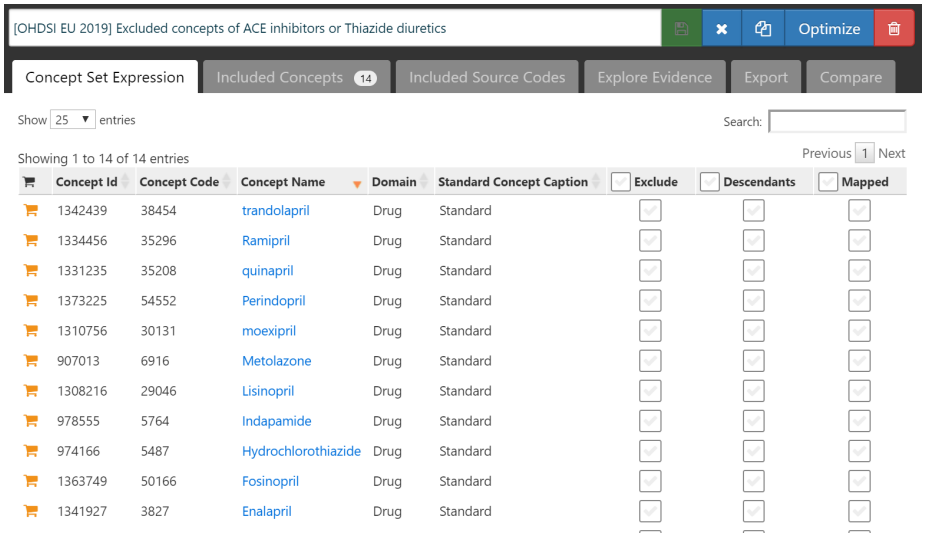



Figure 13.8: Negative Control concept set.

When specifying T, C, and O, note that you can select as many T, C, and O cohorts as you like–this means that you can do many comparisons simultaneously.

Additional outcomes will appear in the table below the 

button. These will be listed in a table with ID and Name columns displayed. Many entries can be displayed in this table.

> Choose your negative control outcomes

Pick concept sets you want to include by clicking on  . Search for the negative control concept sets you previously built as discused in Chapter 19.

Note: The negative controls concept IDs included in the concept set do not include their descendants. Figure 13.8 shows the negative control concept set used in this example.

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

Here, you can specify exactly which covariates you would like to include in your

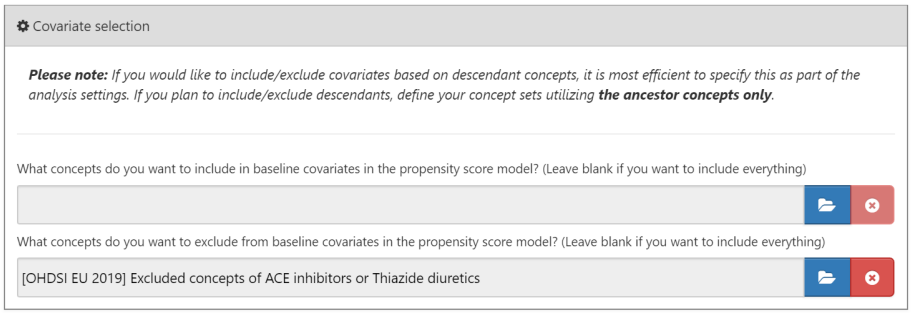



Figure 13.9: Covariate selection window with exclusion concepts.

propensity score model. When specifying covariates *here*, all other covariates (aside from those you specified) are left out. We usually want to include all baseline covariates, letting the LASSO regression build a model that balances all covariates. You might want to specify particular covariates when you are replicating an existing study that manually picked a small number of covariates. These inclusions can be specified in this comparison section or in the analysis section. The option in the analysis section of whether or not to include descendants will apply also here in the comparison section.

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

Rather than specifying which covariates to include, we can instead specify covariates to *exclude*. When we submit a list of concept IDs in this field, we use every covariate except for those that we submitted. We will want to exclude covariates that are very highly correlated with the exposures or else the propensity model will separate the two groups nearly perfectly, making a comparison impossible. These exclusions can be specified in this comparison section or in the analysis section. Exclusions may be comparison specific (exposure drugs), so it often makes sense to specify them here. The option in the analysis section of whether or not to include descendants will apply also here in the comparison section.

In this example, the covariates we want to exclude are ACE inhibitors and thiazides or thiazide diuretic. Figure 13.9 shows we select a concept set that includes all these concepts.

Often we want to include or exclude concepts **and their descendants**. We could specify the concept set to include descendant concepts. However, for various reasons it might be more efficient to not include descendant in the concept set, but rather automatically add them by setting the 'Should descendant concepts be added' option to *yes* in the Covariate Settings section of the Analysis settings that will be discussed later.

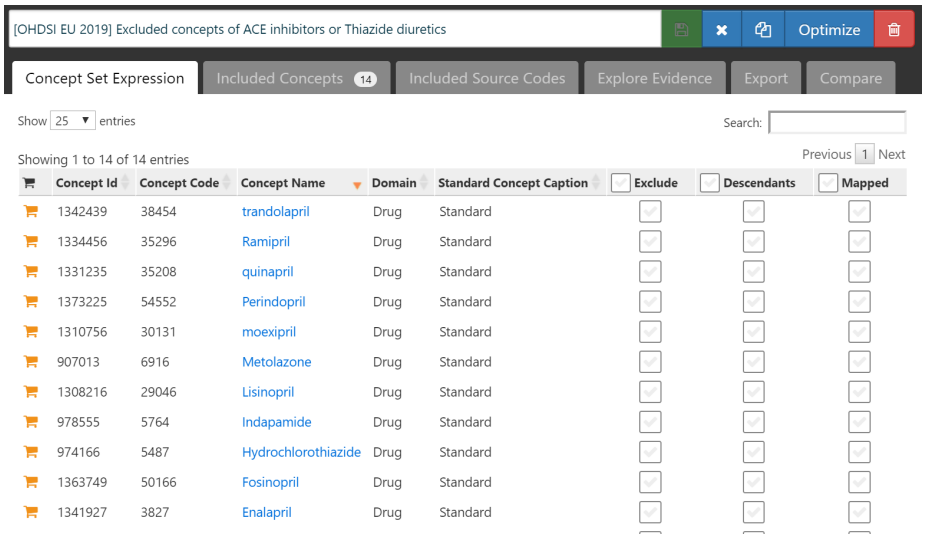



Figure 13.10: The concept set defining the concepts to exclude. Note that no descendantsa have been included. We will specify to include these at analysis time in the Analysis settings.

## 13.4 Implementation the study using R

Now we have completely designed our study we have to implement the study. This will be done using the CohortMethod package to execute our study. It extracts the necessary data from a database in the CDM and can use a large set of covariates for the propensity model.

### 13.4.1 Cohort instantiation

We first need to instantiate the target and outcome cohorts. Instantiating cohorts is described in Chapter 11. The Appendix provides the full definitions of the target (Appendix B.1) and outcome (Appendix B.4) cohorts. In this example we will assume the ACE inhibitors cohort has ID 1, and the angioedema cohort has ID 2.

### 13.4.2 Data extraction

We first need to tell R how to connect to the server. `CohortMethod` uses the `DatabaseConnector` package, which provides a function called `createConnectionDetails`. Type `?createConnectionDetails` for the specific

settings required for the various database management systems (DBMS). For example, one might connect to a PostgreSQL database using this code:

```
library(PatientLevelPrediction)
connDetails <- createConnectionDetails(dbms = "postgresql",
                                       server = "localhost/ohdsi",
                                       user = "joe",
                                       password = "supersecret")

cdmDbSchema <- "my_cdm_data"
cohortsDbSchema <- "scratch"
cohortsDbTable <- "my_cohorts"
cdmVersion <- "5"
```

The last four lines define the `cdmDbSchema`, `cohortsDbSchema`, and `cohortsDbTable` variables, as well as the CDM version. We will use these later to tell R where the data in CDM format live, where the cohorts of interest have been created, and what version CDM is used. Note that for Microsoft SQL Server, database schemas need to specify both the database and the schema, so for example `cdmDbSchema <- "my_cdm_data.dbo"`.

### 13.4.3 Specifying the analyses

## 13.5 Excercises

# Chapter 14

# Patient Level Prediction

*Chapter leads: Peter Rijnbeek & Jenna Reps*

Clinical decision making is a complicated task in which the clinician has to infer a diagnosis or treatment pathway based on the available medical history of the patient and the current clinical guidelines. Clinical prediction models have been developed to support this decision making process and are used in clinical practice in a wide spectrum of specialties. These models predict a diagnostic or prognostic outcome based on a combination of patient characteristics, e.g. demographic information, disease history, treatment history. The number of publications describing clinical prediction models has increased strongly over the last 10 years. An example is the Garvan model that predicts the 5-years and 10-years fractures risk in any elderly man or woman based on age, fracture history, fall history, bone mass density or weight (Nguyen et al., 2008). Many prediction models have been developed in patient subgroups at higher risk that need more intensive monitoring, e.g. the prediction of 30-day mortality after an acute myocardial described by Lee et al. (1995). Also, many models have been developed for asymptomatic subjects in the population, e.g. the famous Framingham risk functions for cardiovascular disease (Wilson et al., 1998), or the models for breast cancer screening (Engel and Fischer, 2015).

Surprisingly, most currently used models are estimated using small datasets and contain a limited set of patient characteristics. For example, in a review of 102 prognostic models in traumatic brain injury showed that three quarters of the models were based on samples with less than 500 patients (Perel et al., 2006). This low sample size, and thus low statistical power, forces the data analyst to make stronger modelling assumptions. The selection of the often limited set of patient characteristics is strongly guided by the expert knowledge at hand. This contrasts sharply with the reality of modern medicine wherein patients generate a rich digital trail, which is well beyond the power of any medical practitioner to fully assimilate. Presently, health care is generating huge amount of patient-

specific information contained in the Electronic Health Record (EHR). This includes structured data in the form of diagnose, medication, laboratory test results, and unstructured data contained in clinical narratives. Currently, it is unknown how much predictive accuracy can be gained by leveraging the large amount of data originating from the complete EHR of a patient.

Massive-scale, patient-specific predictive modeling has become reality due the OHDSI initiative in which the common data model (CDM) allows for uniform and transparent analysis at an unprecedented scale. These large standardized populations contain rich data to build highly predictive large-scale models and also provide immediate opportunity to serve large communities of patients who are in most need of improved quality of care. Such models can inform truly personalized medical care leading hopefully to sharply improved patient outcomes. Furthermore, these models could assist in the design and analysis of randomized controlled trials (RCT) by enabling a better patient stratification or can be utilized to adjust for confounding variables in observational research. More accurate prediction models contribute to targeting of treatment and to increasing cost-effectiveness of medical care.

Advances in machine learning for large dataset analysis have led to increased interest in applying patient-level prediction on this type of data. However, many published efforts in patient-level-prediction do not follow the model development guidelines, fail to perform extensive external validation, or provide insufficient model details that limits the ability of independent researchers to reproduce the models and perform external validation. This makes it hard to fairly evaluate the predictive performance of the models and reduces the likelihood of the model being used appropriately in clinical practice. To improve standards, several papers have been written detailing guidelines for best practices in developing and reporting prediction models.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [1] provides clear recommendations for reporting prediction model development and validation and addresses some of the concerns related to transparency. However, data structure heterogeneity and inconsistent terminologies still make collaboration and model sharing difficult as different researchers are often required to write new code to extract the data from their databases and may define variables differently.

In our paper (Reps et al., 2018), we propose a standardised framework for patient-level prediction that utilizes the OMOP Common Data Model (CDM) and standardized vocabularies, and describe the open-source software that we developed implementing the framework's pipeline. The framework is the first to support existing best practice guidelines and will enable open dissemination of models that can be extensively validated across the network of OHDSI collaborators.

Figure 14.1, illustrates the prediction problem we address. Among a population

[1] https://www.equator-network.org/reporting-guidelines/tripod-statement/

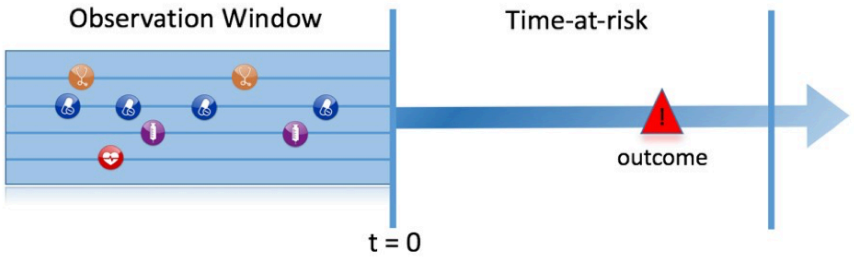



Figure 14.1: The prediction problem.

at risk, we aim to predict which patients at a defined moment in time (t = 0) will experience some outcome during a time-at-risk. Prediction is done using only information about the patients in an observation window prior to that moment in time.

As shown in Table 14.1, to define a prediction problem we have to define t=0 by a target Cohort (T), the outcome we like to predict by an outcome cohort (O), and the time-at-risk (TAR). Furthermore, we have to make design choices for the model we like to develop, and determine the observational datasets to perform internal and external validation.

Table 14.1: Main design choices in a prediction design.

| Choice | Description |
|---|---|
| Target cohort | A cohort for whom we wish to predict |
| Outcome cohort | A cohort representing the outcome we wish to predict |
| Time-at-risk | For what time relative to t=0 do we want to make the prediction? |
| Model | What algorithms using which parameters do we want use, and what predictor variables do we want to include? |

This conceptual framework works for all type of prediction problems:

- Disease onset and progression
  - **Structure**: Amongst patients who are newly diagnosed with *[a disease]*, who will go on to have *[another disease or complication]* within *[time horizon from diagnosis]*?
  - **Example**: Among newly diagnosed atrial fibrilation patients, who will go on to have ischemic stroke in the next three years?
- Treatment choice
  - **Structure**: Amongst patients with *[indicated disease]* who are treated with either *[treatment 1]* or *[treatment 2]*, which patients were treated with *[treatment 1]* (on day 0).
  - **Example**: Among patients with atrial fibrilation who took either warfarin or rivaroxaban, which patients gets warfarin? (e.g. for a propensity model)
- Treatment response
  - **Structure**: Amongst new users of *[a treatment]*, who will experience *[some effect]* in *[time window]* ?
  - **Example**: Which patients with diabetes who start on metformin stay on metform for three years?
- Treatment safety
  - **Structure**: Amongst new users of *[a treatment]*, who will experience

  - **Example**: Amongst new users of warfarin, who will have a GI bleed in one year?
- Treatment adherence
  - **Structure**: Amongst new users of *[a treatment]*, who will achieve *[adherence metric]* at *[time window]*?
  - **Example**: Which patients with diabetes who start on metformin achieve >=80% proportion of days covered at one year?

In the next sections we will explain the best practices for model specification, implementation, and evaluation using OHDSI's Patient-Level Prediction (PLP) framework as guidance.

## 14.1 Designing a hypertension study

The first step is to clearly define the prediction problem. Interestingly, in many published papers the prediction problem is poorly defined, e.g. it is unclear how the index date (start of the target Cohort) is defined. A poorly defined prediction problem does not allow for external validation by others let alone implementation in clinical practice. In the PLP framework we have enforced that we have to define the prediction problem we like to address, in which population we will build the model, which model we will build and how we will evaluate its performance. In this section we will guide you through this process and we will use a "Treatment safety" prediction type as an example.

### 14.1.1 Problem definition

Angioedema is a well known side-effect of ACE inhibitors, and the incidence of angioedema reported in the labeling for ACE inhibitors is in the range of 0.1% to 0.7% (Byrd et al., 2006). Monitoring patients for this adverse effect is important, because although angioedema is rare, it may be life-threatening, leading to respiratory arrest and death (Norman et al., 2013). Further, if angioedema is not initially recognized, it may lead to extensive and expensive workups before it is identified as a cause (Norman et al., 2013; Thompson and Frable, 1993). Other than the higher risk among African-American patients, there are no known predisposing factors for the development of ACE inhibitor–related angioedema (Byrd et al., 2006). Most reactions occur within the first week or month of initial therapy and often within hours of the initial dose (Cicardi et al., 2004). However, some cases may occur years after therapy has begun (O'Mara and O'Mara, 1996).No diagnostic test is available that specifically identifies those at risk. If we could identify those at risk, doctors could act, for example by discontinuing the ACE inhibitorin favor of another hypertension drug.

We will apply the PLP framework to observational healthcare data to address the following patient-level prediction question:

Amongst patients who have just started on an ACE inhibitor for the first time, who will experience angioedema in the following year?

### 14.1.2 Study population definition

The final study population in which we will develop our model is often a subset of the target population, because we will e.g. apply criteria that are dependent on T and O or we want to do sensitivity analyses with subpopulations of T. For this we have to answer the following questions:

- *What is the minimum amount of observation time we require before the start of the target cohort?* This choice could depend on the available patient time in your training data, but also on the time you expect to be available in the data sources you want to apply the model on in the future. The longer the minimum observation time, the more baseline history time is available for each person to use for feature extraction, but the fewer patients will qualify for analysis. Moreover, there could be clinical reasons to choose a short or longer lookback period. For our example, we will use a prior history as lookback period (washout period).
- *Can patients enter the target cohort multiple times?* In the target cohort definition, a person may qualify for the cohort multiple times during different spans of time, for example if they had different episodes of a disease or separate periods of exposure to a medical product. The cohort definition does not necessarily apply a restriction to only let the patients enter once, but in the context of a particular patient-level prediction problem, a user may want to restrict the cohort to the first qualifying episode. In our example, a person can only enter the target cohort once since our criteria was based on first use of an ACE inhibitor.
- *Do we allow persons to enter the cohort if they experienced the outcome before?* Do we allow persons to enter the target cohort if they experienced the outcome before qualifying for the target cohort? Depending on the particular patient-level prediction problem, there may be a desire to predict 'incident' first occurrence of an outcome, in which case patients who have previously experienced the outcome are not 'at-risk' for having a first occurrence and therefore should be excluded from the target cohort. In other circumstances, there may be a desire to predict 'prevalent' episodes, whereby patients with prior outcomes can be included in the analysis and the prior outcome itself can be a predictor of future outcomes. For our prediction example, we will choose not to include those with prior angioedema.
- *How do we define the period in which we will predict our outcome relative to the target cohort start?* We actually have to make two decisions to answer that question. First, does the time-at-risk window start at the date of the start of the target cohort or later? Arguments to make it start

later could be that you want to avoid outcomes that were entered late in the record that actually occurred before the start of the target cohort or you want to leave a gap where interventions to prevent the outcome could theoretically be implemented. Second, you need to define the time-at-risk by setting the risk window end, as some specification of days offset relative to the target cohort start or end dates. For our problem we will predict in a 'time-at-risk' window starting 1 day after the start of the target cohort up to 365 days later.

- *Do we require a minimum amount of time-at-risk?* We have to decide if we want to include patients that did not experience the outcome but did leave the database earlier than the end of our time-at-risk period. These patients may experience the outcome when we do not observe them. For our prediction problem we decide to answer this question with 'Yes, require a mimimum time-at-risk' for that reason. Furthermore, we have to decide if this constraint also applies to persons who experienced the outcome or we will include all persons with the outcome irrespective of their total time at risk. For example, if the outcome is death, then persons with the outcome are likely censored before the full time-at-risk period is complete.

### 14.1.3 Model development settings

To develop the model we have to decide which algorithm(s) we like to train. We see the selection of the best algorithm for a certain prediction problem as an empirical question, i.e. you need to let the data speak for itself and try different approaches to find the best one. There is no algorithm that will work best for all problems (no free lunch). In our framework we therefore aim to implement many algorithms. Furthermore, we made the system modular so you can add your own custom algorithms. This out-of-scope for this chapter but mode details can be found in the *AddingCustomAlgorithms* vignette in the PatientLevelPrediction package.

Our framework currently contains the following algorithms to choose from:

**Regularized Logistic Regression** Lasso logistic regression belongs to the family of generalized linear models, where a linear combination of the variables is learned and finally a logistic function maps the linear combination to a value between 0 and 1. The lasso regularization adds a cost based on model complexity to the objective function when training the model. This cost is the sum of the absolute values of the linear combination of the coefficients. The model automatically performs feature selection by minimizing this cost. We use the Cyclops (Cyclic coordinate descent for logistic, Poisson and survival analysis) package to perform large-scale regularized logistic regression. **Hyper-parameters**: var (starting variance), seed.

**Gradient boosting machines** Gradient boosting machines is a boosting ensemble technique and in our framework it combines multiple decision trees. Boosting works by iteratively adding decision trees but adds more weight to the data-points that are misclassified by prior decision trees in the cost function when training the next tree. We use Extreme Gradient Boosting, which is an efficient implementation of the gradient boosting framework implemented in the xgboost R package available from CRAN. **Hyper-parameters**: ntree (number of trees), max depth (max levels in tree), min rows (minimum data points in in node), learning rate, seed | mtry (number of features in each tree),ntree (number of trees), maxDepth (max levels in tree), minRows (minimum data points in in node),balance (balance class labels), seed.

**Random forest** Random forest is a bagging ensemble technique that combines multiple decision trees. The idea behind bagging is to reduce the likelihood of overfitting, by using weak classifiers, but combining multiple diverse weak classifiers into a strong classifier. Random forest accomplishes this by training multiple decision trees but only using a subset of the variables in each tree and the subset of variables differ between trees. Our packages uses the sklearn learn implementation of Random Forest in python. **Hyper-parameters**: mtry (number of features in each tree),ntree (number of trees), maxDepth (max levels in tree), minRows (minimum data points in in node),balance (balance class labels), seed.

**K-nearest neighbors** K-nearest neighbors (KNN) is an algorithm that uses some metric to find the K closest labelled data-points, given the specified metric, to a new unlabelled data-point. The prediction of the new data-points is then the most prevalent class of the K-nearest labelled data-points. There is a sharing limitation of KNN, as the model requires labelled data to perform the prediction on new data, and it is often not possible to share this data across data sites. We included the BigKnn package developed in OHDSI which is a large scale k-nearest neighbor classifier. **Hyper-parameters**: k (number of neighbours), weighted (weight by inverse frequency).

**Naive Bayes** The Naive Bayes algorithm applies the Bayes' theorem with the "naive" assumption of conditional independence between every pair of features given the value of the class variable. Based on the likelihood the data belongs to a class and the prior distribution of the class, a posterior distribution is obtained. **Hyper-parameters**: none.

**AdaBoost** AdaBoost is a boosting ensemble technique. Boosting works by iteratively adding classifiers but adds more weight to the data-points that are misclassified by prior classifiers in the cost function when training the next classifier. We use the sklearn "AdaboostClassifier" implementation in Python. **Hyper-parameters**: nEstimators (the maximum number of estimators at which boosting is terminated), learningRate (learning rate shrinks the contribution of each classifier by learning_rate. There is a trade-off between learningRate and nEstimators).

**Decision Tree** A decision tree is a classifier that partitions the variable space

using individual tests selected using a greedy approach. It aims to find partitions that have the highest information gain to separate the classes. The decision tree can easily overfit by enabling a large number of partitions (tree depth) and often needs some regularization (e.g., pruning or specifying hyper-parameters that limit the complexity of the model). We use the sklearn "DecisionTreeClassifier" implementation in Python. **Hyper-parameters**: maxDepth (the maximum depth of the tree), minSamplesSplit,minSamplesLeaf, minImpuritySplit (threshold for early stopping in tree growth. A node will split if its impurity is above the threshold, otherwise it is a leaf.), seed,classWeight ("Balance"" or "None").

**Multilayer Perception** Neural networks containing multiple layers that weight their inputs using a non-linear function. The first layer is the input layer, the last layer is the output layer the between are the hidden layers. Neural networks are generally trained using feed forward back-propagation. This is when you go through the network with a data-point and calculate the error between the true label and predicted label, then go backwards through the network and update the linear function weights based on the error. **Hyper-parameters**: size (the number of hidden nodes), alpha (the l2 regularisation), seed.

**Deep Learning** Deep learning such as deep nets, convolutional neural networks or recurrent neural networks are similar to a neural network but have multiple hidden layers that aim to learn latent representations useful for prediction. In a seperate vignette in the PatientLevelPrediction package we describe these models and hyper-parameters in more detail.

Furthermore, we have to decide on the **covariates** that we will use to train our model. In our example, we like to add gender, age, all conditions, drugs and drug groups, and visit counts. We also have to specify in which time windows we will look and we decide to look in year before and any time prior.

### 14.1.4 Model evaluation

Finally, we have to define how we will train and test our model on our data, i.e. how we perform **internal validation**. For this we have to decide how we divide our dataset in a training and testing dataset and how we randomly assign patients to these two sets. Dependent on the size of the training set we can decide how much data we like to use for training, typically this is a 75% - 25% split. If you have very large datasets you can use more data for training. To randomly assign patients to the training and testing set, there are two commonly used approaches:

1. split by person. In this case a random seed is used to assign the patient to either sets.
2. split by time. In this case a time point is used to split the persons, e.g. 75% of the data is before and 25% is after this date. The advantage of this is

that you take into consideration that the health care system has changed over time.

For our prediction model we decide to start with a Regularized Logistic Regression and will use the default parameters. We will do a 75%-25% split by person.

### 14.1.5 Study summary

We now completely defined our study as shown in Table 14.2.

Table 14.2: Main design choices for our study.

| Choice | Value |
|---|---|
| Target cohort | Patients who have just started on an ACE inhibitor for the first time. |
| Outcome cohort | Angioedema. |
| Time-at-risk | 1 day till 365 days from cohort start. We will require at least 364 days at risk. |
| Model | Gradient Boosting Machine with hyper-parameters ntree: 5000, max depth: 4 or 7 or 10 and learning rate: 0.001 or 0.01 or 0.1 or 0.9. Covariates will include gender, age, conditions, drugs, drug groups, and visit count. Data split: 75% train - 25% test, randomly assigned by person. |

We define the target cohort as the first exposure to any ACE inhibitor. Patients are excluded if they have less than 365 days of prior observation time or have prior angioedema.

## 14.2 Implementing the study in R

Now we have completely designed our study we have to implement the study. This will be done using the PatientLevelPrediction package to build patient-level predictive models. The package enables data extraction, model building, and model evaluation using data from databases that are translated into the OMOP CDM.

### 14.2.1 Cohort instantiation

We first need to instantiate the target and outcome cohorts. Instantiating cohorts is described in Chapter 11. The Appendix provides the full definitions

of the target (Appendix B.1) and outcome (Appendix B.4) cohorts. In this example we will assume the ACE inhibitors cohort has ID 1, and the angioedema cohort has ID 2.

### 14.2.2 Data extraction

We first need to tell R how to connect to the server. `PatientLevelPrediction` uses the `DatabaseConnector` package, which provides a function called `createConnectionDetails`. Type `?createConnectionDetails` for the specific settings required for the various database management systems (DBMS). For example, one might connect to a PostgreSQL database using this code:

```
library(PatientLevelPrediction)
connDetails <- createConnectionDetails(dbms = "postgresql",
                                       server = "localhost/ohdsi",
                                       user = "joe",
                                       password = "supersecret")

cdmDbSchema <- "my_cdm_data"
cohortsDbSchema <- "scratch"
cohortsDbTable <- "my_cohorts"
cdmVersion <- "5"
```

The last four lines define the `cdmDbSchema`, `cohortsDbSchema`, and `cohortsDbTable` variables, as well as the CDM version. We will use these later to tell R where the data in CDM format live, where the cohorts of interest have been created, and what version CDM is used. Note that for Microsoft SQL Server, database schemas need to specify both the database and the schema, so for example `cdmDbSchema <- "my_cdm_data.dbo"`.

First it makes sense to verify that the cohort creation has succeeded, by counting the number of cohort entries:

```
sql <- paste("SELECT cohort_definition_id, COUNT(*) AS count",
"FROM @cohortsDbSchema.cohortsDbTable",
"GROUP BY cohort_definition_id")
conn <- connect(connDetails)
renderTranslateQuerySql(connection = conn,
                        sql = sql,
                        cohortsDbSchema = cohortsDbSchema,
                        cohortsDbTable = cohortsDbTable)
```

```
##   cohort_definition_id  count
## 1                    1 527616
## 2                    2   3201
```

Now we can tell PatientLevelPrediction to extract all necessary data for our

analysis. Covariates are extracted using the `FeatureExtraction` package. For more detailed information on the FeatureExtraction package see its vignettes. For our example study we decided to use these settings:

```
covSettings <- createCovariateSettings(useDemographicsGender = TRUE,
                                       useDemographicsAge = TRUE,
                                       useConditionGroupEraLongTerm = TRUE,
                                       useConditionGroupEraAnyTimePrior = TRUE,
                                       useDrugGroupEraLongTerm = TRUE,
                                       useDrugGroupEraAnyTimePrior = TRUE,
                                       useVisitConceptCountLongTerm = TRUE,
                                       longTermStartDays = -365,
                                       endDays = -1)
```

The final step for extracting the data is to run the `getPlpData` function and input the connection details, the database schema where the cohorts are stored, the cohort definition ids for the cohort and outcome, and the washoutPeriod which is the minimum number of days prior to cohort index date that the person must have been observed to be included into the data, and finally input the previously constructed covariate settings.

```
plpData <- getPlpData(connectionDetails = connDetails,
                      cdmDatabaseSchema = cdmDbSchema,
                      cohortDatabaseSchema = cohortsDbSchema,
                      cohortTable = cohortsDbSchema,
                      cohortId = 1,
                      covariateSettings = covariateSettings,
                      outcomeDatabaseSchema = cohortsDbSchema,
                      outcomeTable = cohortsDbSchema,
                      outcomeIds = 2,
                      sampleSize = 10000
)
```

There are many additional parameters for the `getPlpData` function which are all documented in the PatientLevelPrediction manual. The resulting `plpData` object uses the package `ff` to store information in a way that ensures R does not run out of memory, even when the data are large.

Creating the `plpData` object can take considerable computing time, and it is probably a good idea to save it for future sessions. Because `plpData` uses `ff`, we cannot use R's regular save function. Instead, we'll have to use the `savePlpData()` function:

```
savePlpData(plpData, "angio_in_ace_data")
```

We can use the `loadPlpData()` function to load the data in a future session.

### 14.2.3 Additional inclusion criteria

To completely define the prediction problem the final study population is obtained by applying additional constraints on the two earlier defined cohorts, e.g., a minumim time at risk can be enforced (`requireTimeAtRisk, minTimeAtRisk`) and we can specify if this also applies to patients with the outcome (`includeAllOutcomes`). Here we also specify the start and end of the risk window relative to target cohort start. For example, if we like the risk window to start 30 days after the at-risk cohort start and end a year later we can set `riskWindowStart = 30` and `riskWindowEnd = 365`. In some cases the risk window needs to start at the cohort end date. This can be achieved by setting `addExposureToStart = TRUE` which adds the cohort (exposure) time to the start date.

In the example below all the settings we defined for our study are imposed:

```
population <- createStudyPopulation(plpData = plpData,
                                     outcomeId = 2,
                                     washoutPeriod = 364,
                                     firstExposureOnly = FALSE,
                                     removeSubjectsWithPriorOutcome = TRUE,
                                     priorOutcomeLookback = 9999,
                                     riskWindowStart = 1,
                                     riskWindowEnd = 365,
                                     addExposureDaysToStart = FALSE,
                                     addExposureDaysToEnd = FALSE,
                                     minTimeAtRisk = 364,
                                     requireTimeAtRisk = TRUE,
                                     includeAllOutcomes = TRUE,
                                     verbosity = "DEBUG"
)
```

### 14.2.4 Model Development

In the set function of an algorithm the user can specify a list of eligible values for each hyper-parameter. All possible combinations of the hyper-parameters are included in a so-called grid search using cross-validation on the training set. If a user does not specify any value then the default value is used instead.

For example, if we use the following settings for the gradientBoostingMachine: ntrees=c(100,200), maxDepth=4 the grid search will apply the gradient boosting machine algorithm with ntrees=100 and maxDepth=4 plus the default settings for other hyper-parameters and ntrees=200 and maxDepth=4 plus the default settings for other hyper-parameters. The hyper-parameters that lead to the bestcross-validation performance will then be chosen for the final model.

For our problem we choose to build a logistic regression model with the default hyper-parameters

```
gbmModel <- setGradientBoostingMachine(ntrees = 5000,
                                       maxDepth = c(4,7,10),
                                       learnRate = c(0.001,0.01,0.1,0.9))
```

The `runPlP` function uses the population, `plpData`, and model settings to train and evaluate the model. We can use the testSplit (person/time) and testFraction parameters to split the data in a 75%-25% split and run the patient-level prediction pipeline:

```
gbmResults <- runPlp(population = population,
                     plpData = plpData,
                     modelSettings = gbmModel,
                     testSplit = 'person',
                     testFraction = 0.25,
                     nfold = 2,
                     splitSeed = 1234)
```

Under the hood the package will now use the R xgboost package to fit a a gradient boosting machine model using 75% of the data and will evaluate the model on the remaining 25%. A results data structure is returned containing information about the model, its performance etc.

In the `runPlp` function there are several parameters to save the `plpData`, `plpResults`, `plpPlots`, `evaluation`, etc. objects which are all set to `TRUE` by default.

You can save the model using:

```
savePlpModel(gbmResults$model, dirPath = "model")
```

You can load the model using:

```
plpModel <- loadPlpModel("model")
```

You can also save the full results structure using:

```
savePlpResult(gbmResults, location = "gbmResults")
```

To load the full results structure use:

```
lrResults <- loadPlpResult("gbmResults")
```

## 14.3 Implementing the study in ATLAS

The script we created manually above can also be automatically created using a powerful feature in ATLAS. By creating a new prediction study (left menu)

you can select the Target and Outcome as created in ATLAS, set all the study parameters, and then you can download a R package that you can use to execute your study. What is really powerful is that you can add multiple Ts, Os, covariate settings etc. The package will then run all the combinations of automatically as separate analyses. The screenshots below explain this process.

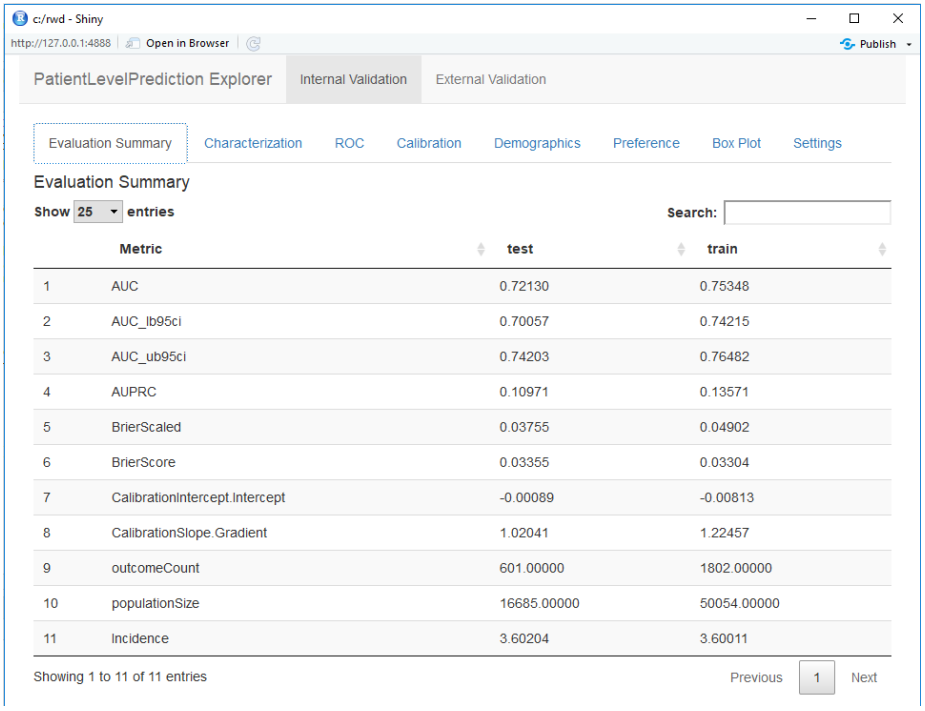
**Todo: add description of how to implement study using ATLAS**

By opening the R package in R studio and building the package you can run the study using the `execute` function. Theres is also an example `CodeToRun.R` script available in the `extras` folder of the package with extra instructions.

## 14.4 Internal validation

Once we execute the study, the `runPlp` function returns the trained model and the evaluation of the model on the train/test sets. You can interactively view the results by running: `viewPlp(runPlp = gbmResults)`. This will open a Shiny App in your browser in which you can view all performance measures created by the framework, including interactive plots, as shown in Figure **??**.

**Todo: update Shiny app screenshot with hypertension example**




To generate and save all the evaluation plots to a folder run the following code:

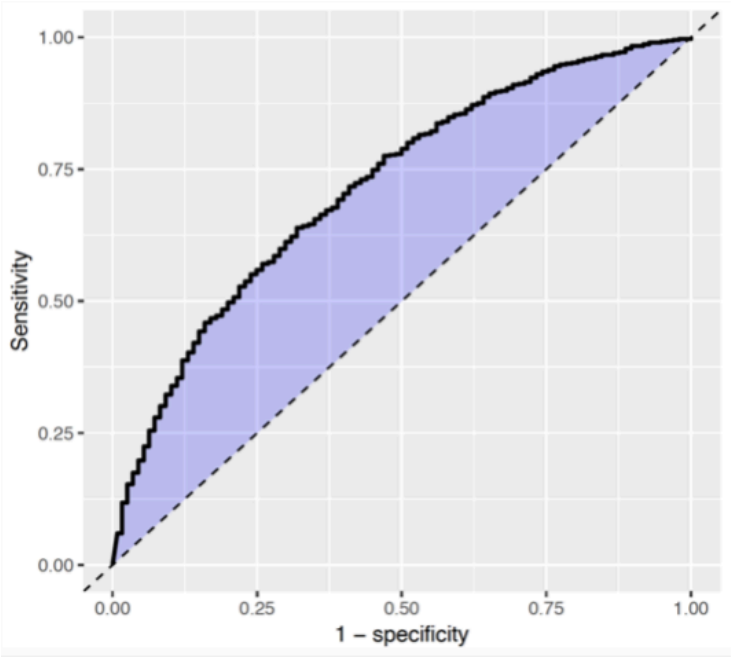



Figure 14.2: The Receiver Operating Characteristics (ROC) curve.

```
plotPlp(gbmResults, "plots")
```

The plots are described in more detail in the next sections.

### 14.4.1 Discrimination

The Receiver Operating Characteristics (ROC) plot shows the sensitivity against 1-specificity on the test set. The plot illustrates how well the model is able to discriminate between the people with the outcome and those without. The dashed diagonal line is the performance of a model that randomly assigns predictions. The higher the area under the ROC plot the better the discrimination of the model. Figure 14.2 is created by changing the probability threshold to assign the positive class.

**Todo: update plots with hypertension example**

### 14.4.2 Calibration

The calibration plot (Figure 14.3) shows how close the predicted risk is to the observed risk. The diagonal dashed line thus indicates a perfectly calibrated

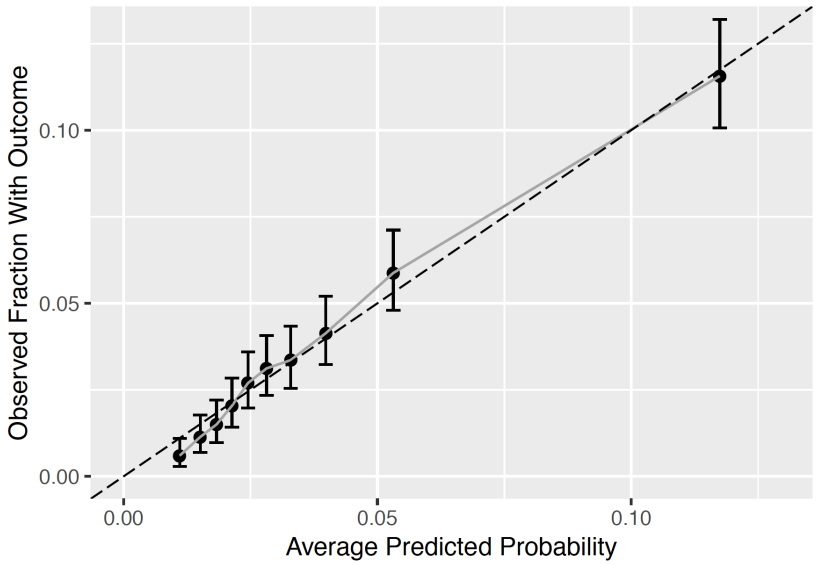



Figure 14.3: Calibration plot.

model. The ten (or fewer) dots represent the mean predicted values for each quantile plotted against the observed fraction of people in that quantile who had the outcome (observed fraction). The straight black line is the linear regression using these 10 plotted quantile mean predicted vs observed fraction points. The straight vertical lines represented the 95% lower and upper confidence intervals of the slope of the fitted line.

### 14.4.3 Smooth Calibration

Similar to the traditional calibration shown above the Smooth Calibration plot shows the relationship between predicted and observed risk. the major difference is that the smooth fit allows for a more fine grained examination of this. Whereas the traditional plot will be heavily influenced by the areas with the highest density of data the smooth plot will provide the same information for this region as well as a more accurate interpretation of areas with lower density. the plot also contains information on the distribution of the outcomes relative to predicted risk.

However, the increased information gain comes at a computational cost. It is recommended to use the traditional plot for examination and then to produce the smooth plot for final versions. To create the smooth calibarion plot you have to run the follow command:

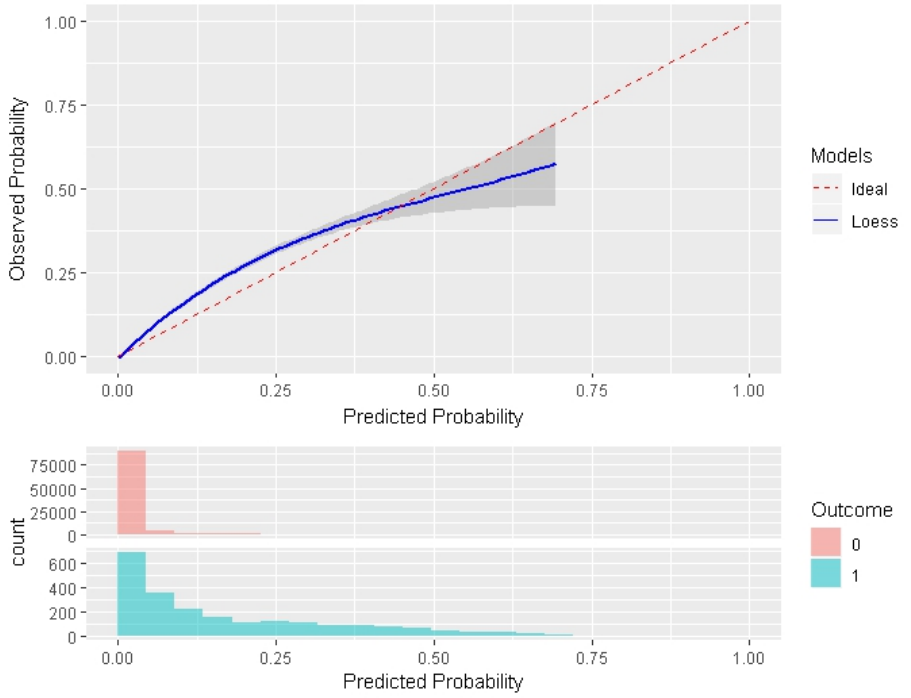



Figure 14.4: Smooth calibration plot.

```
plotSmoothCalibration(gbmResults)
```

See the help function for more information, on how to set the smoothing method etc.

Figure 14.4 shows an example from another study that better demonstrates the impact of using a smooth calibration plot. The default line fit would not highlight the miss-calibration at the lower predicted probability levels that well.

### 14.4.4 Preference distribution

The preference distribution plot (Figure 14.5) shows the preference score distributions for people in the test set with the outcome (red) without the outcome (blue).

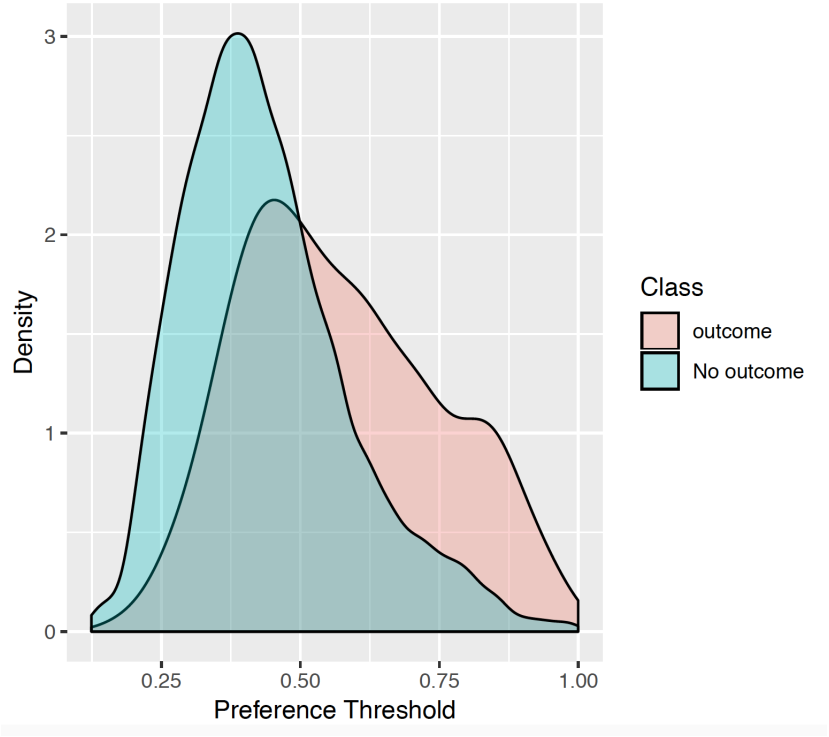



Figure 14.5: Preference distribution plot.

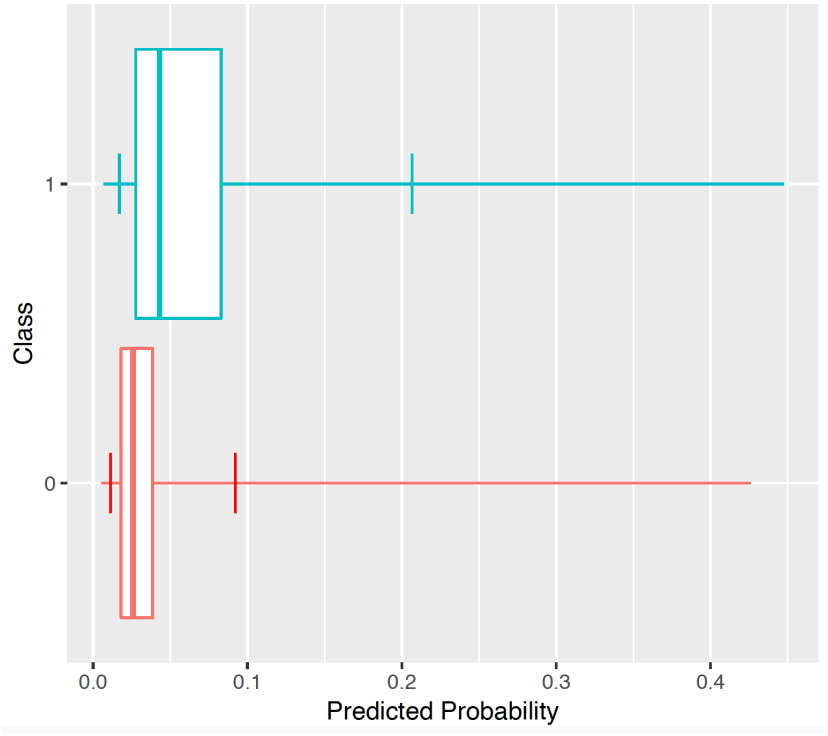



Figure 14.6: Predicted probability distribution.

### 14.4.5 Predicted probability distribution

The prediction distribution box plot shows the predicted risks of the people in the test set with the outcome (blue) and without the outcome (red).

The box plots in Figure 14.6 show that the predicted probability of the outcome is indeed higher for those with the outcome but there is also overlap between the two distribution which lead to an imperfect discrimination.

### 14.4.6 Test-Train similarity

The test-train similarity is assessed by plotting the mean covariate values in the train set against those in the test set for people with and without the outcome.

The results in Figure 14.7 for our example look very promising since the mean values of the covariates are on the diagonal.

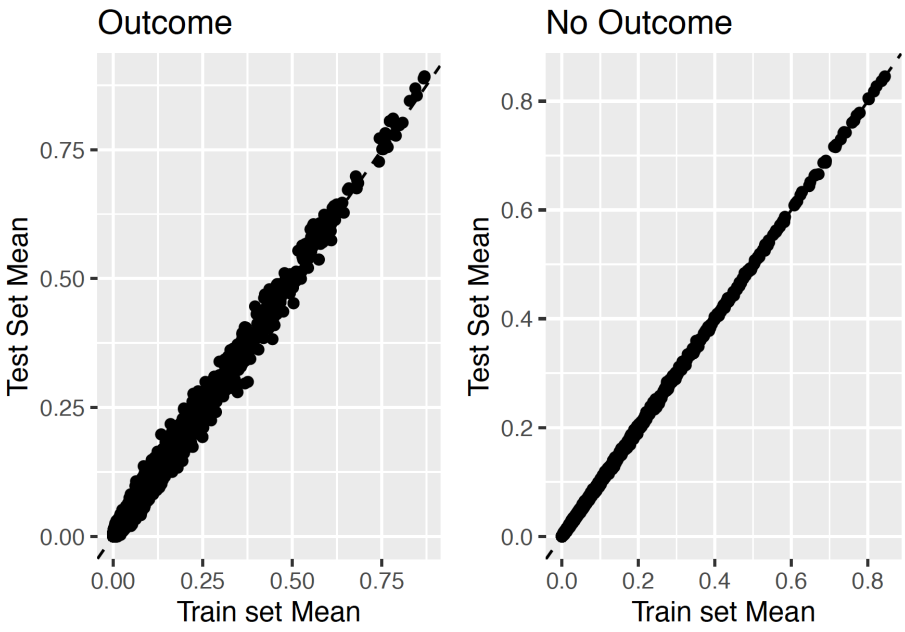



Figure 14.7: Predicted probability distribution.

### 14.4.7 Variable scatter plot

The variable scatter plot shows the mean covariate value for the people with the outcome against the mean covariate value for the people without the outcome. The color of the dots corresponds to the inclusion (green) or exclusion in the model (blue), respectively. It is highly recommended to use the Shiny App since this allows you to hoover over a covariate to show more details (name, value etc).

Figure 14.8 shows that the mean of most of the covariates is higher for subjects with the outcome compared to those without.

### 14.4.8 Precision recall

Precision (P) is defined as the number of true positives (TP) over the number of true positives plus the number of false positives (FP):

$$P = \frac{TP}{TP + FP}$$

Recall (R) is defined as the number of true positives over the number of true positives plus the number of false negatives (FN):

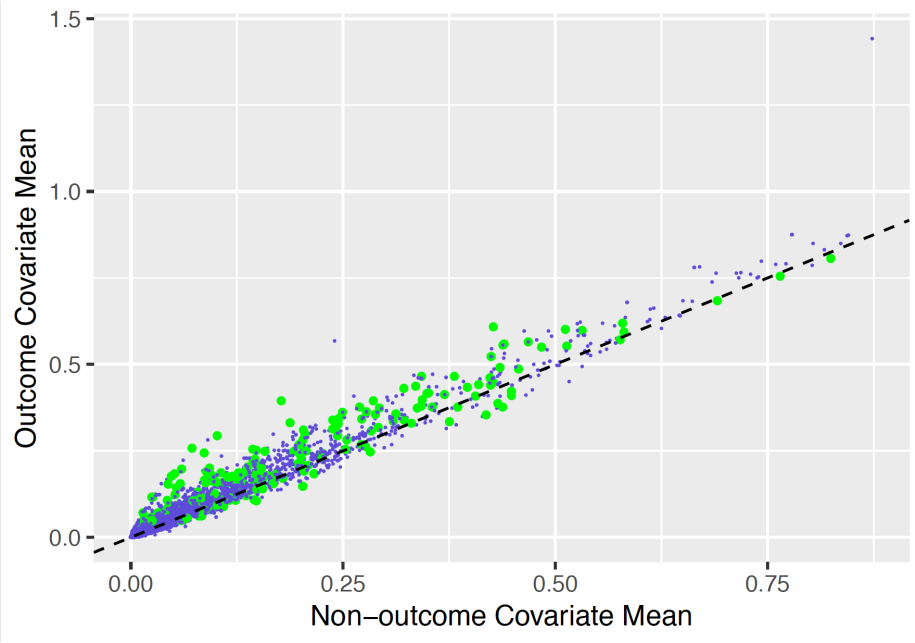



Figure 14.8: Predicted probability distribution.

$$R = \frac{TP}{TP + FN}$$

These quantities are also related to the (F1) score, which is defined as the harmonic mean of precision and recall.

$$F1 = 2 \cdot \frac{P \cdot R}{P + R}$$

Note that the precision can either decrease or increase if the threshold is lowered. Lowering the threshold of a classifier may increase the denominator, by increasing the number of results returned. If the threshold was previously set too high, the new results may all be true positives, which will increase precision. If the previous threshold was about right or too low, further lowering the threshold will introduce false positives, decreasing precision. For Recall the denominator does not depend on the classifier threshold (Tp+Fn is a constant). This means that lowering the classifier threshold may increase recall, by increasing the number of true positive results. It is also possible that lowering the threshold may leave recall unchanged, while the precision fluctuates.

Figure 14.9 shows the tradeoff between precision and recall.

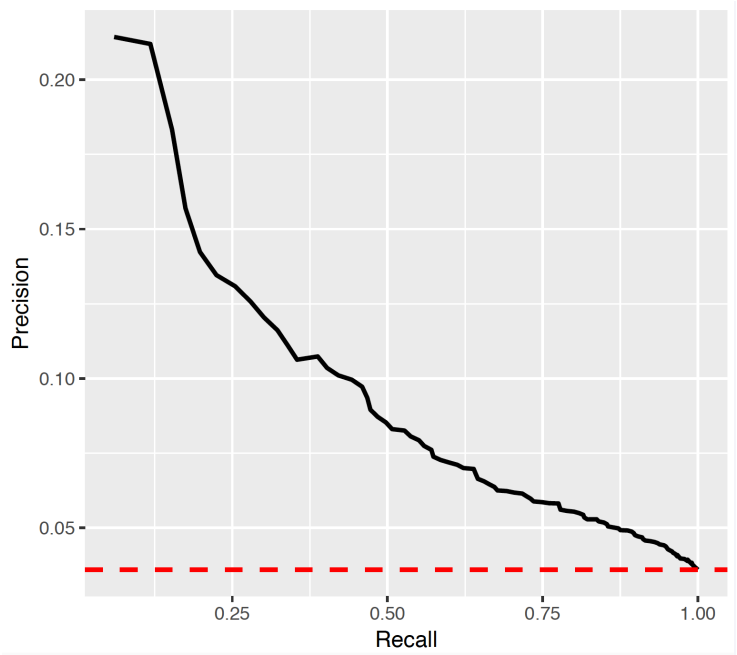



Figure 14.9: Precision-recall plot.

### 14.4.9 Demographic summary

Figure 14.10 shows for females and males the expected and observed risk in different age groups together with a confidence area. The results show that our model is well calibrated across gender and age groups.

## 14.5 External validation

We recommend to always perform external validation, i.e. apply the final model on as much new datasets as feasible and evaluate its performance. Here we assume the data extraction has already been peformed on a second database and stored in the `newData` folder. We load the model we previously fitted from the `model` folder:

```
# load the trained model
plpModel <- loadPlpModel("model")

#load the new plpData and create the population
plpData <- loadPlpData("newData")
```


Figure 14.10: Precision-recall plot.

```
population <- createStudyPopulation(plpData = plpData,
                                     outcomeId = 2,
                                     washoutPeriod = 364,
                                     firstExposureOnly = FALSE,
                                     removeSubjectsWithPriorOutcome = TRUE,
                                     priorOutcomeLookback = 9999,
                                     riskWindowStart = 1,
                                     riskWindowEnd = 365,
                                     addExposureDaysToStart = FALSE,
                                     addExposureDaysToEnd = FALSE,
                                     minTimeAtRisk = 364,
                                     requireTimeAtRisk = TRUE,
                                     includeAllOutcomes = TRUE
)

# apply the trained model on the new data
validationResults <- applyModel(population, plpData, plpModel)
```

To make things easier we also provide the `externalValidatePlp` function for performing external validation that also extracts the required data. This function is described in the package manual.

## 14.6 Journal paper generation

We have added functionality to automatically generate a word document you can use as start of a journal paper. It contains many of the generated study details and results. If you have performed external validation these results will can be added as well. Optionally, you can add a "Table 1" that contains data on many covariates for the target population. You can create the draft journal paper by running this function:

```
createPlpJournalDocument(plpResult = <your plp results>,
                         plpValidation = <your validation results>,
                         plpData = <your plp data>,
                         targetName = "<target population>",
                         outcomeName = "<outcome>",
                         table1 = F,
                         connectionDetails = NULL,
                         includeTrain = FALSE,
                         includeTest = TRUE,
                         includePredictionPicture = TRUE,
                         includeAttritionPlot = TRUE,
                         outputLocation = "<your location>")
```

For more details see the help page of the function.

## 14.7 Excercises

# Part IV

# Evidence Quality

# Chapter 15

# Evidence Quality

> Loss of fidelity begins with the movement of data from the doctor's brain to the medical record.

*Clem McDonald, MD Director, Lister Hill Center for Biomedical Informatics National Library of Medicine, USA*

OHDSI views validation as a holistic set of processes necessary to achieve the highest quality reproducible evidence from diverse data sources.

Four components: - Data quality (data validation) - Clinical validity - Software validity - Method validity

# Chapter 16

# Data Quality

## 16.1 Introduction

Kahn et al. define data quality as consisting of three components: (1) conformance (do data values adhere to do specified standard and formats?; subtypes: value, relational and computational conformance); (2) completeness (are data values present?); and (3) plausibility (are data values believable?; subtypes uniqueness, atemporal; temporal) (Kahn et al., 2016)

Kahn additionaly defines two contexts: verification and validation. Verification focuses on model and data constraints and does not rely on external reference. Validation focuses on data expectations that are derived from comparison to a relative gold standard and uses external knowledge.

| Term | Subtype | Validation example |
|---|---|---|
| Conformance | Value | Providers are only assigned valid medical specialties. |
| | Relational | Prescribing provider identifier is present in drug dispensation data. |
| | Computational | Computed eGFR value conforms to the expected value for a test case patient scenario. |
| Completeness | n/a (no subtypes defined) | A drug product withdrawn from the market at a specific absolute historic date shows expected drop in dispensation. |
| Plausibility | Uniqueness | A zip code for a location does not refer to vastly conflicting geographical areas. |
| | Atemporal | Use of a medication (by age group) for a specific disease agrees with the age pattern for that disease. |
| | Temporal | Temporal pattern of an outbreak of a disease (e.g., Zika) agrees with external source pattern. |

Kahn introduces the term *data quality check* (sometimes refered to as data quality rule) that tests whether data conform to a given requirement (e.g., implausible age of 141 of a patient (due to incorrect birth year or missing death event)). In support of checks, he also defines *data quality measure* (sometimes refered to as pre-computed analysis) as data analysis that supports evaluation of a check. For example, distribution of days of supply by drug concept.

Two types of DQ checks can be distinguished(Weiskopf and Weng, 2013)

- general checks
- study-specific checks

From the point of researcher analyzing the data, the desired situation is that data is free from erros that could have been prevented. *ETL data errors* are errors introduced during extract-tranform-load proces. A special type of ETL data error is *mapping error* that results from incorrect mapping of the data from the source terminology (e.g., Korean national drug terminology) into the target data model's standard terminology (e.g., RxNorm and RxNorm Extension). A *source data error* is an error that is already present in the source data due to various cuases (e.g., human typo during data entry).

Data quality can also be seen as a component in a larger effort refered to as *evidence quality* or *evidence validation*. Data quality would fall in this framework under *data validation*.

## 16.2 Achilles Heel tool

Since 2014, a component of the OHDSI Achilles tool called Heel was used to check data quality.(Huser et al., 2018)

### 16.2.1 Precomputed Analyses

In support of data characterization, Achilles tool pre-computes number of data analyses. Each pre-computed analysis has an analysis ID and a short description of the analysis. For example, "715: Distribution of days_supply by drug_concept_id" or "506: Distribution of age at death by gender". List of all pre-computed analyses (for Achilles version 1.6.3) as available at https://github.com/OHDSI/Achilles/blob/v1.6.3/inst/csv/achilles/achilles_analysis_details.csv

Achilles has more than 170 pre-computed analysis that support not only data quality checks but also general data characterization (outside data quality context) such as data density visualizations. The pre-computations are largely guided by the CDM relational database schema and analyze most terminology-based data columns, such as condition_concept_id or

place_of_service_concept_id. Pre-computations results are stored in table ACHILLES_RESULTS and ACHILLES_RESULTS_DIST.

### 16.2.2 Example DQ check

In complete data about general population, a range of services is provided by a range of providers (with many specialties). A data completness rule with rule_id of 38 evaluates data completness in the PROVIDER table. Checking optional fields in CDM (such as provider specialty) lead to a notification severity output. Analysis Rule 38 triggers a notification if count of distinct specialties <2. It relies on a derived measure `Provider:SpeciatlyCnt`. The rule SQL-formulated logic can be found here: https://github.com/OHDSI/Achilles/blob/v1.6.3/inst/sql/sql_server/heels/serial/rule_38.sql

### 16.2.3 Overview of existing DQ Heel checks

Achilles developers maintain a list of all DQ checks in an overview file. For version 1.6.3, this overview is available here https://github.com/OHDSI/Achilles/blob/v1.6.3/inst/csv/heel/heel_rules_all.csv Each DQ check has a rule_id.

Checks are classified into CDM conformance checks and DQ checks.

Depending on the severity of the problem, the Heel output can be error, warning or notification.

## 16.3 Study-specific checks

The chapter has so far focused on general DQ checks. Such checks are executed regardless of the single research question context. The assumption is that a researcher would formulate additional DQ checks that are required for a specific research question.

We use case studies to demostrate study-specific checks.

### 16.3.1 Outcomes

For an international analysis, part of OHDSI study diagnostics (for a give dataset) may involve checking whether coding practices (that are country specific) affect a cohort definition. A stringent cohort definition may lead to zero cohort size in one (or multiple dataesets).

### 16.3.2 Laboratory data

A diabetes study may utilize HbA1c measurement. A 2018 OHDSI study (https://www.ncbi.nlm.nih.gov/pubmed/30646124) defined a cohort 'HbA1c8Moderate' (see https://github.com/rohit43/DiabetesTxPath/blob/master/inst/settings/CohortsToCreate.csv)

# Chapter 17

# Clinical Validity

# Chapter 18

# Software Validity

*Chapter lead: Martijn Schuemie*

The central question of sofware validity is

> Does the software do what it is expected to do?

In broad strokes there are two approaches to ensure software validity: by using a software development process aimed at creating valid software, and by testing whether the software is valid. Here we focus specifically on the OHDSI Methods Library, the set of R packages used in population-level estimation and patient-level prediction. The OHDSI Population-Level Estimation Workgroup and the OHDSI Patient-Level Prediction Workgroup together are responsible for developing and maintaining the OHDSI Methods Library. The OHDSI Population-Level Estimation Workgroup is headed by Drs. Marc Suchard and Martijn Schuemie. The OHDSI Patient-Level Prediction Workgroup his headed by Drs. Peter Rijnbeek and Jenna Reps.

## 18.1 Software Development Process

The OHDSI Methods Library is developed by the OHDSI community. Proposed changes to the Library are discussed in two venues: The GitHub issue trackers and the OHDSI Forums. Both are open to the public. Any member of the community can contribute software code to the Library, however, final approval of any changes incorporated in the released versions of the software is performed by the OHDSI Population-Level Estimation Workgroup and OHDSI Patient-Level Prediction Workgroup leadership only.

Users can install the Methods Library in R directly from the master branches in the GitHub repositories, or through a system known as 'drat' that is always up-to-date with the master branches. A number of the Methods Library packages

are available through R's Comprehensive R Archive Network (CRAN), and this number is expected to increase over time.

Reasonable software development and testing methodologies are employed by OHDSI to maximize the accuracy, reliability and consistency of the Methods Library performance. Importantly, as the Methods Library is released under the terms of the Apache License V2, all source code underlying the Methods Library, whether it be in R, C++, SQL, or Java is available for peer review by all members of the OHDSI community, and the public in general. Thus, all the functionality embodied within Methods Library is subject to continuous critique and improvement relative to its accuracy, reliability and consistency.

### 18.1.1 Source Code Management

All of the Methods Library's source code is managed in the source code version control system 'git' publicly assessible via GitHub. The OHDSI Methods Library repositories are access controlled. Anyone in the world can view the source code, and any member of the OHDSI community can submit changes through so-called pull requests. Only the OHDSI Population-Level Estimation Workgroup and Patient-Level Prediction Workgroup leadership can approve such request, make changes to the master branches, and release new versions. Continuous logs of code changes are maintained within the GitHub repositories and reflect all aspects of changes in code and documentation. These commit logs are available for public review.

New versions are released by the OHDSI Population-Level Estimation Workgroup and Patient-Level Prediction Workgroup leadership as needed. A new release starts by pushing changes to a master branch with a package version number (as defined in the DESCRIPTION file inside the package) that is greater than the version number of the previous release. This automatically triggers checking and testing of the package. If all tests are passed, the new version is automatically tagged in the version control system and the package is automatically uploaded to the OHDSI drat repository. New versions are numbered using three-component version number:

- New micro versions (e.g. from 4.3.2 to 4.3.3) indicate bug fixes only. No new functionality, and forward and backward compatibility are guaranteed
- New minor versions (e.g. from 4.3.3 to 4.4.0) indicate added functionality. Only backward compatibility is guaranteed
- New major versions (e.g. from 4.4.0 to 5.0.0) indicate major revisions. No guarantees are madef in terms of compatibility

### 18.1.2 Documentation

All packages in the Methods Library are documented through R's internal documentation framework. Each package has a package manual that describes every function available in the package. To promote alignment between the function documentation and the function implementation, the roxygen2 software is used to combine a function's documentation and source code in a single file. The package manual is available on demand through R's command line interface, as a PDF in the package repositories, and as a web page. In addition, many packages also have vignettes that highlight specific use cases of a package. All Method Library source code is available to end users. Feedback from the community is facilitated using GitHub's issue tracking system and the OHDSI Forums.

### 18.1.3 Availability of Current and Historical Archive Versions

Current and historical versions of the Methods Library packages are available in two locations: First, the GitHub version control system contains the full development history of each package, and the state of a package at each point in time can be reconstructed and retrieved. Most importantly, each released version is tagged in GitHub. Second, the released R source packages are stored in the OHDSI GitHub drat repository.

### 18.1.4 Maintenance, Support and Retirement

Each current version of the Methods Library is actively supported by OHDSI with respect to bug reporting, fixes and patches. Issues can be reported through GitHub's issue tracking system, and through the OHDSI forums. Each package has a package manual, and zero, one or several vignettes. Online video tutorials are available, and in-person tutorials are provided from time to time.

### 18.1.5 Qualified Personnel

Members of OHDSI community represent multiple statistical disciplines and are based at academic, not-for-profit and industry-affiliated institutions on multiple continents.

All leaders of the OHDSI Population-Level Estimation Workgroup and OHDSI Patient-Level Prediction Workgroup hold PhDs from accredited academic institutions and have published extensively in peer reviewed journals.

### 18.1.6 Physical and Logical Security

The OHDSI Methods Library is hosted on the GitHub system. GitHub's security measures are described at https://github.com/security. Usernames and passwords are required by all members of the OHDSI community contribute modifications to the Methods Library, and only the Population-Level Estimation Workgroup and Patient-Level Prediction Workgroup leadership can makes changes to the master branches. User accounts are limited in access based upon standard security policies and functional requirements.

### 18.1.7 Disaster Recovery

The OHDSI Methods Library is hosted on the GitHub system. GitHub's disaster recovery facilities are described at https://github.com/security.

## 18.2 Testing

We distinguish between two types of tests performed on the Methods Library: Tests for individual functions in the packages (so-called 'unit tests'), and tests to determine whether analyses implemented using the Methods Library produce reliable and accurate results (we will call this 'method tests').

### 18.2.1 Unit test

A large set of automated validation tests is maintained and upgraded by OHDSI to enable the testing of source code against known data and known results. Each test begins with specifying some simple input data, then executes a function in one of the packages on this input, and evaluates whether the output is exactly what would be expected. For simple functions, the expected result is often obvious (for example when performing propensity score matching on example data containing only a few subjects), for more complicated functions the expected result may be generated using combinations of other functions available in R (for example, Cyclops, our large-scale regression engine, is tested amongst others by comparing results on simple problems with other regression routines in R). We aim for these tests in total to cover 100% of the lines of executable source code. Appendix A lists the locations of the tests in each package. These tests are automatically performed when changes are made to a package (specifically, when changes are pushed to the package repository). Any errors noted during testing automatically trigger emails to the leadership of the Workgroups, and must be resolved prior to release of a new version of a package. The results of the unit tests can be found in the locations specified in Appendix A. The source code and expected results for these tests are available for review and

use in other applications as may be appropriate. These tests are also available to end users and/or system administrators and can be run as part of their installation process to provide further documentation and objective evidence as to the accuracy, reliability and consistency of their installation of the Methods Library.

## 18.3 Conclusions

The purpose of this chapter is to document evidence to provide a high degree of assurance that the Methods Library can be used in observational studies to consistently produce reliable and accurate estimates. Both through adoption of best software development practices during the software lifecycle, as well as continuous extensive testing of individual components of the software and the start-to-finish application of the methods library on a gold standard aim to ensure the validity of the Methods Library. However, use of the Methods Library does not guarantee validity of a study, since validity depends on many other components outside of the Methods Library as well, including appropriate study design, exposure and outcome definitions, and data quality. It is important to note that there is a significant obligation on the part of the end-user's organization to define, create, implement and enforce the Method Library installation, validation and utilization related Standard Operating Procedures (SOPs) within the end-user's environment. These SOPs should define appropriate and reasonable quality control processes to manage end-user related risk within the applicable operating framework. The details and content of any such SOPs are beyond the scope of this document.

# Chapter 19

# Method Validity

*Chapter lead: Martijn Schuemie*

When considering method validity we aim to answer the question

> Is this method valid for answering this question?

Where 'method' includes not only the study design, but als the data and the implementation of the design. Method validity is therefore somewhat of a catch-all; It is often not possible to observe good method validity without good data quality, clinical validity, and software validity. Those aspects of evidence quality should have already been addressed separately before we consider method validity.

The core activity when establishing method validity is evaluating whether important assumptions in the analysis have been met. For example, we assume that propensity-score matching makes two populations comparable, but we need to evaluate whether this is the case. Where possible, empirical tests should be performed to test these assumptions. We can for example generate diagnostics to show that our two populations are indeed comparable on a wide range of characteristics after matching. In OHDSI we have developed a wide range of standardized diagnostics that should be generated and evaluated whenever an analysis is performed. Some of these diagnostics are specific to certain stud designs, whereas others are more generic.

## 19.1 Design-specific diagnostics

For each study design there are diagnostics specific to such a design. Here we review some of the standard diagnostics included in the OHDSI Methods Library R packages. This review is not exhaustive, and we recommend the reader to

consult the documentation for each method to learn about all implemented diagnostics.

### 19.1.1 Diagnostics for cohort method

In the comparative cohort design we compare two cohorts, for example representing two treatment choices, and we want to evaluate whether the treatment choice has an effect on the risk of some outcome of interest. For the effect size estimate w to be valid, it is essential that the two groups are comparable in all relevant aspects except the treatment choice. In observational data, this comparability is by no means guaranteed, and quite often there is a reason why one group gets a treatment while the group does not, leading to fundamental differences between the groups. We often employ propensity scores to make the two groups comparable again, but that assumes there is at least some commonality between the two groups. This assumption can be tested by reviewing the preference score plot as shown in Figure 19.1 (The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups). we can evaluate whether there are patients that had some probability of receiving either treatment. In Figure 19.1 we see large numbers of people on the left and right for whom their treatment choice could have been predicted fairly accurately based on the baseline characteristics, meaning that without adjustment the two groups are incomparable. However, we also observe a substantial area of overlap, the purple area, where people where likely to get either treatment. This suggests that with some adjument, for example using propensity score matching, the two groups can be made comparable. It is important to note that a large overlap can also be due to an unpredictive propensity model, for example because key characteristics were not included in the model. A lack of overlap can be due to including variables directly related to the exposure, such as including the procedure code for an injection if one of the treatments is an injectable. This needs to be ruled out by examining the propensity model.

Once we believe there is some hope of making the two groups comparable, we need to evaluate whether we indeed succeed by examining a large number of baseline characteristics after adjustment. Figure 19.2 shows the absolute standardized difference of the mean between the two groups for a large number of covariates, both before and after matching on the propensity score. A rule-of-thumb that is often used is to consider any variabel with absolute standardized difference of the mean $< 0.1$ to be in balance. We see in Figure 19.2 that many covariates show imbalance before matching, but matching achieves balance on all covariates.

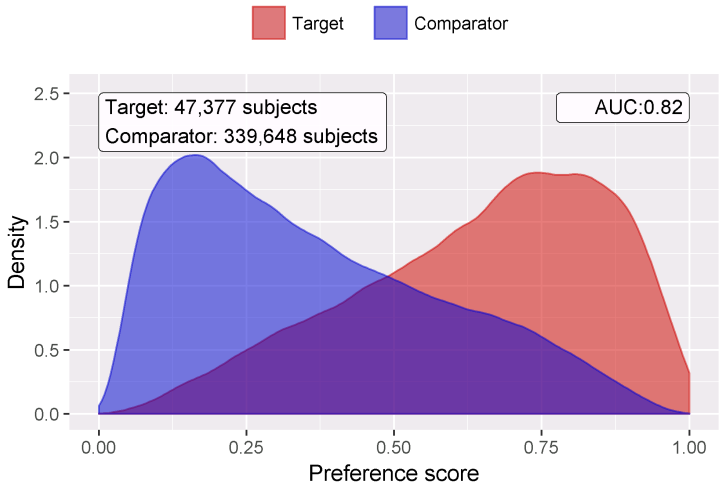



Figure 19.1: Preference score distribution. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other.

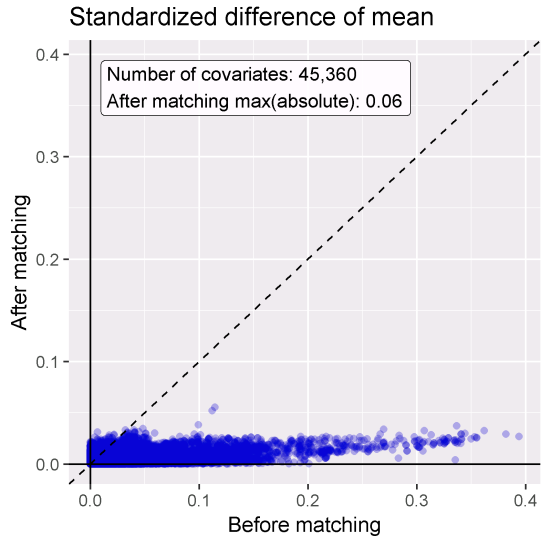



Figure 19.2: Covariate balance before and after matching. Each dot represents the standardizes difference of means for a single covariate before and after matching on the propensity score.

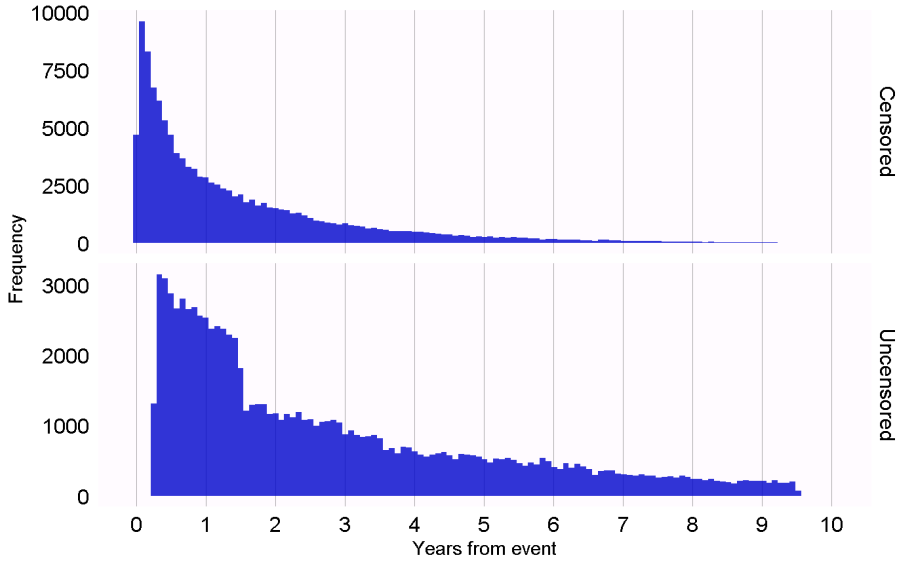



Figure 19.3: Time to observation end for those that are censored, and those that uncensored.

### 19.1.2 Diagnostics for SCCS

One assumption in the self-controlled case series (SCCS) design is that the end of observation is independent of the outcome. This assumption is often violated in the case of serious, potentially lethal, events such as myocardial infarction. We can evaluate whether the assumption holds by generating the plot shown in Figure 19.3, which shows a histograms of the time to obsevation period end for those that are censored, and those that uncensored. In our data we consider those whose observation period ends at the end date of data capture (the date when observation stopped for the entire data base, for example the date of extraction, or the study end date) to be uncensored, and all others to be censored. In Figure 19.3 we see only minor differences between the two distributions, suggesting our assumptions holds.

## 19.2 Diagnostics for all estimation

Some diagnostics are applicable for all population-level estimation studies. These require the inclusion of control hypotheses, research questions where the answer is already known. We can then evaluate whether our design produces results in line with the truth. Controls can be divided into negative controls and positive controls.

### 19.2.1 Negative and positive controls

Negative controls are exposure-outcome pairs where one believes no causal effect exists, and including negative controls or 'falsification endpoints' (Prasad and Jena, 2013) has been recommended as a means to detect confounding (Lipsitch et al., 2010), selection bias and measurement error (Arnold et al., 2016). For example, in one study (Zaadstra et al., 2008) investigating the relationship between childhood diseases and later multiple sclerosis (MS), the authors include three negative controls that are not believed to cause MS: a broken arm, concussion, and tonsillectomy. Two of these three controls produce statistically significant associations with MS, suggesting that the study may be biased. We should select negative controls that are comparable to our hypothesis of interest, which means we typically select exposure-outcome pairs that either have the same exposure as the hypothesis of interest (so-called 'outcome controls') or the same outcome ('exposure controls). In OHDSI we have developed a semi-automated procedure for selecting negative controls (Voss et al., 2016). In brief, information from literature, product labels, and spontaneous reporting is automatically extracted and synthesized to produce a candidate list of outcomes with no known links with any hypertension treatment. We rank-order this list by prevalence in an observational database and manually review these in order.

To understand the behavior of a method when the true relative risk is smaller or greater than one requires the use of positive controls, where the null is believed to not be true. Unfortunately, real positive controls for observational research tend to be problematic for three reasons. First, in most research contexts, for example when comparing the effect of two treatments, there is a paucity of positive controls relevant for that specific context. Second, even if positive controls are available, the magnitude of the effect size may not be known with great accuracy, and often depends on the population in which one measures it. Third, when treatments are widely known to cause a particular outcome, this shapes the behavior of physicians prescribing the treatment, for example by taking actions to mitigate the risk of unwanted outcomes, thereby rendering the positive controls useless as a means for evaluation (Noren et al., 2014). In OHDSI we therefore use synthetic positive controls (Schuemie et al., 2018), created by modifying a negative control through injection of additional, simulated occurrences of the outcome during the time at risk of the exposure. One issue that stands important is the preservation of confounding. The negative controls may show strong confounding, but if we inject additional outcomes randomly, these new outcomes will not be confounded, and we may therefore be optimistic in our evaluation of our capacity to deal with confounding for positive controls. To preserve confounding, we want the new outcomes to show similar associations with baseline subject-specific covariates as the original outcomes. To achieve this, we fit large-scale predictive models for each negative control using $L_1$ regularized survival regression (Suchard et al., 2013). We insert new outcomes by drawing from the per-subject predicted probabilities within the exposed population until we achieve the desired incidence rate ratio. Figure 19.4 depicts this

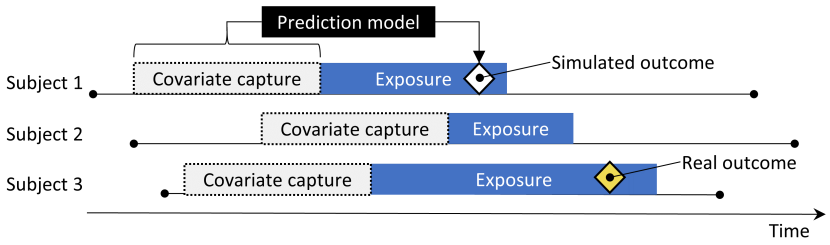



Figure 19.4: Synthesizing positive controls from negative controls.

process.

### 19.2.2 Metrics

Based on the estimates of a particular method for the negative and positive controls, we can then understand the operating characteristic by computing a range of metrics, for example:

- **Area Under the receiver operator Curve (AUC)**: the ability to discriminate between positive and negative controls.
- **Coverage**: how often the true effect size is within the 95% confidence interval.
- **Mean precision**: precision is computed as 1 / (standard error)2, higher precision means narrower confidence intervals. We can use the geometric mean to account for the skewed distribution of the precision.
- **Mean squared error (MSE)**: Mean squared error between the log of the effect size point-estimate and the log of the true effect size.
- **Type 1 error**: For negative controls, how often was the null rejected (at alpha = 0.05). This is equivalent to the false positive rate and 1 - specificity.
- **Type 2 error**: For positive controls, how often was the null not rejected (at alpha = 0.05). This is equivalent to the false negative rate and 1 - sensitivity.
- **Non-estimable**: For how many of the controls was the method unable to produce an estimate? There can be various reasons why an estimate cannot be produced, for example because there were no subjects left after propensity score matching, or because no subjects remained having the outcome.

Depending on our use case, we can evaluate whether these operating characteristics are suitable for our goal. For example, if we wish to perform signal detection, we may care about type I and type II error, or if we are willing to modify our alpha threshold, we may inspect the AUC instead.

### 19.2.3 Empirical calibration

Often the type I error (at alpha = 0.05) is larger than 5%, and the coverage of the 95% confidence interval is lower than 95%. OHDSI has developed processes for calibration p-values and confidence intervals to restore these operating characteristics to nominal.

For p-value calibration (Schuemie et al., 2014) we estimate the empirical null distribution using the observed estimates for negative controls; We fit a Gaussian probability distribution to the estimates, taking into account the sampling error of each estimate. Using this null distribution we then compute the calibrated p-value for the hypothesis of interest, considering both random error and systematic error.

For confidence inteval calibration (Schuemie et al., 2018) we estimate a systematic error distribution, which we assume is Gaussian with a mean and standard deviation linearly related to the logarithm of the true effect size. Using the estimated distribution, we then generate calibrated confidence intervals considering both random and systematic error. Typically, but not necessarily, the calibrated confidence interval is wider than the nominal confidence interval, reflecting the problems unaccounted for in the standard procedure (such as unmeasured confounding, selection bias and measurement error) but accounted for in the calibration.

Both p-value calibration and confidence interval calibration are implemented in the EmpiricalCalibration package.

### 19.2.4 Replication across sites

Another form of method validation can come from executing the study across several different databases that possibly represent different populations, different health care systems, and different data capture processes. Prior research has shown that executing the same study design across different databases can produce vastly different effect size estimates (Madigan et al., 2013), suggesting the design does not adequately address the different biases found in the different databases. However, not observing heterogeneity of effects does not guarantee an unbiased estimate. It is not unlikely that all databases share a similar bias, and that all estimates are therefore consistently wrong.

### 19.2.5 Sensitivity analyses

When designing a study there are often design choices that are uncertain. For example, should propensity score matchign of stratification be used? If stratification is used, how many strata? What is the appropriate time-at-risk? When faced with such uncertainty, one solution is to evaluate various options, and

observe the sensitivity of the results to the design choice. If the estimate remains the same under various options, we can say the study is robust to the uncertainty.

This definition of sensitivity analysis should not be confused with the definitions used by others such as Rosenbaum (2005), who define sensitivity analysis to 'appraise how the conclusions of a study might be altered by hidden biases of various magnitudes'.

## 19.3 Diagnostics for all prediction

Todo

## 19.4 Method validation in practice

Example: risk of angioedema and AMI in new users of ACE inhibitors compared to new users of thiazide and thiazide-like diuretics

How to select negative controls using ATLAS

- Create a concept set containing both target and comparator exposure concepts.
- Go to the 'Explore evidence' tab and click 'Generate'
- Manually review negative controls, considering
- Does the drug not cause the outcome?
- Does the drug not prevent / treat the outcome?
- Does the negative control appear in the data?

Include negative and positive controls.

Compute metrics

- Need to add functions to MethodEvaluation

Generate calibration plots

Calibrate CI and p-value

- Use EmpiricalCalibration package

## 19.5 Advanced: OHDSI Methods Benchmark

Todo: add text on OHDSI Methods Benchmark

# Part V

# OHDSI Studies

# Chapter 20

# Study steps

Writing the protocol, OHDSI style: http://www.ohdsi.org/web/wiki/lib/exe/fetch.php?media=projects:workgroups:wg_study_protocols_eastern_hemisphere.pptx

Study reproducibility (Martijn has some slides that might help: http://www.ohdsi.org/web/wiki/lib/exe/fetch.php?media=projects:workgroups:wg_study_reproducability.pptx )

# Chapter 21

# OHDSI Network Research

Contributors: Greg Klebanov, Vojtech Huser, list others

What is OHDSI Network?

- OHDSI Community and Network Research
- International Open Science Networks
- OHDSI US
- OHDSI EU and EHDEN
- OHDSI APAC

OHDSI Network Study Process

- Goals
- Workflow Overview
- Structure of Studies
- Protocol and IRB issues
- Existing framework (de-identified [time shifted] OMOP dataset under existing IRB protocol
- Overcoming Network Study Challenges
- Data Privacy, Security and Compliance
- Data Quality
- Running OHDSI Methods in Isolated Environment
- OMOP CDM Versioning

Tools, Platforms and Study Automation * OHDSI Methods support for Network Studies * LEGEND (should we have it here?) * OHDSI ARACHNE Network Platform

Opportunities, future trends and Roadmap

## 21.1 OHDSI Network Study Examples

### 21.1.1 Endometriosis study

An endometriosis characterization study (available at https://github.com/molliemckillop/Endometriosis-Phenotype-Characterization) works with two cohorts. They are defined in cohorts.csv file (see here https://github.com/molliemckillop/Endometriosis-Phenotype-Characterization/blob/master/inst/settings/cohorts.csv).

After creating a cohort table, it is populated by executing this command here by infering a name of a '.sql' file from the previously defined cohort file. A createCohorts function is executed next. (see https://github.com/molliemckillop/Endometriosis-Phenotype-Characterization/blob/master/R/createCohorts.R). An SQL file that is generated by Atlas populates the cohort table with specific person_ids that fulfill the cohort definition.

## 21.2 Excercises

### 21.2.1 Defining a cohort

Q: Study the code for the x study and determine whether the cohort definition is available on the public OHDSI server. It if it, what is the cohort ID there?

A:

# Appendix A

# Glossary

Cohort A cohort is a list of person_ids with start and end date. It is stored in a study specific cohort table or a CDM specified cohort table can also be used. Cohort can be represented as .json file. It is used for import and export but not during an analysis. OHDSI tools use SQL so Atlas also generates a .sql file that creates the cohort during analysis.

Parametized SQL code An SQL code that allows for use of parameters. Parameters are prefixed with @. Such code has to be "rendered". Synonym: OHDSI SQL code.

# Appendix B

# Cohort definitions

This Appendix contains cohort definitions used throughout the book.

## B.1 ACE inhibitors

**Initial Event Cohort**

People having any of the following:

- a drug exposure of *ACE inhibitors* (Table B.1) for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: all events per person.

Limit qualifying cohort to: all events per person.

**End Date Strategy**

Custom Drug Era Exit Criteria This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of *ACE inhibitors* (Table B.1)

- allowing 30 days between exposures
- adding 0 days after exposure end

**Cohort Collapse Strategy**

Collapse cohort by era with a gap size of 30 days.

**Concept Set Definitions**

Table B.1: ACE inhibitors

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 1308216 | Lisinopril | NO | YES | NO |
| 1310756 | moexipril | NO | YES | NO |
| 1331235 | quinapril | NO | YES | NO |
| 1334456 | Ramipril | NO | YES | NO |
| 1335471 | benazepril | NO | YES | NO |
| 1340128 | Captopril | NO | YES | NO |
| 1341927 | Enalapril | NO | YES | NO |
| 1342439 | trandolapril | NO | YES | NO |
| 1363749 | Fosinopril | NO | YES | NO |
| 1373225 | Perindopril | NO | YES | NO |

## B.2 New users of ACE inhibitors as first-line monotherapy for hypertension

**Initial Event Cohort**

People having any of the following:

- a drug exposure of *ACE inhibitors* (Table B.2) for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

**Inclusion Rules**

Inclusion Criteria #1: has hypertension diagnosis in 1 yr prior to treatment

Having all of the following criteria:

- at least 1 occurrences of a condition occurrence of *Hypertensive disorder* (Table B.3) where event starts between 365 days Before and 0 days After index start date

Inclusion Criteria #2: Has no prior antihypertensive drug exposures in medical history

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *Hypertension drugs* (Table B.4) where event starts between all days Before and 1 days Before index start date

Inclusion Criteria #3: Is only taking ACE as monotherapy, with no concomitant combination treatments

Having all of the following criteria:

- exactly 1 distinct occurrences of a drug era of *Hypertension drugs* (Table B.4) where event starts between 0 days Before and 7 days After index start date

Limit qualifying cohort to: earliest event per person.

**End Date Strategy**

Custom Drug Era Exit Criteria. This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of *ACE inhibitors* (Table B.2)

- allowing 30 days between exposures
- adding 0 days after exposure end

**Cohort Collapse Strategy**

Collapse cohort by era with a gap size of 0 days.

**Concept Set Definitions**

Table B.2: ACE inhibitors

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 1308216 | Lisinopril | NO | YES | NO |
| 1310756 | moexipril | NO | YES | NO |
| 1331235 | quinapril | NO | YES | NO |
| 1334456 | Ramipril | NO | YES | NO |
| 1335471 | benazepril | NO | YES | NO |
| 1340128 | Captopril | NO | YES | NO |
| 1341927 | Enalapril | NO | YES | NO |
| 1342439 | trandolapril | NO | YES | NO |
| 1363749 | Fosinopril | NO | YES | NO |
| 1373225 | Perindopril | NO | YES | NO |

Table B.3: Hypertensive disorder

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 316866 | Hypertensive disorder | NO | YES | NO |

Table B.4: Hypertension drugs

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 904542 | Triamterene | NO | YES | NO |
| 907013 | Metolazone | NO | YES | NO |
| 932745 | Bumetanide | NO | YES | NO |
| 942350 | torsemide | NO | YES | NO |
| 956874 | Furosemide | NO | YES | NO |
| 970250 | Spironolactone | NO | YES | NO |
| 974166 | Hydrochlorothiazide | NO | YES | NO |
| 978555 | Indapamide | NO | YES | NO |
| 991382 | Amiloride | NO | YES | NO |
| 1305447 | Methyldopa | NO | YES | NO |
| 1307046 | Metoprolol | NO | YES | NO |
| 1307863 | Verapamil | NO | YES | NO |
| 1308216 | Lisinopril | NO | YES | NO |
| 1308842 | valsartan | NO | YES | NO |
| 1309068 | Minoxidil | NO | YES | NO |
| 1309799 | eplerenone | NO | YES | NO |
| 1310756 | moexipril | NO | YES | NO |
| 1313200 | Nadolol | NO | YES | NO |
| 1314002 | Atenolol | NO | YES | NO |
| 1314577 | nebivolol | NO | YES | NO |
| 1317640 | telmisartan | NO | YES | NO |
| 1317967 | aliskiren | NO | YES | NO |
| 1318137 | Nicardipine | NO | YES | NO |
| 1318853 | Nifedipine | NO | YES | NO |
| 1319880 | Nisoldipine | NO | YES | NO |
| 1319998 | Acebutolol | NO | YES | NO |
| 1322081 | Betaxolol | NO | YES | NO |
| 1326012 | Isradipine | NO | YES | NO |
| 1327978 | Penbutolol | NO | YES | NO |
| 1328165 | Diltiazem | NO | YES | NO |
| 1331235 | quinapril | NO | YES | NO |
| 1332418 | Amlodipine | NO | YES | NO |
| 1334456 | Ramipril | NO | YES | NO |
| 1335471 | benazepril | NO | YES | NO |
| 1338005 | Bisoprolol | NO | YES | NO |
| 1340128 | Captopril | NO | YES | NO |
| 1341238 | Terazosin | NO | YES | NO |
| 1341927 | Enalapril | NO | YES | NO |
| 1342439 | trandolapril | NO | YES | NO |
| 1344965 | Guanfacine | NO | YES | NO |
| 1345858 | Pindolol | NO | YES | NO |
| 1346686 | eprosartan | NO | YES | NO |

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 1346823 | carvedilol | NO | YES | NO |
| 1347384 | irbesartan | NO | YES | NO |
| 1350489 | Prazosin | NO | YES | NO |
| 1351557 | candesartan | NO | YES | NO |
| 1353766 | Propranolol | NO | YES | NO |
| 1353776 | Felodipine | NO | YES | NO |
| 1363053 | Doxazosin | NO | YES | NO |
| 1363749 | Fosinopril | NO | YES | NO |
| 1367500 | Losartan | NO | YES | NO |
| 1373225 | Perindopril | NO | YES | NO |
| 1373928 | Hydralazine | NO | YES | NO |
| 1386957 | Labetalol | NO | YES | NO |
| 1395058 | Chlorthalidone | NO | YES | NO |
| 1398937 | Clonidine | NO | YES | NO |
| 40226742 | olmesartan | NO | YES | NO |
| 40235485 | azilsartan | NO | YES | NO |

## B.3 Acute myocardial infarction (AMI)

**Initial Event Cohort**

People having any of the following:

- a condition occurrence of *Acute myocardial Infarction* (Table B.5)

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

For people matching the Primary Events, include: Having any of the following criteria:

- at least 1 occurrences of a visit occurrence of *Inpatient or ER visit* (Table B.6) where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: all events per person.

Limit qualifying cohort to: all events per person.

**End Date Strategy**

Date Offset Exit Criteria. This cohort defintion end date will be the index event's start date plus 7 days

**Cohort Collapse Strategy**

Collapse cohort by era with a gap size of 180 days.

**Concept Set Definitions**

Table B.5: Inpatient or ER visit

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 314666 | Old myocardial infarction | YES | YES | NO |
| 4329847 | Myocardial infarction | NO | YES | NO |

Table B.6: Inpatient or ER visit

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 262 | Emergency Room and Inpatient Visit | NO | YES | NO |
| 9201 | Inpatient Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | NO | YES | NO |

## B.4 Angioedema

**Initial Event Cohort**

People having any of the following:

- a condition occurrence of *Angioedema* (Table B.7)

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

For people matching the Primary Events, include: Having any of the following criteria:

- at least 1 occurrences of a visit occurrence of *Inpatient or ER visit* (Table B.8) where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: all events per person.

Limit qualifying cohort to: all events per person.

**End Date Strategy**

This cohort defintion end date will be the index event's start date plus 7 days

**Cohort Collapse Strategy**

Collapse cohort by era with a gap size of 30 days.

**Concept Set Definitions**

Table B.7: Angioedema

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 432791 | Angioedema | NO | YES | NO |

Table B.8: Inpatient or ER visit

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 262 | Emergency Room and Inpatient Visit | NO | YES | NO |
| 9201 | Inpatient Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | NO | YES | NO |

## B.5 New users of Thiazide-like diuretics as first-line monotherapy for hypertension

**Initial Event Cohort**

People having any of the following:

- a drug exposure of *Thiazide or thiazide-like diuretic* (Table B.9) for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

**Inclusion Rules**

Inclusion Criteria #1: has hypertension diagnosis in 1 yr prior to treatment

Having all of the following criteria:

- at least 1 occurrences of a condition occurrence of *Hypertensive disorder* (Table B.10) where event starts between 365 days Before and 0 days After index start date

Inclusion Criteria #2: Has no prior antihypertensive drug exposures in medical history

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *Hypertension drugs* (Table B.11) where event starts between all days Before and 1 days Before index start date

Inclusion Criteria #3: Is only taking ACE as monotherapy, with no concomitant combination treatments

Having all of the following criteria:

- exactly 1 distinct occurrences of a drug era of *Hypertension drugs* (Table B.11) where event starts between 0 days Before and 7 days After index start date

Limit qualifying cohort to: earliest event per person.

**End Date Strategy**

Custom Drug Era Exit Criteria. This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of *Thiazide or thiazide-like diuretic* (Table B.9)

- allowing 30 days between exposures
- adding 0 days after exposure end

**Cohort Collapse Strategy**

Collapse cohort by era with a gap size of 0 days.

**Concept Set Definitions**

Table B.9: Thiazide or thiazide-like diuretic

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 907013 | Metolazone | NO | YES | NO |
| 974166 | Hydrochlorothiazide | NO | YES | NO |
| 978555 | Indapamide | NO | YES | NO |
| 1395058 | Chlorthalidone | NO | YES | NO |

Table B.10: Hypertensive disorder

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 316866 | Hypertensive disorder | NO | YES | NO |

Table B.11: Hypertension drugs

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 904542 | Triamterene | NO | YES | NO |
| 907013 | Metolazone | NO | YES | NO |

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 932745 | Bumetanide | NO | YES | NO |
| 942350 | torsemide | NO | YES | NO |
| 956874 | Furosemide | NO | YES | NO |
| 970250 | Spironolactone | NO | YES | NO |
| 974166 | Hydrochlorothiazide | NO | YES | NO |
| 978555 | Indapamide | NO | YES | NO |
| 991382 | Amiloride | NO | YES | NO |
| 1305447 | Methyldopa | NO | YES | NO |
| 1307046 | Metoprolol | NO | YES | NO |
| 1307863 | Verapamil | NO | YES | NO |
| 1308216 | Lisinopril | NO | YES | NO |
| 1308842 | valsartan | NO | YES | NO |
| 1309068 | Minoxidil | NO | YES | NO |
| 1309799 | eplerenone | NO | YES | NO |
| 1310756 | moexipril | NO | YES | NO |
| 1313200 | Nadolol | NO | YES | NO |
| 1314002 | Atenolol | NO | YES | NO |
| 1314577 | nebivolol | NO | YES | NO |
| 1317640 | telmisartan | NO | YES | NO |
| 1317967 | aliskiren | NO | YES | NO |
| 1318137 | Nicardipine | NO | YES | NO |
| 1318853 | Nifedipine | NO | YES | NO |
| 1319880 | Nisoldipine | NO | YES | NO |
| 1319998 | Acebutolol | NO | YES | NO |
| 1322081 | Betaxolol | NO | YES | NO |
| 1326012 | Isradipine | NO | YES | NO |
| 1327978 | Penbutolol | NO | YES | NO |
| 1328165 | Diltiazem | NO | YES | NO |
| 1331235 | quinapril | NO | YES | NO |
| 1332418 | Amlodipine | NO | YES | NO |
| 1334456 | Ramipril | NO | YES | NO |
| 1335471 | benazepril | NO | YES | NO |
| 1338005 | Bisoprolol | NO | YES | NO |
| 1340128 | Captopril | NO | YES | NO |
| 1341238 | Terazosin | NO | YES | NO |
| 1341927 | Enalapril | NO | YES | NO |
| 1342439 | trandolapril | NO | YES | NO |
| 1344965 | Guanfacine | NO | YES | NO |
| 1345858 | Pindolol | NO | YES | NO |
| 1346686 | eprosartan | NO | YES | NO |
| 1346823 | carvedilol | NO | YES | NO |
| 1347384 | irbesartan | NO | YES | NO |
| 1350489 | Prazosin | NO | YES | NO |
| 1351557 | candesartan | NO | YES | NO |

| Concept Id | Concept Name | Excluded | Descendants | Mapped |
|---|---|---|---|---|
| 1353766 | Propranolol | NO | YES | NO |
| 1353776 | Felodipine | NO | YES | NO |
| 1363053 | Doxazosin | NO | YES | NO |
| 1363749 | Fosinopril | NO | YES | NO |
| 1367500 | Losartan | NO | YES | NO |
| 1373225 | Perindopril | NO | YES | NO |
| 1373928 | Hydralazine | NO | YES | NO |
| 1386957 | Labetalol | NO | YES | NO |
| 1395058 | Chlorthalidone | NO | YES | NO |
| 1398937 | Clonidine | NO | YES | NO |
| 40226742 | olmesartan | NO | YES | NO |
| 40235485 | azilsartan | NO | YES | NO |

# Bibliography

Arnold, B. F., Ercumen, A., Benjamin-Chung, J., and Colford, J. M. (2016). Brief Report: Negative Controls to Detect Selection Bias and Measurement Bias in Epidemiologic Studies. *Epidemiology*, 27(5):637–641.

Byrd, J. B., Adam, A., and Brown, N. J. (2006). Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am*, 26(4):725–737.

Cicardi, M., Zingale, L. C., Bergamaschini, L., and Agostoni, A. (2004). Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch. Intern. Med.*, 164(8):910–913.

Engel, C. and Fischer, C. (2015). Breast cancer risks and risk prediction models. *Breast Care (Basel)*, 10(1):7–12.

Farrington, C. P. (1995). Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics*, 51(1):228–235.

Farrington, C. P., Anaya-Izquierdo, K., Whitaker, H. J., Hocine, M. N., Douglas, I., and Smeeth, L. (2011). Self-controlled case series analysis with event-dependent observation periods. *Journal of the American Statistical Association*, 106(494):417–426.

Hernan, M. A. and Robins, J. M. (2016). Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am. J. Epidemiol.*, 183(8):758–764.

Huser, V., Kahn, M. G., Brown, J. S., and Gouripeddi, R. (2018). Methods for examining data quality in healthcare integrated data repositories. *Pacific Symposium on Biocomputing. Pacific Symposium on Biocomputing*, 23:628–633.

Kahn, M. G., Callahan, T. J., Barnard, J., Bauck, A. E., Brown, J., Davidson, B. N., Estiri, H., Goerg, C., Holve, E., Johnson, S. G., Liaw, S.-T., Hamilton-Lopez, M., Meeker, D., Ong, T. C., Ryan, P., Shang, N., Weiskopf, N. G., Weng, C., Zozus, M. N., and Schilling, L. (2016). A Harmonized Data Quality

Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. *EGEMS (Washington, DC)*, 4(1):1244.

Lee, K. L., Woodlief, L. H., Topol, E. J., Weaver, W. D., Betriu, A., Col, J., Simoons, M., Aylward, P., Van de Werf, F., and Califf, R. M. (1995). Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*, 91(6):1659–1668.

Lipsitch, M., Tchetgen Tchetgen, E., and Cohen, T. (2010). Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*, 21(3):383–388.

Maclure, M. (1991). The case-crossover design: a method for studying transient effects on the risk of acute events. *Am. J. Epidemiol.*, 133(2):144–153.

Madigan, D., Ryan, P. B., Schuemie, M., Stang, P. E., Overhage, J. M., Hartzema, A. G., Suchard, M. A., DuMouchel, W., and Berlin, J. A. (2013). Evaluating the impact of database heterogeneity on observational study results. *Am. J. Epidemiol.*, 178(4):645–651.

Magid, D. J., Shetterly, S. M., Margolis, K. L., Tavel, H. M., O'Connor, P. J., Selby, J. V., and Ho, P. M. (2010). Comparative effectiveness of angiotensin-converting enzyme inhibitors versus beta-blockers as second-line therapy for hypertension. *Circ Cardiovasc Qual Outcomes*, 3(5):453–458.

Nguyen, N. D., Frost, S. A., Center, J. R., Eisman, J. A., and Nguyen, T. V. (2008). Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int*, 19(10):1431–1444.

Noren, G. N., Caster, O., Juhlin, K., and Lindquist, M. (2014). Zoo or savannah? Choice of training ground for evidence-based pharmacovigilance. *Drug Saf*, 37(9):655–659.

Norman, J. L., Holmes, W. L., Bell, W. A., and Finks, S. W. (2013). Life-threatening ACE inhibitor-induced angioedema after eleven years on lisinopril. *J Pharm Pract*, 26(4):382–388.

O'Mara, N. B. and O'Mara, E. M. (1996). Delayed onset of angioedema with angiotensin-converting enzyme inhibitors: case report and review of the literature. *Pharmacotherapy*, 16(4):675–679.

Perel, P., Edwards, P., Wentz, R., and Roberts, I. (2006). Systematic review of prognostic models in traumatic brain injury. *BMC Med Inform Decis Mak*, 6:38.

Perkins, N. J., Cole, S. R., Harel, O., Tchetgen Tchetgen, E. J., Sun, B., Mitchell, E. M., and Schisterman, E. F. (2017). Principled approaches to missing data in epidemiologic studies. *American journal of epidemiology*, 187(3):568–575.

Powers, B. J., Coeytaux, R. R., Dolor, R. J., Hasselblad, V., Patel, U. D., Yancy, W. S., Gray, R. N., Irvine, R. J., Kendrick, A. S., and Sanders, G. D. (2012). Updated report on comparative effectiveness of ACE inhibitors, ARBs, and direct renin inhibitors for patients with essential hypertension: much more data, little new information. *J Gen Intern Med*, 27(6):716–729.

Prasad, V. and Jena, A. B. (2013). Prespecified falsification end points: can they validate true observational associations? *JAMA*, 309(3):241–242.

Reps, J. M., Schuemie, M. J., Suchard, M. A., Ryan, P. B., and Rijnbeek, P. R. (2018). Design and implementation of a standardized framework to generate and evaluate patient-level prediction models using observational healthcare data. *Journal of the American Medical Informatics Association*, 25(8):969–975.

Rosenbaum, P. and Rubin, D. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70:41–55.

Rosenbaum, P. R. (2005). *Sensitivity Analysis in Observational Studies*. American Cancer Society.

Ryan, P. B., Schuemie, M. J., and Madigan, D. (2013). Empirical performance of a self-controlled cohort method: lessons for developing a risk identification and analysis system. *Drug Saf*, 36 Suppl 1:95–106.

Sabroe, R. A. and Black, A. K. (1997). Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. *Br. J. Dermatol.*, 136(2):153–158.

Schuemie, M. J., Hripcsak, G., Ryan, P. B., Madigan, D., and Suchard, M. A. (2018). Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proc. Natl. Acad. Sci. U.S.A.*, 115(11):2571–2577.

Schuemie, M. J., Ryan, P. B., DuMouchel, W., Suchard, M. A., and Madigan, D. (2014). Interpreting observational studies: why empirical calibration is needed to correct p-values. *Stat Med*, 33(2):209–218.

Simpson, S. E., Madigan, D., Zorych, I., Schuemie, M. J., Ryan, P. B., and Suchard, M. A. (2013). Multiple self-controlled case series for large-scale longitudinal observational databases. *Biometrics*, 69(4):893–902.

Suchard, M. A., Simpson, S. E., Zorych, I., Ryan, P., and Madigan, D. (2013). Massive parallelization of serial inference algorithms for a complex generalized linear model. *ACM Trans. Model. Comput. Simul.*, 23(1):10:1–10:17.

Suissa, S. (1995). The case-time-control design. *Epidemiology*, 6(3):248–253.

Thompson, T. and Frable, M. A. (1993). Drug-induced, life-threatening angioedema revisited. *Laryngoscope*, 103(1 Pt 1):10–12.

Tian, Y., Schuemie, M. J., and Suchard, M. A. (2018). Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *Int J Epidemiol*, 47(6):2005–2014.

Toh, S., Reichman, M. E., Houstoun, M., Ross Southworth, M., Ding, X., Hernandez, A. F., Levenson, M., Li, L., McCloskey, C., Shoaibi, A., Wu, E., Zornberg, G., and Hennessy, S. (2012). Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch. Intern. Med.*, 172(20):1582–1589.

Vandenbroucke, J. P. and Pearce, N. (2012). Case-control studies: basic concepts. *Int J Epidemiol*, 41(5):1480–1489.

Voss, E. A., Boyce, R. D., Ryan, P. B., van der Lei, J., Rijnbeek, P. R., and Schuemie, M. J. (2016). Accuracy of an Automated Knowledge Base for Identifying Drug Adverse Reactions. *J Biomed Inform*.

Weiskopf, N. G. and Weng, C. (2013). Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *Journal of the American Medical Informatics Association: JAMIA*, 20(1):144–151.

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C., DePalma, S. M., Gidding, S., Jamerson, K. A., Jones, D. W., MacLaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A., Williamson, J. D., and Wright, J. T. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, 138(17):e426–e483.

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., and Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, 97(18):1837–1847.

Zaadstra, B. M., Chorus, A. M., van Buuren, S., Kalsbeek, H., and van Noort, J. M. (2008). Selective association of multiple sclerosis with infectious mononucleosis. *Mult. Scler.*, 14(3):307–313.

Zaman, M. A., Oparil, S., and Calhoun, D. A. (2002). Drugs targeting the renin-angiotensin-aldosterone system. *Nat Rev Drug Discov*, 1(8):621–636.