

The Book of OHDSI

Observational Health Data Science and Informatics

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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 standardize 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 organized in five major sections:

- I) The OHDSI Community
- II) Uniform data representation
- III) Data Analytics
- IV) Evidence Quality
- V) OHDSI Studies

Each section has multiple chapters, and each chapter aims to follow the following main outline: Introduction, Theory, Practice, Exercises.

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TODO: make list of contributors complete

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Part I

The OHDSI Community

Chapter 1

Mission, vision, values

Chapter lead: George Hripcsak

1.1 Our Mission

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

Observational Health Data Sciences and Informatics (OHDSI, pronounced as “Odyssey”) is an open science collaborative whose mission is 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.

OHDSI envisions a world in which observational research produces a comprehensive understanding of health and disease. Observational data are generated in the regular course of health care or as part of normal behavior, and they may be collected through health care systems and processes like electronic health records, insurance claims, and prescription services, or through methods like personal monitoring devices. Observational data are voluminous, representative of the world’s diversity, and reflect real-world practice, but because they are not generated by engineered experiments, they are subject to bias such as confounding so that causal conclusions must be drawn carefully. For example, does ibuprofen cause headaches? Because people take ibuprofen to treat headache pain, it will be difficult to tell whether ibuprofen is causing a headache or treating it, especially because the reporting of the timing of symptoms and drugs is often imperfect.

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.

OHDSI addresses the full pipeline of generating observational evidence: collecting data from around the world, translating data from many nations to a common form, developing new methods to draw causal conclusions, writing software that executes those methods on gigantic databases, writing user interfaces to help researchers run those methods, engaging clinical researchers to ask clinical questions, creating a network of researchers to help answer those questions, working together to interpret the evidence, and investing in the community to promote communication and diversity. OHDSI strives to make all its community's proceeds open and publicly accessible, including the methods, tools, and evidence that it generates. This encourages broad participation and promotes trust. Through openness and appropriate methods, OHDSI strives to achieve reproducibility, generating accurate, repeatable, and well-calibrated evidence that is necessary for health improvement. Getting there requires innovation; it encourages disruptive thinking to bring fresh methodological approaches to the task of generating evidence. OHDSI succeeds through its community. Everyone is welcome to actively participate in OHDSI, be they a patient, a health professional, a researcher, or someone who simply believes in OHDSI's cause. The community moves forward through collaboration to address the real world needs of our community's participants. It gains the trust of the community through beneficence, protecting the rights of individuals and organizations within the community at all times. Protecting privacy is a critical concern. OHDSI does not collect data centrally, but instead creates a federated database, which means each data source keeps its data local, following the laws and regulations under which the data were collected. Each site converts its data to the OMOP CDM, allowing researchers to distribute research questions across the network in the form of an OHDSI protocol so that sites can voluntarily run those protocols without local software development and return results to that researcher. They can then collaboratively interpret the evidence without ever having access to individual patient's data.

OHDSI's open science community approach, coupled with its open-source tools, has enabled tremendous advances in observational research. One of the first OHDSI network analyses examined treatment pathways across three chronic diseases: diabetes, depression, and hypertension. Published in the Proceedings of the National Academy of Science, it was one of the largest observational studies ever conducted, with results from 11 data sources covering more than 250 million patients and

revealed tremendous geographic differences and patient heterogeneity in treatment choices that had never been previously observable. OHDSI has developed new statistical methods for confounding adjustment and evaluating the validity of observational evidence for causal inference, and has applied these approaches in multiple contexts, from an individual safety surveillance question in epilepsy to a large-scale population-level effect estimation study for comparative effectiveness of depression treatments. The OHDSI community has also established a framework for how to responsibly apply machine-learning algorithms to observational healthcare data, which has been applied across various therapeutic areas.

1.4 Summary



- OHDSI’s mission is to improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.
- Our vision is a world in which observational research produces a comprehensive understanding of health and disease.
- This is achieved through our objectives of innovation, reproducibility, community, collaboration, openness, and beneficence.

Chapter 2

Collaborators

Chapter lead: Patrick Ryan

History of OHDSI

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

Governance at local sites

Chapter 3

Open Science

Chapter lead: Kees van Bochove

From the inception of the OHDSI community, the goal was to establish an international collaborative by building on open science values, such as the use of open source software, public availability of all conference proceedings and materials, and transparent, open access publication of generated medical evidence. But what exactly is open science? And how could OHDSI build an open science or open data strategy around medical data, which is very privacy sensitive and typically not open at all for good reasons? Why is it so important to have reproducibility of analysis, and how does the OHDSI community aim to achieve this? These are some of the questions that we touch on in this chapter.

3.1 Open Science

The term ‘open science’ has been used since the nineties, but really gained traction in the 2010s, during the same period OHDSI was born. Wikipedia (Wikipedia, 2019a) defines it as “the movement to make scientific research (including publications, data, physical samples, and software) and its dissemination accessible to all levels of an inquiring society, amateur or professional”, and goes on to state that it is typically developed through collaborative networks. Although the OHDSI community never positioned itself explicitly as an ‘open science’ collective or network, the term is frequently used to explain the driving concepts and principles behind OHDSI. For example, in 2015, Jon Duke presented OHDSI as “An Open Science Approach to Medical Evidence Generation”¹, and in 2019, the EHDEN projects’ introductory webinar hailed the OHDSI network approach as “21st Century Real World Open Science”². Indeed, as we shall see in this chapter, many of the practices of open science can be found in today’s OHDSI community. One could argue that the OHDSI community is a grassroots open science collective driven by a shared desire for improving the transparency and reliability of medical evidence generation.

Open science or “Science 2.0” (Wikipedia, 2019b) approaches mean to address a number of perceived problems within the current scientific practice. Information technology has led to an explosion of

¹https://www.ohdsi.org/wp-content/uploads/2014/07/ARM-OHDSI_Duke.pdf

²<https://www.ehden.eu/webinars/>

data generation and analysis methods, and for individual researchers, it is very hard to keep up with all literature published in their area of expertise. This holds even more true for medical doctors who have a practice to run as day job, but still need to keep abreast of the latest medical evidence. In addition, there is growing concern that many experiments may suffer from poor statistical designs, publication bias, p-hacking and similar statistical problems, and are hard to reproduce. The traditional method of correcting these problems, peer review of published articles, often fails to identify and tackle these problems. The special 2018 Nature edition on “Challenges in irreproducible research”³ includes several examples of this. A group of authors attempting to apply systematic peer review on the articles in their field found that, for various reasons, it was very hard to get the errors they identified rectified. Especially hard to correct are those experiments that have a flawed experimental design to begin with. In the words of Ronald Fisher: “To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of.” (Wikiquote, 2019) The authors encountered common statistical problems such as poor randomization designs leading to false conclusions about statistical significance, miscalculations in meta-analyses, and inappropriate baseline comparisons. (Allison et al., 2016) Another paper from the same collection, taking experiences from physics as an example, argues that it is critical to not only provide access to the underlying data, but also to publish and properly document the data processing and analysis scripts to achieve full reproducibility. (Chen et al., 2018)

The OHDSI community addresses these challenges in its own way, and puts significant emphasis on the importance of generating medical evidence at scale. As stated in Schuemie et al. (2018b), while the current paradigm “centers on generating one estimate at a time using a unique study design with unknown reliability and publishing (or not) one estimate at a time”, the OHDSI community “advocates for high-throughput observational studies using consistent and standardized methods, allowing evaluation, calibration and unbiased dissemination to generate a more reliable and complete evidence base.” This is achieved by a combination of a network of medical data sources that map their data to the OMOP common data model, open source analytics code that can be used and verified by all, and large-scale baseline data such as the condition occurrences published at howoften.org. In the following paragraphs, concrete examples are provided and the open science approach of OHDSI is detailed further using the four principles of Open Standards, Open Source, Open Data and Open Discourse as a guide. The chapter is concluded with a brief reference to the FAIR principles and outlook for OHDSI from an open science perspective.

3.2 Open Science in Action: the Study-a-thon

A recent development in the community is the emergence of ‘study-a-thons’: short, concentrated face to face gatherings of a multidisciplinary group of scientists aimed at answering an important clinically relevant research question using the OMOP data model and the OHDSI tools. A nice example is the 2018 Oxford study-a-thon, which is explained in an EHDEN webinar (<https://youtu.be/X5yu0JoL6xs>) which provides a walkthrough of the process and also highlights the openly available results. In the period leading up to the study-a-thon, the participants propose medically relevant research questions to study, and one or more research questions are selected to study during the

³<https://www.nature.com/collections/prbfkwmwvz>

study-a-thon itself. Data is provided through participants that have access to patient-level data in OMOP format and are able to run queries on these data sources. Much of the actual study-a-thon time is devoted to discussing the statistical approach (see also the next chapter 4), the suitability of the data sources, the results which are interactively produced and the follow-up questions that are inevitably raised by these results. In the case of the Oxford study-a-thon, the questions centered around studying adverse post-surgical effects of different knee replacement methods, and the results were published interactively during the study-a-thon using the OHDSI forums and tools 9. The OHDSI tools such as ATLAS facilitate rapid creation, exchange, discussion and tests of cohort definitions, which greatly speeds up the initial process of achieving consensus on problem definition and choice of methods. Thanks to the usage of the OMOP Common Data Model by the involved data sources and the availability of the OHDSI open source patient level prediction packages 14, it was possible to create a prediction model for 90-day post-operative mortality in one day, and validate the model externally in several large data sources the day after. The study-a-thon also resulted in a traditional peer-reviewed paper (Development and validation of patient-level prediction models for adverse outcomes following total knee arthroplasty, Ross Williams, Daniel Prieto-Alhambra et al., manuscript in preparation), which took of course months to process through peer review. But the fact that the analysis scripts and results for several healthcare databases covering hundreds of millions of patient records were conceived, produced and published from scratch within a week, illustrates the fundamental improvements OHDSI can bring to medical science, reducing the turnaround time for evidence to become available from months to days.

3.3 Open Standards

A very significant community resource that is maintained in the OHDSI community is the OMOP Common Data Model 5 and associated Standardized Vocabularies 6. The model itself is scoped to capture observational healthcare data, and was originally meant to analyze associations between exposures such as drugs, procedures, devices etc. and outcomes such as conditions and measurements, and is now extended for various analysis use cases (see also 8). However, harmonizing healthcare data worldwide from a wide variety of coding systems, healthcare paradigm and different types of healthcare sources requires a massive amount of ‘mappings’ between source codes and their closest standardized counterparts. The OMOP Standardized Vocabulary is further described in chapter 6 and includes mappings from hundreds of medical coding systems that are in used worldwide, and is browsable through the OHDSI Athena tool. By providing these vocabularies and mappings as a freely available community resource, OMOP and the OHDSI community make a significant contribution to healthcare data analytics and is by several accounts the most comprehensive model for this purpose, representing approximately 1.2 billion healthcare records worldwide (Garza et al., 2016)⁴.

3.4 Open Source

Another key resource the OHDSI community provides are open source programs. These can be divided in several categories, such as the helper tools to map data to OMOP 7, the OHDSI Methods Library which contain a powerful suite of commonly used statistical methods, open source code for

⁴<https://www.ema.europa.eu/en/events/common-data-model-europe-why-which-how>

published observational studies, and ATLAS, Athena and other infrastructure-related software which underpins the OHDSI ecosystem⁹. See chapter 9 for a detailed overview. From an open science perspective, one of the most important resources is the code for the actual execution of studies, such as studies from the OHDSI Research Network²¹. In turn, these programs leverage the fully open source OHDSI stack, which can be inspected, reviewed and contributed to via GitHub. For example, network studies often build on the Methods Library, which ensures a consistent re-use of statistical methods across analytical use cases. See the 18 chapter for a more detailed overview of how the use of and collaboration on open source software in OHDSI ultimately underpins the quality and reliability of the generated evidence.

3.5 Open Data

Because of the privacy-sensitive nature of healthcare data, fully open comprehensive patient-level datasets are typically not available. However, it is possible to leverage OMOP mapped datasets to publish important aggregated data and results sets, such as the earlier mentioned howoften.org and other public result sets that are published to data.ohdsi.org. Also, the OHDSI community provides simulated datasets such as SynPUF for testing and development purposes, and the OHDSI Research Network²¹ can be leveraged to run studies in a network of available datasources that have mapped their data to OMOP. In order to make the mapping between the source data and the OMOP CDM transparent, it is encouraged for data sources to re-use the OHDSI ETL or ‘mapping’ tools and publish their mapping code as open source as well.

3.6 Open Discourse

Open standards, open source and open data are great assets, but left by themselves, they will not impact medical practice. Key to the open science practice and impact of OHDSI is the implementation of medical evidence generation and the translation of the science to medical practice. The OHDSI community has now several annual OHDSI Symposia, in the United States and Europe, and dedicated communities of practice in a.o. China and Korea. These symposia discuss the advancements in statistical methods, data and software tooling, the standardized vocabularies, and all other aspects of the OHDSI open source community. The OHDSI forums⁵ and wiki⁶ facilitate thousands of researchers worldwide in practicing observational research. The community calls⁷ and the code, issues and pull requests in Github⁸ constantly evolve the open community assets such as code and the CDM, and in the OHDSI Network Studies, global observational research is practiced in an open and transparent way using hundreds of millions of patient records worldwide. Openness and open discourse is encouraged throughout the community, and this very book is written via an open process facilitated by the OHDSI wiki, community calls and a GitHub repository⁹. It needs to be stressed however that without all the OHDSI collaborators, the processes and tools would be empty shells.

⁵<https://forums.ohdsi.org>

⁶<https://www.ohdsi.org/web/wiki>

⁷<https://www.ohdsi.org/web/wiki/doku.php?id=projects:overview>

⁸<https://github.com/ohdsi>

⁹<https://github.com/OHDSI/TheBookOfOhdsi>

Indeed, one could argue that the true value of the OHDSI community is with its members, who share a vision of improving health through collaborative and open science, as discussed in Chapter. 1

3.7 OHDSI and the FAIR Guiding Principles

This last paragraph of the chapter takes a look at the current state of the OHDSI community and tooling, using the FAIR Data Guiding Principles published in Wilkinson et al. (2016).

3.7.1 Findability

Any healthcare database that is mapped to OMOP and used for analytics, should from a scientific perspective be persisted for future reference and reproducibility. The use of persistent identifiers for OMOP databases is not yet widespread, partly because these databases are often contained behind firewalls and on internal networks and not necessarily connected to the internet. However, it is of course entirely possible to publish summaries of the databases as a descriptor record that can be referenced for e.g. citation purposes. This method is followed in for example the EMIF catalog¹⁰, which provides a comprehensive record of the database in terms of data gathering purpose, sources, vocabularies and terms, access control mechanisms, license, consents etc. (Oliveira et al., 2019) This approach is further developed in the IMI EHDEN project.

3.7.2 Accessibility

Accessibility of OMOP mapped data through an open protocol is typically achieved through the SQL interface, which combined with the OMOP CDM provides a standardized and well-documented method for accessing OMOP data. However, as discussed above, OMOP sources are often not directly available over the internet for security reasons. Creating a secure worldwide healthcare data network that is accessible for researchers is an active research topic and operational goal of projects like IMI EHDEN. However, what can be openly published are results of analyses in multiple OMOP databases, as shown through OHDSI initiatives such as LEGEND and howoften.org.

3.7.3 Interoperability

Interoperability is arguably the strong suit of the OMOP data model and OHDSI tooling. In order to build a strong network of medical data sources worldwide which can be leveraged for evidence generation, achieving interoperability between healthcare data sources is key, and this is achieved through the OMOP model and Standardized Vocabularies. However, by sharing cohort definitions and statistical approaches, the OHDSI community goes beyond code mapping and also provides a platform to build an interoperable understanding of the analysis methods for healthcare data. Since healthcare systems such as hospitals are often the source of record for OMOP data, the interoperability of the OHDSI approach could be further enhanced by alignment with operational healthcare

¹⁰<https://emif-catalogue.eu>

interoperability standards such as HL7 FHIR, HL7 CIMI and openEHR. The same is true for alignment with clinical interoperability standards such as CDISC and biomedical ontologies. Especially in areas such as oncology, this is an important topic, and the Oncology Working Group and Clinica Trials Working Group in the OHDSI community provide good examples of forums where these issues are actively discussed. In terms of references to other data and specifically ontology terms, ATLAS and OHDSI Athena are important tools, as they allow the exploration of the OMOP Standardized Vocabularies in the context of other available medical coding systems.

3.7.4 Reusability

The FAIR principles around reusability focus on important issues such as the data license, provenance (clarifying how the data came in existence) and the link to relevant community standards. Data licensing is a complicated topic, especially across jurisdictions, and it would fall outside of the scope of this book to cover it extensively. However, it is important to state that if you intend for your data (e.g. analysis results) to be freely used by others, it is good practice to explicitly provide these permissions via a data license. This is not yet a common practice for most data that can be found on internet, and the OHDSI community is unfortunately not an exception here. The data provenance of OMOP databases is a very interesting topic, as there are potential improvements for making these available in an automated way, provided the ETL and mapping tools would persist metadata about for example the used CDM version, Standardized Vocabularies release, custom code lists etc. The OHDSI ETL tools do not currently produce this information automatically, but working groups such as the Data Quality Working Group and Metadata Working Group actively work on these. Another important aspect is the provenance of the underlying databases itself, for example it is important to know if a hospital or GP information system was replaced or changed, and when known data omissions or other data issues occurred historically. Exploring ways to attach this metadata systematically in the OMOP CDM is the domain of the Metadata Working Group.

3.8 Conclusions

To conclude, the OHDSI community itself can be seen as an open science community that is actively pursuing the interoperability and reproducibility of medical evidence generation. It also advocates a paradigm shift from single study and single estimate medical research to large-scale systematic evidence generation, where facts such as baseline occurrence are known and the evidence focuses on statistically estimating the effects of interventions and treatments from real world healthcare sources.

Chapter 4

Where to begin

Chapter leads: Hamed Abedtash and Krista Kostka

“A journey of a thousand miles begins with a single step.” - Lao Tzu

The OHDSI community represents a mosaic of stakeholders across academia, industry and government-entities. Our work benefits a range of individuals and organizations, including patients, providers, and researchers, as well as health care systems, industry, and government agencies. This benefit is achieved by improving both the quality of healthcare data analytics as well as the usefulness of healthcare data to these stakeholders. We believe observational research is a field which benefits greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.

4.1 Joining the Journey

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. OHDSI maintains an inclusive membership model. To become an OHDSI collaborator requires no membership fee. Collaboration is as simple as raising a hand to be included in the yearly OHDSI membership count. Involvement is entirely at-will. A collaborator can have any level of contribution within the community, ranging from someone who attends weekly community calls to leading network studies or OHDSI working groups. Collaborators do not have to be data holders to be considered active members of the community. The OHDSI community aims to serve data holders, researchers, health care providers and patients & consumers alike. A record of collaborator profiles are maintained and periodically updated on the OHDSI website. Membership is fostered via OHDSI community calls, workgroups and regional chapters.

4.1.1 OHDSI Community Calls

OHDSI Community Calls are a weekly forum to spotlight ongoing activity within the OHDSI community. Held every Tuesday from 12-1pm ET, these teleconferences are a time for the OHDSI

community to come together to share recent developments and recognize the accomplishments of individual collaborators, working groups and the community as a whole. Each week's meeting is recorded, and presentations are archived in the OHDSI website resources.

All OHDSI Collaborators are welcome to participate in this weekly teleconference and encouraged to propose topics for community discussion. OHDSI Community Calls can be a forum to share research findings, present and seek feedback for active works-in-progress, demonstrate open-source software tools under development, debate community best practices for data modeling and analytics, and brainstorm future collaborative opportunities for grants/publications/conference workshops. If you are a Collaborator with a topic for an upcoming OHDSI Collaborator meeting, you are invited to post your thoughts on the OHDSI Forums.

As a newcomer to the OHDSI community, it's highly encouraged to add this call to your calendar to get acquainted with what's happening across the OHDSI network. Newcomers are invited to introduce themselves on their first call and tell the community about themselves, their background and what brought them to OHDSI. If you'd like to join an OHDSI call, please contact Maura Beaton (beaton@ohdsi.org) for the latest dial-in details or consult the OHDSI wiki. Community call topics vary from week-to-week. Consult the OHDSI Weekly Digest on the OHDSI forum for more information on weekly presentation topics.

4.1.2 OHDSI Workgroups

OHDSI has a variety of ongoing projects lead by workgroup teams. Each workgroup has its own leadership team which determine the project's objectives, goals and artefacts to be contributed to the community. Workgroup participation is open to all who have an interest in contributing to the project objectives and goals. Workgroups may be long-standing, strategic objectives or short-term projects to accomplish a specific need in the community. Workgroup meeting cadence is determined by the project leadership and will vary from group to group. A list of the active workgroups is maintained on the OHDSI Wiki.

May update to include a graphic of the workgroups by use case

4.1.3 OHDSI Regional Chapters

An OHDSI regional chapter represents a group of OHDSI collaborators located in a geographic area who wish to hold local networking events and meetings to address problems specific to their geographic location. Today, OHDSI regional chapters include OHDSI in Europe, OHDSI in South Korea and OHDSI in China. If you would like to set-up an OHDSI regional chapter in your region, you may do so by following the OHDSI regional chapter process outlined on the OHDSI website.

4.1.4 OHDSI Research Network

Many OHDSI collaborators are interested in converting their data into the OMOP Common Data Model. The OHDSI research network represents a diverse, global community of observational

databases that have undergone Extract-Transform-Load (ETL) processes to become OMOP compliant. If your journey in the OHDSI community includes transforming data, there are numerous community resources available to aid you in your journey including tutorials on the OMOP CDM and Vocabularies, freely available tools to assist with conversion [ExtractTransformLoad] and work-groups targeting specific domains or types of data conversions. The OHDSI collaborators are encouraged to utilize the OHDSI forum to discuss and troubleshoot challenges that arise during CDM conversions.

4.2 Navigating Your Odyssey in OHDSI

As discussed in the previous section, there are many ways to begin your journey in the OHDSI community. Collaborators often find the journey from initial interest in OHDSI to actively contributing to be as circuitous as Homer’s Odyssey. For those interested in running OHDSI research studies, the simplest way to navigate your path forward is to learn how to speak in “OHDSI” terms.

4.2.1 How to Translate Your Research Question into an OHDSI Framework

The OHDSI community has a wide range of standardized analytic tools depending on the type of question you are formulating. In the following chapters, we will discuss the intricacies of these frameworks as well as the open source tools and code available to conduct these analyses. In this section, we will briefly discuss how to take your question and reframe it in OHDSI-speak, what analytical methods and tools are appropriate for data analysis, and where you can find the resources within the OHDSI community.

4.2.1.1 Step 1: Identify the proper framework

Before formulating your research question for execution on OHDSI platform, it is important to understand which OHDSI framework suits the objectives of research question, whether it is a “clinical characterization”, “population-level estimation”, or “patient-level prediction”. Characterization provides answers to “What happened to them” questions, [PopulationLevelEstimation] responses to “What are the causal effects” questions, and [PatientLevelPrediction] answers “What will happen to them” questions. To learn more about the OHDSI use cases, please refer to Chapter 8.

Once you understand the relationship between OHDSI framework and different study types you will be using, you can then further refine your question into OHDSI-speak. There are examples of study categories that correspond to each OHDSI framework:

- **Clinical characterization**
 - Disease natural history
 - Incidence rate
 - Prevalence
 - Treatment utilization
 - Treatment pathway
 - Quality improvement

- **Population-level effect estimation**

- Safety surveillance
- Effect estimation
- Comparative effectiveness

- **Patient-level prediction**

- Precision Medicine
- Disease onset and progression
- Treatment choice
- Disease interception
- Treatment response
- Treatment safety
- Treatment adherence

Many people start with a simple characterization (e.g., how many people have angioedema? How often does a patient receive ACE inhibitors?). Even if you are thinking about an estimation or prediction question, you'll probably want to start with preliminary characterization analyses to understand your target and outcome cohorts. In fact, estimation and prediction studies produce characterization results as part of their standardized outputs.

The tool below also provides a crosswalk of the type of question with a desired output you may be formulating to what OHDSI framework may be most appropriate for that question.

- If your question is:

- How many patients...?
- How often does...?
- What proportion of patients...?
- What is the distribution of values for lab...?
- What are the HbA1c levels for patients with...?
- What are the [lab values] for patients...?
- What is the median length of exposure for patients on....?
- What are the trends over time in...?
- What are other drugs that these patients are using?
- What are concomitant therapies?
- Do we have enough cases of...?
- Would it be feasible to study X...?
- What are the demographics of...?
- What are the risk factors of...? (if identifying a specific risk factor, maybe estimation, not prediction)
- What are the predictors of...?

- And the desired output is:

- Count or percentage
- Averages
- Descriptive statistics
- Incidence rate
- Prevalence
- Cohort
- Rule-based phenotype

- Drug utilization
- Disease natural history
- Adherence
- Comorbidity profile
- Treatment pathways
- Line of therapy
- Then you're probably asking for:
 - **Clinical characterization**
- If your question is:
 - What is the effect of...?
 - What if I do intervention...?
 - Which treatment works better?
 - What is the risk of X on Y?
 - What is the time-to-event of...?
- And the desired output is:
 - Relative risk
 - Hazards ratio
 - Odds ratio
 - Average treatment effect
 - Causal effect
 - Association
 - Correlation
 - Safety surveillance
 - Comparative effectiveness
- Then you're probably asking for:
 - **Population-level effect estimation**
- If your question is:
 - What is the chance that this patient will...?
 - Who are candidates for...?
- And the desired output is:
 - Probability for an individual
 - Prediction model
 - High/low risk groups
 - Probabilistic phenotype
- Then you're probably asking for:
 - **Patient-level prediction**

4.2.1.2 Step 2: Frame research question in OHDSI-speak

You now know from the previous step what OHDSI framework best suits your research question. Depending on the study objectives, an OHDSI-compliant research question should be structured in a way that explicitly describes the target population, the output(s) of interest, and analysis method (if applicable).

The list below provides OHDSI-speak template and example questions for different study categories as the best practice to formulate research questions. The subsequent chapters will explain the analyt-

ical methods to run your study.

Study Category	Template Question	Example
Disease onset and progression	Amongst patients who are newly diagnosed with [insert the disease of interest], which patients will go on to have [another disease or related complication] within [time horizon from diagnosis]?	Among newly diagnosed AFib patients, which patients will go onto to have ischemic stroke in next 3 years ? Among newly diagnosed Melanoma , which patients will go onto to have brain cancer in next 6 months ?
Treatment choice	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)?	Among AFib patients who took either warfarin or dabigatran , which patients got warfarin? (as defined for propensity score model)
Treatment response	Amongst patients who are new users of [insert the chronically-used drug of interest], which patients will [insert desired effect] in [time window]?	Which patients with T2DM who start metformin stay on metformin after 3 years ?
Treatment safety	Amongst patients who are new users of [insert the drug of interest], which patients will experience [insert your favorite known adverse event from the drug profile] within [time horizon following exposure start]?	Among new users of warfarin , which patients will have GI bleeding in 1 year ?
Treatment adherence	Amongst patients who are new users of [insert the chronically-used drug of interest], which patients will achieve [adherence metric threshold] at [time horizon]?	Which patients with T2DM who start on metformin will achieve >=80% proportion of days covered at 1 year ?

Study Category	Template Question	Example
Comparative effectiveness	To compare the risk of [Insert the outcome of interest] between [Insert the target exposure] and [Insert the comparator cohort], we will estimate the population-level effect of exposure on the [Insert the metric of analysis model here: hazards for Cox/ odds for logistic / rate ratio for Poisson] of the outcome during the period from [Insert the time-at-risk start: e.g. 1 day after exposure start] to [Insert the time-at-risk end: e.g. 30 days after exposure end].	To compare the risk of angioedema between new users of levetiracetam and new users of phenytoin , we will estimate the population-level effect of exposure on the hazards of the outcome during the period from 1 day after exposure start to 0 days after exposure end .

4.2.2 Example of a Study in OHDSI-speak

You're a researcher interested in studying the effects of ACE inhibitor monotherapy vs. thiazide diuretic monotherapy on the outcomes of acute myocardial infarction and angioedema as first-line treatment for hypertension. You understand that based on the OHDSI literature, you are asking a population-level effect estimation question but first, you need to do some homework on how to characterize this particular treatment of interest.

4.2.2.1 Characterization Questions

Acute myocardial infarction is a cardiovascular complication that can occur in patients with high blood pressure, so effective treatment for hypertension should reduce the risk. Angioedema is a known side effect of ACE inhibitors, which is rare but potentially serious. You start by creating [Cohorts] for the exposures of interest (new users of ACE inhibitors and new users of thiazide diuretics). You perform a Characterization analysis to summarize baseline characteristics of these exposure populations, including demographics, comorbid conditions, and concomitant medications. You perform another characterization analysis to estimate the incidence of selected outcomes within these exposure populations. Here, you ask ‘how often does 1) acute myocardial infarction and 2) angioedema occur during the period of exposure to ACE inhibitors and thiazide diuretics?’ These characterizations allow us to assess the feasibility of conducting a [PopulationLevelEstimation], to evaluate whether the two treatment groups are comparable, and to identify ‘risk factors’ that might predict which treatment choice that patients made.

4.2.2.2 Population-Level Estimation Question

The population-level effect estimation study estimates the relative risk of ACE inhibitor vs. thiazide use for the outcomes of AMI and angioedema. Here, you further evaluate through study diagnostics and negative controls whether we can produce a reliable estimate of the average treatment effect.

Independent of whether there is a causal effect of the exposures, you are also interested in trying to determine which patients are at highest risk of the outcomes. (This is a patient-level prediction problem). Here, you develop a prediction model that evaluates: amongst the patients who are new users of ACE inhibitors, which patients are at highest risk of developing acute myocardial infarction during the 1 year after starting treatment. The model allows us to predict, for a patient who has just been prescribed ACE for the first time, based on events observed from their medical history, what is the chance that they will experience AMI in the next 1 year.

4.2.3 More real example questions

In this section, we provide more real examples of questions as they have been submitted to the community. We have also reframed them to the OHDSI-speak format (if needed) and mapped them to OHDSI analytic frameworks:

Unframed question we've heard from potential researchers	Reframed Question in OHDSI-speak (<i>italics denote additions to the original question for clarification</i>)	OHDSI Framework
Among patients addicted to opioids, what is the proportion of patients taking benzos concurrently?	Amongst opioid-addicted patients, how many patients did concurrently use benzodiazepines <i>any time over the last 5 years of data?</i>	Clinical characterization
Among patients newly diagnosed with cancer, how many received guideline-concordant care?	Amongst newly diagnosed cancer patients, how many patients did receive guideline-concordant care <i>over the last 5 years of data?</i>	Clinical characterization
Among patients diagnosed with pneumonia, who develops ocular retinopathy within 2 years?	Amongst patients who are <i>newly diagnosed with</i> pneumonia, which patients will develop ocular retinopathy after 2 years?	Patient-level prediction

Unframed question we've heard from potential researchers	Reframed Question in OHDSI-speak (<i>italics denote additions to the original question for clarification</i>)	OHDSI Framework
Among Patients with an ICD9/10 for psoriasis over the last 5 years, how many presented with major adverse cardiovascular events (e.g., heart attack, stroke, MI, atrial fibrillation)? What were the red cell distribution width (RDW) values for these patients?	Amongst diagnosed patients with psoriasis over the last 5 years <i>of data</i> , how many patients experienced major cardiovascular adverse events <i>any time during the study period</i> ? Amongst diagnosed patients with psoriasis over the last 5 years of data, what were <i>max-min range, median, IQR, mean, and SD</i> of red cell distribution width (RDW) values <i>any time during the study period</i> ?	Clinical characterization
How many patients had a shoulder arthroscopy in the last year?	How many patients did undergo arthroscopy <i>procedure</i> in the last year?	Clinical characterization
Among patients with neuro-degenerative Parkinson's disease, onset age 65 or older, how many subsequently suffered from brain stroke or dementia?	Amongst patients diagnosed with neurodegenerative Parkinson's disease who were 65 years or older at onset, how many patients experienced brain stroke or dementia <i>after diagnosis</i> ?	Clinical characterization
What are the rates of chemotherapy-induced neutropenia and subsequent chemotherapy withdrawal in patients taking cisplatin?	Amongst patients who take cisplatin, what is the rate of developing chemotherapy-induced neutropenia <i>per 1,000 patient per year over the last 2 years of data</i> ?	Clinical characterization
Among outpatients, how many presented with ADHD were taking Ritalin for the last 6 months?	Amongst admitted patients in ambulatory setting <i>over the last year of data</i> , how many ADHD patients did use Ritalin within the last 6 months <i>prior to last visit</i> ?	Clinical characterization

4.3 Summary

****add if needed****

Part II

Uniform Data Representation

Chapter 5

The Common Data Model

Chapter lead: Clair Blacketer

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). In this chapter we provide an overview of the data model itself, as well as design, conventions, and discussion of select tables.

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.

An overview of all the tables in the CDM is provided in Figure 5.1.

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:

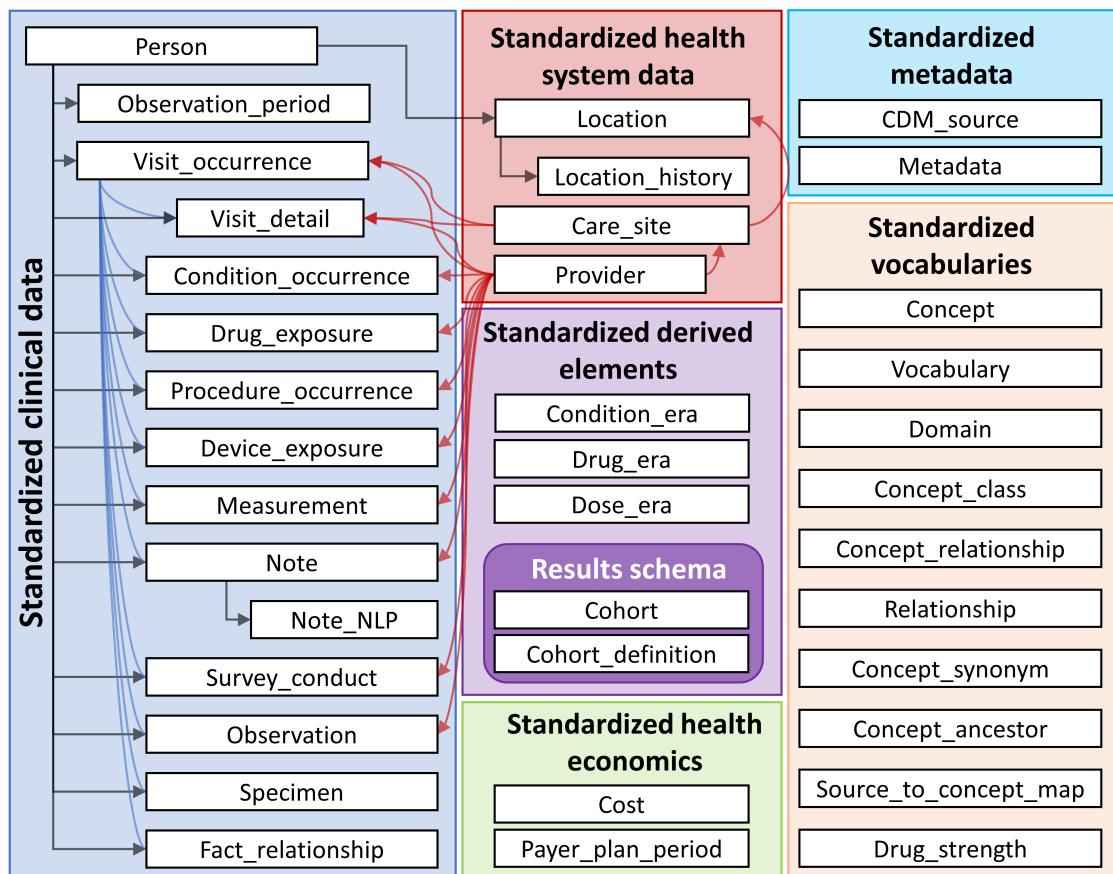


Figure 5.1: Overview of all tables in the CDM version 6.0. Note that not all relationships between tables are shown.

- **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 when 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. Here, a relational data model is one where the data is represented as a collection of tables linked by primary and foreign keys.
- **Rationale for domains:** Domains are identified and separately defined in an entity-relationship model if they have an analysis use case (conditions, for example) and the domain has specific attributes that are not otherwise applicable. All other data can be preserved as an observation in the observation table 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 current version, 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_DEFINITION, though more will likely be added over the course of v6.0 point releases. The COHORT and COHORT_DEFINITION tables are meant to describe groups of interest that the user might define, as detailed in chapter 11. 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.

Note: While the data model itself is platform-independent, many of the tools that have been built to work with it require certain specifications. For more about this please see chapter 9.

5.2.4 General conventions of domains

One of the ways in which the CDM is standardized is by the use of concept domains. Domains refer to the nature of a clinical entity and define the event table or field in an event table where a data record should be stored. This idea is covered fully in chapter 6, but it is also important to the understanding of the data model, so we touch on it here again. All standard concepts in the OMOP vocabularies are organized into 30 domains, as shown in table 5.1. Domains, like concepts, are a major reason why every researcher who uses the OMOP CDM is considered to be “speaking the same language.” Once source codes from a native database are mapped to standard concepts (see section 5.2.7) the concepts themselves dictate which table they belong in by use of domains. In this way, a researcher using the CDM always knows where a record should be located rather than having to guess.

Table 5.1: Number of standard concepts belonging to each domain.

Concept Count	Domain_Id
1731378	Drug
477597	Device
257000	Procedure
163807	Condition
145898	Observation
89645	Measurement
33759	Spec Anatomic Site
17302	Meas Value
1799	Specimen
1215	Provider Specialty
1046	Unit
944	Metadata
538	Revenue Code
336	Type Concept
194	Relationship
183	Route
180	Currency
158	Payer
123	Visit
51	Cost
50	Race
13	Plan Stop Reason
11	Plan
6	Episode
6	Sponsor
5	Meas Value Operator
3	Spec Disease Status
2	Gender
2	Ethnicity
1	Observation Type

5.2.5 General conventions of fields

Variable names across all tables follow one convention:

Table 5.2: Field name conventions.

Notation	Description
[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]_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]_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 is 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”.

5.2.6 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 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.

5.2.7 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 5.2 shows that the ICD9CM code for TB is 011.

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 5.3 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 the standard concept-source code 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



Pulmonary tuberculosis

DETAILS	
Domain ID	Condition
Concept Class ID	3-dig nonbill code
Vocabulary ID	ICD9CM
Concept ID	44828631
Concept code	011
Invalid reason	Valid
Standard concept	Non-standard
Synonyms	Pulmonary tuberculosis
Valid start	12/31/1969
Valid end	12/30/2099

Figure 5.2: 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 5.3: SNOMED code for Pulmonary Tuberculosis

schema tables. These tables are fully specified in the CDM Wiki¹.

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 painful journey I had to convince everyone how much pain I was in.

Lauren had been experiencing endometriosis symptoms for many years; 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:

¹<https://github.com/OHDSI/CommonDataModel/wiki>

Table 5.3: 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.
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	1	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 as shown in Table 5.4 is most similar to EHR data in that we only have records of her encounters from which to determine her observation period.

Table 5.4: Lauren's healthcare encounters.

Encounter ID	Start date	Stop date	Type
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 5.5: 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.
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?

As an example let's represent the inpatient encounter in Table 5.4 in the VISIT_OCCURRENCE table.

Table 5.6: The VISIT_OCCURRENCE table.

Column name	Value	Explanation
visit_occurrence_id	514	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.
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 start. 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 ("Visit derived from EHR encounter record") 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 (“Home”).
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 (“Assisted Living Facility”).
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 in 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 name	Value	Explanation
condition_occurrence_id	964	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 (“EHR encounter diagnosis”) is used as the encounters are similar to electronic health records. Concept IDs in this field should be in the “Condition Type” vocabulary.
condition_status_concept_id	0	If known, this 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.

Column name	Value	Explanation
visit_occurrence_id	509	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	266599000	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.
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 dysmenorrhea 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 table 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 exposures are 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 name	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.
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-day 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 ("Prescription written") 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.
refills	NULL	The number of refills after the initial prescription. If 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.

Column name	Value	Explanation
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 exposed to. Lauren took her acetaminophen orally so the concept ID 4132161 ("Oral") 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	509	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.
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, the NDC code for "Acetaminophen 325 MG Oral Tablet".
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 an 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 name	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
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 (“EHR order list entry”) 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	0	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 (“Bilateral procedure”) 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.

Column name	Value	Explanation
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.
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	304435002	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.

5.4 Additional Information

This chapter covers only a portion of the tables available in the OMOP CDM as examples of how data is represented. You are encouraged to visit the wiki site <https://github.com/OHDSI/CommonDataModel/wiki> for more information.

5.5 Summary



- The OMOP CDM is designed to support the conduct of research to identify and evaluate associations between interventions and outcomes
- The OMOP CDM is a “person-centric” model
- Source codes are represented as standard concept ids

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

Chapter leads: Clair Blacketer & Erica Voss

7.1 Introduction

In order to get from the native/raw data to the OMOP Common Data Model (CDM) we have to create an extract, transform, and load (ETL) process. This process should restructure the data to the CDM, and add mappings to the Standardized Vocabularies, and is typically implemented as a set of automated scripts, for example SQL scripts. It is important that this ETL process is repeatable, so that it can be rerun whenever the source data is refreshed.

Creating an ETL is usually a large undertaking. Over the years, we have developed best practices, consisting of four major steps:

1. Data experts and CDM experts together design the ETL.
2. People with medical knowledge create the code mappings.
3. A technical person implements the ETL.
4. All are involved in quality control.

In this chapter we will discuss each of these steps in detail. Several tools have been developed by the OHDSI community to support some of these steps, and these will be discussed as well. We close this chapter with a discussion of CDM and ETL maintenance.

7.2 Step 1: Design the ETL

It is important to clearly separate the design of the ETL from the implementation of the ETL. Designing the ETL requires extensive knowledge of both the source data, as well as the CDM. Implementing the ETL on the other hand typically relies mostly on technical expertise on how to make the ETL computationally efficient. If we try to do both at once, we are likely to get stuck in nitty-gritty details, while we should be focusing on the overall picture.

Two closely-integrated tools have been developed to support the ETL design process: White Rabbit, and Rabbit-in-a-Hat.

7.2.1 White Rabbit

To initiate an ETL process on a database you need to understand your data, including the tables, fields, and content. This is where the White Rabbit tool comes in; it scans your data and creates a report containing all the information necessary to begin designing the ETL. All source code and installation instructions, as well as a link to the manual, are available on GitHub¹.

Scope and Purpose

White Rabbit's main function is to perform a scan of the source data, providing detailed information on the tables, fields, and values that appear in a field. The source data can be in comma-separated text files, or in a database (MySQL, SQL Server, Oracle, PostgreSQL, Microsoft APS, Microsoft Access, Amazon RedShift). The scan will generate a report that can be used as a reference when designing the ETL, for instance by using it in conjunction with the Rabbit-In-a-Hat tool. White Rabbit differs from standard data profiling tools in that it attempts to prevent the display of personally identifiable information (PII) data values in the generated output data file.

Process Overview

The typical sequence for using the software to scan source data:

1. Set working folder, the location on the local desktop computer where results will be exported.
2. Connect to the source database or CSV text file and test connection.
3. Select the tables of interest for the scan and scan the tables.
4. White Rabbit creates an export of information about the source data.

Setting a Working Folder

After downloading and installing the White Rabbit application, the first thing you need to do is set a working folder. Any files that White Rabbit creates will be exported to this local folder. Use the “Pick Folder” button shown in Figure 7.1 to navigate in your local environment where you would like the scan document to go.

Connection to a Database

White Rabbit supports delimited text files and various database platforms. Hover the mouse over the various fields to get a description of what is required. More detailed information can be found in the manual.

Scanning the Tables in a Database

After connecting to a database, you can scan the tables contained therein. A scan generates a report containing information on the source data that can be used to help design the ETL. Using the Scan tab shown in Figure 7.2 you can either select individual tables in the selected source database by clicking on “Add” (Ctrl + mouse click), or automatically select all tables in the database by clicking on “Add all in DB”.

¹<https://github.com/OHDSI/WhiteRabbit>.

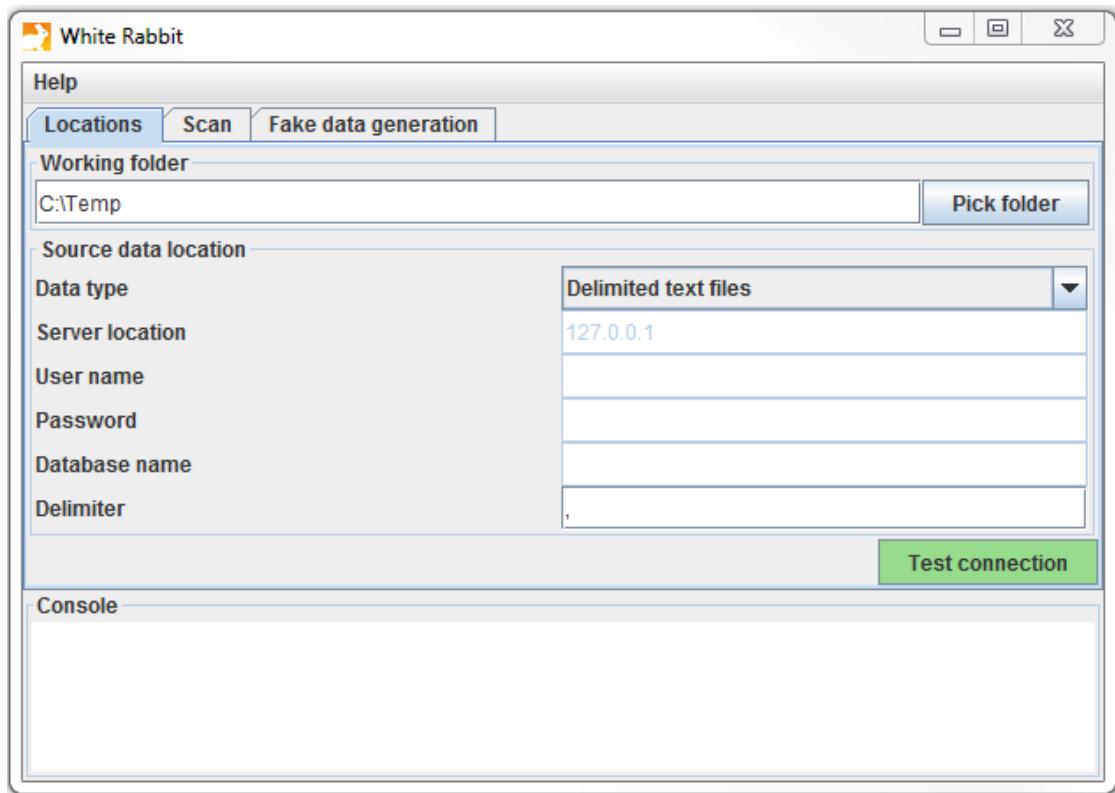


Figure 7.1: The "Pick Folder" button allows the specification of a working folder for the White Rabbit application.

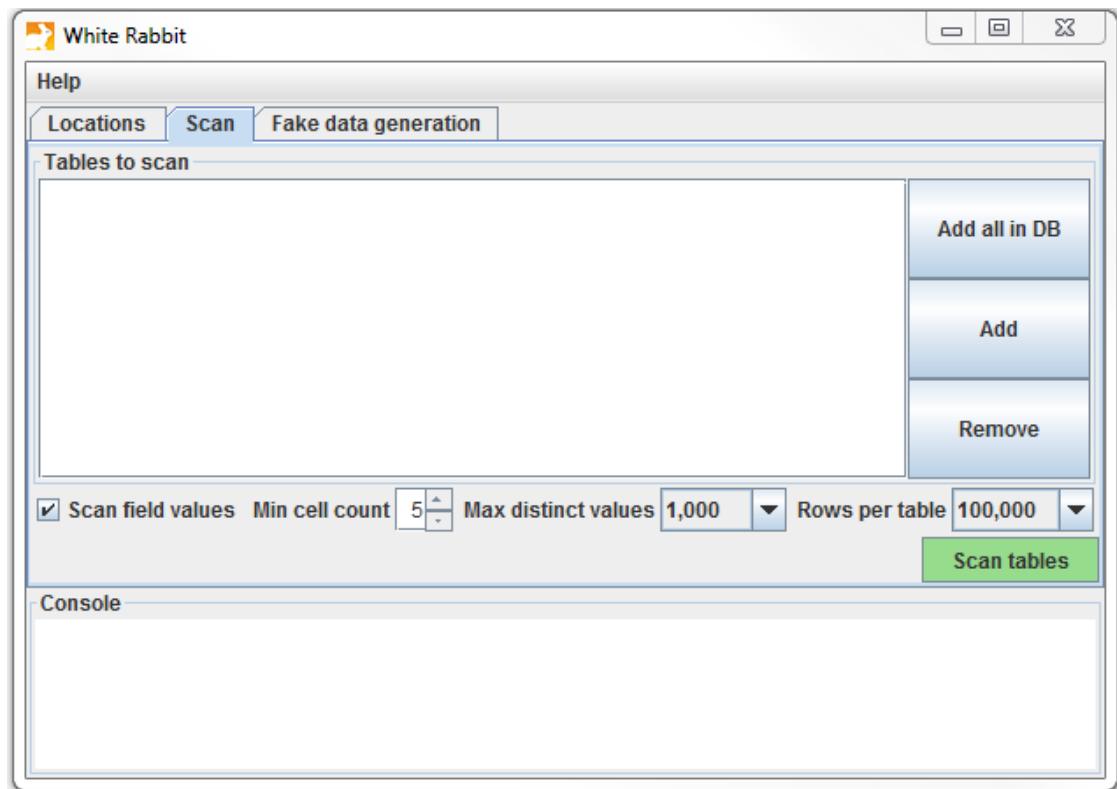


Figure 7.2: White Rabbit Scan tab.

The screenshot shows a Microsoft Excel spreadsheet with a tab titled "Overview". The spreadsheet contains data from two scanned tables: "dbo.allergies" and "dbo.careplans". The columns represent various metadata about the fields in these tables, such as Type, Max length, and the number of rows checked.

A	B	C	D	E	F	G
1 Table	Field	Type	Max length	N rows	N rows checked	Fraction empty
2 dbo.allergies	start	date	10	3184	3184	0
3 dbo.allergies	stop	date	10	3184	3184	0.725188442
4 dbo.allergies	patient	varchar	36	3184	3184	0
5 dbo.allergies	encounter	varchar	36	3184	3184	0
6 dbo.allergies	code	varchar	9	3184	3184	0
7 dbo.allergies	description	varchar	24	3184	3184	0
8						
9 dbo.careplans	id	varchar	36	30199	30199	0
10 dbo.careplans	start	date	10	30199	30199	0
11 dbo.careplans	stop	date	10	30199	30199	0.057849598
12 dbo.careplans	patient	varchar	36	30199	30199	0
13 dbo.careplans	encounter	varchar	36	30199	30199	0
14 dbo.careplans	code	varchar	15	30199	30199	0
15 dbo.careplans	description	varchar	62	30199	30199	0
16 dbo.careplans	reasoncode	varchar	9	30199	30199	0.050796384
17 dbo.careplans	reasondescription	varchar	56	30199	30199	0.050796384
18						

Figure 7.3: Example overview tab from a scan report.

There are a few setting options as well with the scan:

- Checking the “Scan field values” tells WhiteRabbit that you would like to investigate which values appear in the columns.
- “Min cell count” is an option when scanning field values. By default this is set to 5, meaning values in the source data that appear less than 5 times will not appear in the report.
- “Rows per table” is an option when scanning field values. By default, White Rabbit will scan 100,000 randomly selected rows in the table.

Once all settings are completed, press the “Scan tables” button. After the scan is completed the report will be written to the working folder.

Interpreting the Scan Report

Once the scan is complete, an Excel file is generated in the selected folder with one tab present for each table scanned as well as an overview tab. The overview tab lists all tables scanned, each field in each table, the data type of each field, the maximum length of the field, the number of rows in the table, the number of rows scanned, and how often each field was found to be empty. Figure 7.3. shows an example overview tab.

The tabs for each of the tables show each field, the values in each field, and the frequency of each value. Each source table column will generate two columns in the Excel. One column will list all distinct values that have a “Min cell count” greater than what was set at time of the scan. If a list of unique values was truncated, the last value in the list will be “List truncated”, this indicates that there are one or more additional unique source values that appear less than the number entered in the “Min cell count”. Next to each distinct value will be a second column that contains the frequency (the number of times that value occurs in the sample). These two columns (distinct values and frequency)

	A	B
1	Sex	Frequency
2	2	61491
3	1	35401
4	List truncated...	

Figure 7.4: Example values for a single column.

will repeat for all the source columns in the table profiled in the workbook.

The report is powerful in understanding your source data by highlighting what exists. For example, if the results shown in Figure 7.4 were given back on the “Sex” column within one of the tables scanned, we can see that there were two common values (1 and 2) that appeared 61,491 and 35,401 times respectively. WhiteRabbit will not define 1 as male and 2 as female; the data holder will typically need to define source codes unique to the source system. However these two values (1 & 2) are not the only values present in the data because we see this list was truncated. These other values appear with very low frequency (defined by “Min cell count”) and often represent incorrect or highly suspicious values. When generating an ETL we should not only plan to handle the high-frequency gender concepts 1 and 2 but the other low-frequency values that exist within this column.

7.2.2 Rabbit-In-a-Hat

With the White Rabbit scan in hand, we have a clear picture of the source data. We also know the full specification of the CDM. Now we need to define the logic to go from one to the other. This design activity requires thorough knowledge of both the source data and the CDM. The Rabbit-in-a-Hat tools is specifically designed to support a team having these expertises. In a typical setting, the ETL design team sits together in a room, while Rabbit-in-a-Hat is projected on a screen. In a first round, the table-to-table mappings can be collaboratively decided, after which field-to-field mappings can be designed, while defining the logic by which values will be transformed. Rabbit-In-a-Hat comes with the White Rabbit software.

Scope and purpose

Rabbit-In-a-Hat is designed to read and display a White Rabbit scan document. White Rabbit generates information about the source data while Rabbit-In-a-Hat uses that information and through a graphical user interface to allow a user to connect source data to tables and columns within the CDM. Rabbit-In-a-Hat generates documentation for the ETL process, it does not generate code to create an ETL.

Process Overview

The typical sequence for using this software to generate documentation of an ETL:

1. Scanned results from WhiteRabbit completed.
2. Open scanned results; interface displays source tables and CDM tables.
3. Connect source tables to CDM tables where the source table provides information for that corresponding CDM table.

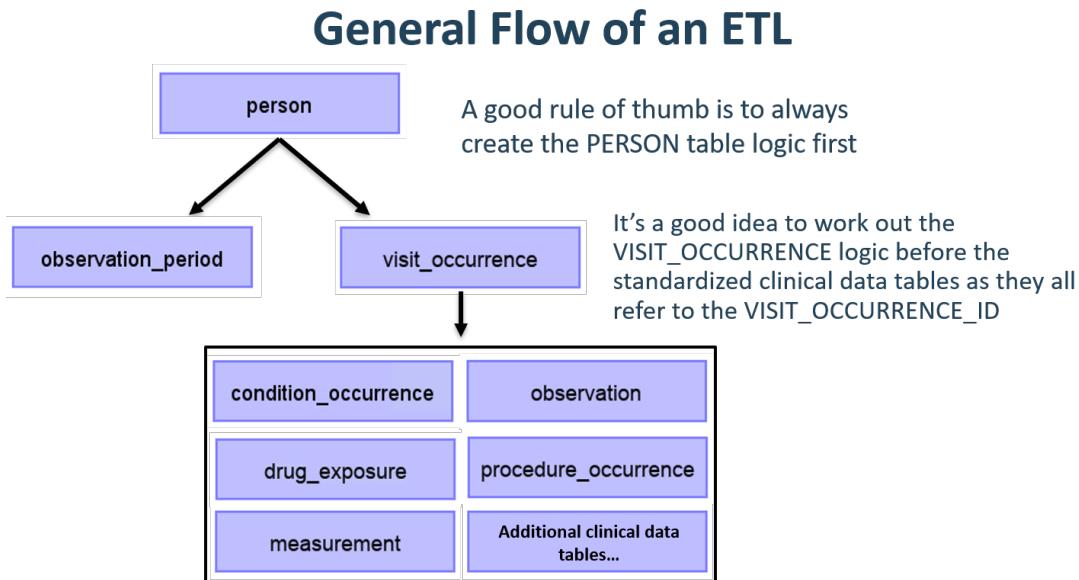


Figure 7.5: General flow of an ETL and which tables to map first.

4. For each source table to CDM table connection, further define the connection with source column to CDM column detail.
5. Save Rabbit-In-a-Hat work and export to a MS Word document.

Writing ETL Logic

Once you have opened your White Rabbit scan report in Rabbit-In-a-Hat you are ready to begin designing and writing the logic for how to convert the source data to the OMOP CDM. As an example, the next few sections will depict how some of the tables in the Synthea² database might look during conversion.

General Flow of an ETL

Since the CDM is a person-centric model it is always a good idea to start mapping the PERSON table first. Every clinical event table (CONDITION_OCCURRENCE, DRUG_EXPOSURE, PROCEDURE_OCCURRENCE, etc.) refers back to the PERSON table by way of the person_id so working out the logic for the PERSON table first makes it easier later on. After the PERSON table a good rule of thumb is to convert the OBSERVATION_PERIOD table next. Each person in a CDM database should have at least one OBSERVATION_PERIOD and, generally, most events for a person fall within this timeframe. Once the PERSON and OBSERVATION_PERIOD tables are done the dimensional tables like PROVIDER, CARE_SITE, and LOCATION are typically next. The final table logic that should be worked out prior to the clinical tables is VISIT_OCCURRENCE. Often this is the most complicated logic in the entire ETL and it is some of the most crucial since most events that occur during the course of a person's patient journey will happen during visits. Once those tables are finished it is your choice which CDM tables to map and in which order.

²Synthea™ is a patient generator that aims to model real patients. Data are created based on parameters passed to the application. The structure of the data can be found here: <https://github.com/synthetichealth/synthea/wiki>.

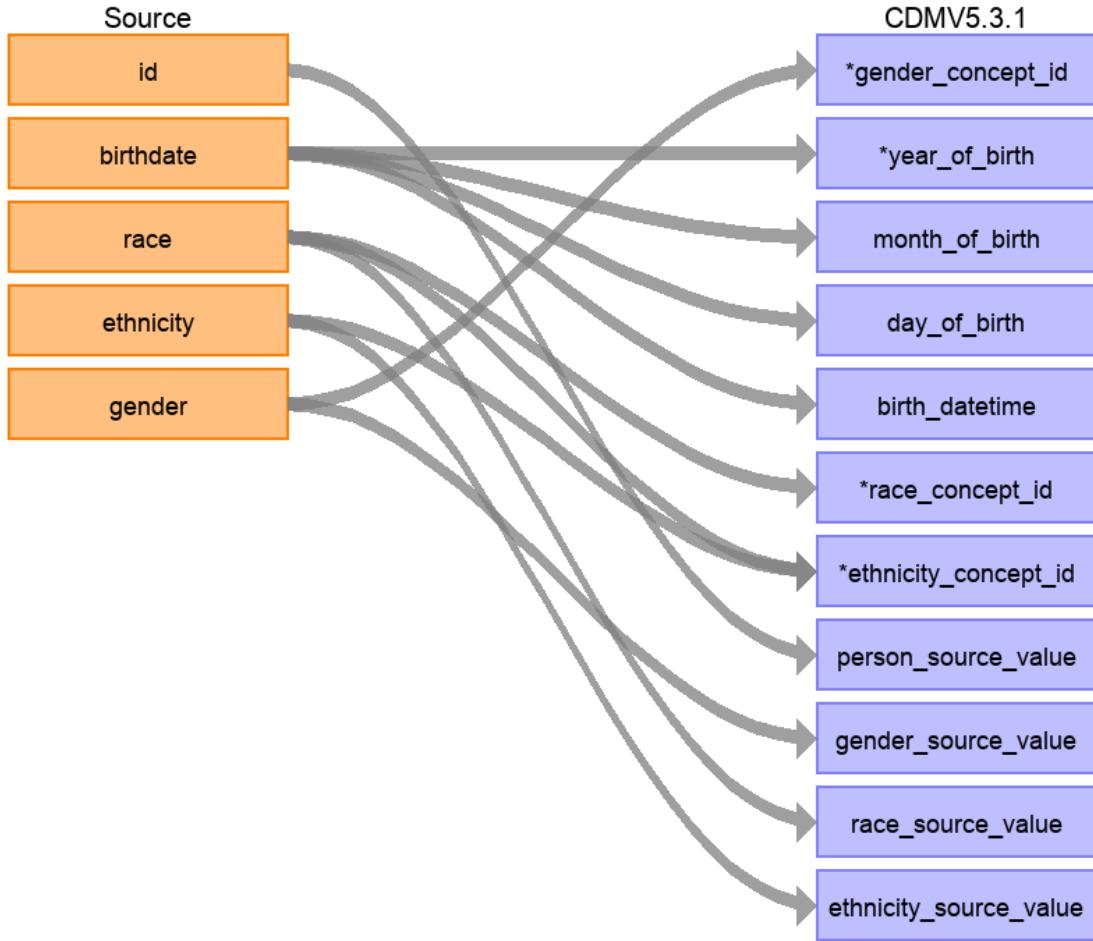


Figure 7.6: Mapping of Synthea Patients table to CDM PERSON table.

It is often the case that, during CDM conversion, you will need to make provisions for intermediate tables. This could be for assigning the correct visit_occurrence_ids to events, or for mapping source codes to standard concepts (doing this step on the fly is often very slow). This is 100% allowed and encouraged. What is discouraged is the persistence and reliance on these tables once the conversion is complete.

7.2.2.1 Mapping Example: Person table

The Synthea data structure contains 20 columns in the patients table but not all were needed to populate the PERSON table, as seen in Figure 7.6. This is very common and should not be cause for alarm. In this example many of the data points in the Synthea patients table that were not used in the CDM PERSON table were additional identifiers like patient name, driver's license number, and passport number.

The table below shows the logic that was imposed on the Synthea patients table to convert it to the CDM PERSON table. The 'Comment field' column gives explanations for why the logic was

chosen.

Table 7.1: ETL logic to convert the Synthea Patients table to CDM PERSON table.

Destination Field	Source field	Logic & comments
person_id		Autogenerate. The person_id will be generated at the time of implementation. This is because the id value from the source is a varchar value while the person_id is an integer. The id field from the source is set as the person_source_value to preserve that value and allow for error-checking if necessary.
gender_concept_id	gender	When gender = ‘M’ then set gender_concept_id to 8507, when gender = ‘F’ then set to 8532. Drop any rows with missing/unknown gender. These two concepts were chosen as they are the only two standard concepts in the gender domain. The choice to drop patients with unknown genders tends to be site-based, though it is recommended they are removed as people without a gender are excluded from analyses.
year_of_birth	birthdate	Take year from birthdate
month_of_birth	birthdate	Take month from birthdate
day_of_birth	birthdate	Take day from birthdate
birth_datetime	birthdate	With midnight as time 00:00:00. Here, the source did not supply a time of birth so the choice was made to set it at midnight.
race_concept_id	race	When race = ‘WHITE’ then set as 8527, when race = ‘BLACK’ then set as 8516, when race = ‘ASIAN’ then set as 8515, otherwise set as 0. These concepts were chosen because they are the standard concepts belonging to the race domain that most closely align with the race categories in the source.
ethnicity_concept_id	race ethnicity	When race = ‘HISPANIC’, or when ethnicity in (‘CENTRAL_AMERICAN’, ‘DOMINICAN’, ‘MEXICAN’, ‘PUERTO_RICAN’, ‘SOUTH_AMERICAN’) then set as 38003563, otherwise set as 0. This is a good example of how multiple source columns can contribute to one CDM column. In the CDM ethnicity is represented as either hispanic or not hispanic so values from both the source column race and source column ethnicity will determine this value.

Destination Field	Source field	Logic & comments
location_id		
provider_id		
care_site_id		
person_source_value	id	
gender_source_value	gender	
gender_source_concept_id		
race_source_value	race	
race_source_concept_id		
ethnicity_source_value	ethnicity	In this case the ethnicity_source_value will have more granularity than the ethnicity_concept_id.
ethnicity_source_concept_id		

For more examples on how the Synthea dataset was mapped to the CDM please see the full specification document ³.

7.3 Step 2: Create the code mappings

More and more code systems are added to the Vocabulary, so it may well be that the coding systems in the data are already included and mapped. Check the VOCABULARY table to see which vocabularies are included. To extract the mapping from non-standard concepts (e.g. ICD-10CM codes) to standard concepts (e.g. SNOMED codes), we can use the records in the CONCEPT_RELATIONSHIP table having relationship_id = “Maps to”. For example, to find the Standard concept ID for the ICD-10CM code I21 (“Acute Myocardial Infarction”), we can use the following SQL:

```
SELECT concept_id_2 standard_concept_id
FROM concept_relationship
INNER JOIN concept source_concept
ON concept_id = concept_id_1
WHERE concept_code = 'I21'
AND vocabulary_id = 'ICD10CM'
AND relationship_id = 'Maps to';
```

standard_concept_id
312327

Unfortunately, sometimes the source data uses coding systems that are not in the Vocabulary. In this case, a mapping has to be created from the source coding system to the Standard Concepts. Code mapping can be a daunting task, especially when there are many codes in the source coding system. There are several things that can be done to make the task easier:

³<https://ohdsi.github.io/ETL-Synthea/>

- Focus on the most frequently used codes. A code that is never used or used maybe just once or twice is not worth the effort of mapping, since it will never be used in a real study.
- Make use of existing information whenever possible. For example, many national drug coding systems have been mapped to ATC. Although ATC is not detailed enough for many purposes, the concept relationships between ATC and RxNorm can be used to make good guesses of what the right RxNorm codes are.
- Use Usagi.

7.3.1 Usagi

Usagi is a tool to aid the manual process of creating a code mapping. It can make suggested mappings based on textual similarity of code descriptions. If the source codes are only available in a foreign language, we have found that Google Translate often gives surprisingly good translation of the terms into English. Usagi allows the user to search for the appropriate target concepts if the automated suggestion is not correct. Finally, the user can indicate which mappings are approved to be used in the ETL. Usagi is available on GitHub⁴.

Scope and purpose

Source codes that need mapping are loaded into the Usagi (if the codes are not in English additional translations columns are needed). A term similarity approach is used to connect source codes to Vocabulary concepts. However these code connections need to be manually reviewed and Usagi provides an interface to facilitate that. Usagi will only propose concepts that are marked as Standard concepts in the Vocabulary.

Process Overview

The typical sequence for using this software is:

1. Load codes from your sources system (“source codes”) that you would like to map to Vocabulary concepts.
2. Usagi will run term similarity approach to map source codes to Vocabulary concepts.
3. Leverage Usagi interface to check, and where needed, improve suggested mappings. Preferably an individual who has experience with the coding system and medical terminology should be used for this review.
4. Export final map generated by Usagi into the Vocabulary’s SOURCE_TO_CONCEPT_MAP.

Importing Source Codes into Usagi

Export source codes from source system into a CSV or Excel (.xlsx) file. This should at least have columns containing the source code and an English source code description, however additional information about codes can be brought over as well (e.g. dose unit, or the description in the original language if translated). In addition to information about the source codes, the frequency of the code should preferably also be brought over, since this can help prioritize which codes should receive the most effort in mapping (e.g. you can have 1,000 source codes but only 100 are truly used within the system). If any source code information needs translating to English, use Google Translate to do that.

⁴<https://github.com/OHDSI/Usagi>

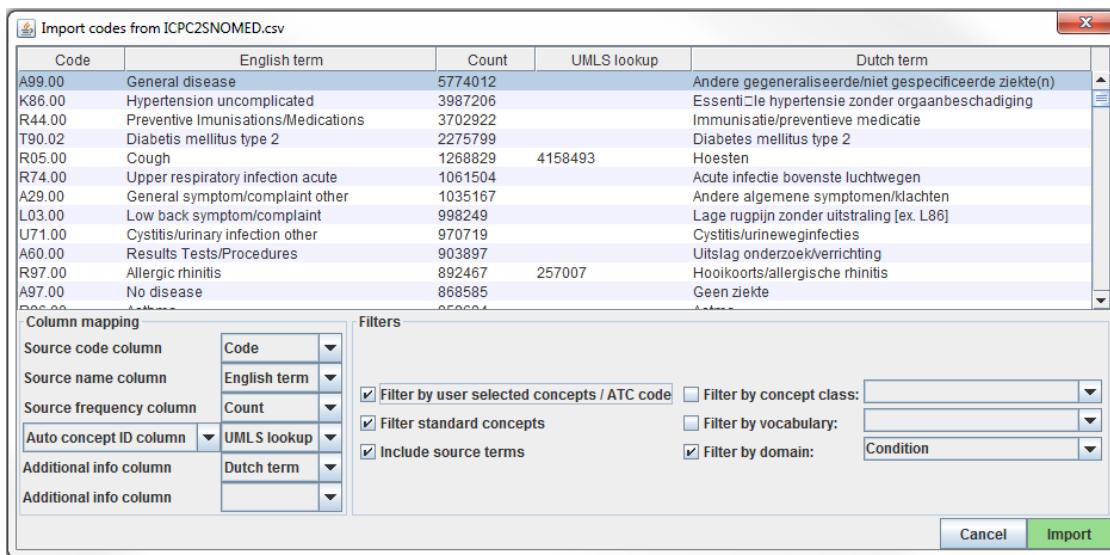


Figure 7.7: Usagi source code input screen.

Note: source code extracts should be broken out by domain (i.e. drugs, procedures, conditions, observations) and not lumped into one large file.

Source codes are loaded into Usagi from the File → Import codes menu. From here an “Import codes ...” will display as seen in Figure 7.7. In this figure, the source code terms were in Dutch and were also translated into English. Usagi will leverage the English translations to map to the standard vocabulary.

The “Column mapping” section (bottom left) is where you define for Usagi how to use the imported table. If you mouse hover over the drop downs, a pop-up will appear defining each column. Usagi will not use the Additional info column(s) as information to associate source codes to Vocabulary concept codes; however this additional information may help the individual reviewing the source code mapping and should be included.

Finally, in the “Filters” section (bottom right) you can set some restrictions for Usagi when mapping. For example, in Figure 7.7, the user is mapping the source codes only to concepts in the Condition domain. By default, Usagi only maps to Standard Concepts, but if the the option ‘Filter standard concepts’ is turned off, Usagi will also consider Classification Concepts. Hover your mouse over the different filters for additional information about the filter.

One special filter is Filter by automatically selected concepts / ATC code. If there is information that you can use to restrict the search, you can do so by providing a list of CONCEPT_IDs or an ATC code in the column indicated in the Auto concept ID column (semicolon-delimited). For example, in the case of drugs there might already be ATC codes assigned to each drug. Even though an ATC code does not uniquely identify a single RxNorm drug code, it does help limit the search space to only those concepts that fall under the ATC code in the Vocabulary. To use the ATC code, follow these steps:

1. In the Column mapping section, switch from “Auto concept ID column” to “ATC column”
2. In the Column mapping section, select the column containing the ATC code as “ATC column”.

The screenshot shows the Usagi software interface for creating code mappings. It consists of three main sections:

- Overview table:** A grid showing the current mapping of source codes to concepts. Columns include Status, Source code, Source term, Frequency, Dutch term, Match score, Concept ID, Concept name, Domain, Concept class, Vocabulary, Concept code, Standard concept, and Parents/Children. A red box highlights the "Overview table" section.
- Selected mapping:** A detailed view of a specific mapping row. It shows Source code (R05.00), Source term (Cough), Frequency (1268829), and various concept details like Concept ID (4158493), Concept name (C/O- cough), and Concept class (Condition). A red box highlights the "Selected mapping" section.
- Search facility:** A search interface with a query input field, filters (including "Filter by user selected concepts / ATC code" which is checked), and a results table. The results table lists various terms like Cough, Calcough, No cough, Hough, Dry cough, etc., with their corresponding Concept ID, Concept name, Domain, Concept class, Vocabulary, Concept code, Standard concept, Parents, and Children. A red box highlights the "Search facility" section.

Figure 7.8: Usagi source code input screen.

3. Turn on the “Filter by user selected concepts / ATC code” on in the Filters section.

You can also use other sources of information than the ATC code to restrict as well. In the example shown in the figure above, we used a partial mapping derived from UMLS to restrict the Usagi search. In that case we will need to use “Auto concept ID column”.

Once all your settings are finalized, click the “Import” button to import the file. The file import will take a few minutes as it is running the term similarity algorithm to map source codes.

Reviewing Source Code to Vocabulary Concept Maps

Once you have imported your input file of source codes, the mapping process begins. In Figure 7.8, you see the Usagi screen is made up of 3 main sections: an overview table, the selected mapping section, and place to perform searches. Note that in any of the tables, you can right-click to select the columns that are shown or hidden to reduce the visual complexity.

Approving a Suggested Mapping

The Overview Table shows the current mapping of source codes to concepts. Right after importing source codes, this mapping contains the automatically generated suggested mappings based on term similarity and any search options. In the example in Figure 7.8, the English names of Dutch condition codes were mapped to standard concepts in the Condition domain, because the user restricted the search to that domain. Usagi compared the source code descriptions to concept names and synonyms to find the best match. Because the user had selected “Include source terms” Usagi also considered the names and synonyms of all source concepts in the vocabulary that map to a particular concept. If Usagi is unable to make a mapping, it will map to the CONCEPT_ID = 0.

It is suggested that someone with experience with coding systems help map source codes to their associated standard vocabulary. That individual will work through code by code in the Overview Table to either accept the mapping Usagi has suggested or choose a new mapping. For example in Figure 7.8 we see that the Dutch term “Hoesten” which was translated to the English term “Cough”. Usagi used “Cough” and mapped it to the Vocabulary concept of “4158493-C/O - cough”. There was a matching score of 0.58 associated to this matched pair (matching scores are typically 0 to 1 with 1 being a confident match), a score of 0.58 signifies that Usagi is not very sure of how well it has mapped this Dutch code to SNOMED. Let us say in this case, we are okay with this mapping, we can approve it by hitting the green “Approve” button in the bottom right hand portion of the screen.

Searching for a New Mapping

There will be cases where Usagi suggests a map and the user will be left to either try to find a better mapping or set the map to no concept (CONCEPT_ID = 0). In the example given in Figure 7.8, we see for the Dutch Term “Hoesten”, which was translated to “Cough”. Usagi’s suggestion was restricted by the concept identified in our automatically derived mapping from UMLS, and the result might not be optimal. In the Search Facility, we could search for other concepts using either the actual term itself or a search box query.

When using the manual search box, one should keep in mind that Usagi uses a fuzzy search, and does not support structured search queries, so for example not supporting boolean operators like AND and OR.

To continue our example, suppose we used the search term “Cough” to see if we could find a better mapping. On the right of the Query section of the Search Facility, there is a Filters section, this provides options to trim down the results from the Vocabulary when searching for the search term. In this case we know we want to only find standard concepts, and we allow concepts to be found based on the names and synonyms of source concepts in the vocabulary that map to those standard concepts.

When we apply these search criteria we find “254761-Cough” and feel this may be an appropriate Vocabulary concept to map to our Dutch code. In order to do that we can hit the “Replace concept” button, which you will see in the Selected Source Code section update, followed by the “Approve” button. There is also an “Add concept” button, this allows for multiple standardized Vocabulary concepts to map to one source code (e.g. some source codes may bundle multiple diseases together while the standardized vocabulary may not).

Concept information

When looking for appropriate concepts to map to, it is important to consider the “social life” of a concept. The meaning of a concept might depend partially on its place in the hierarchy, and sometimes there are “orphan concepts” in the vocabulary with few or no hierarchical relationships, which would be ill-suited as target concepts. Usagi will often report the number of parents and children a concept has, and it is also possible to show more information by pressing ALT + C, or selecting view → Concept information in the top menu bar.

Figure 7.9 shows the concept information panel. It shows general information about a concept, as well as its parents, children, and other source codes that map to the concept. Users can use this panel to navigate the hierarchy and potentially choose a different target concept.

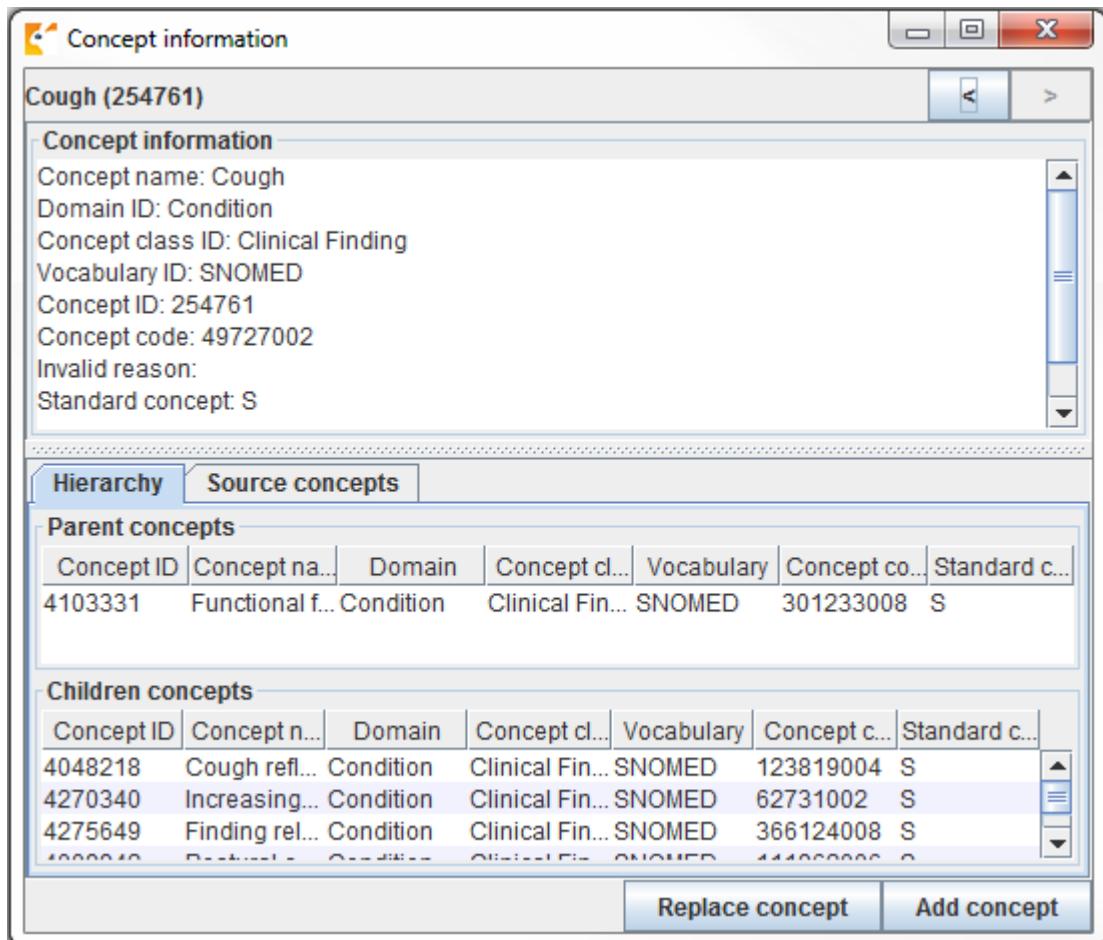


Figure 7.9: Usagi concept information panel.

Continue to move through this process, code by code, until all codes have been checked. In the list of source codes at the top of the screen, by selecting the column heading you can sort the codes. Often we suggest going from the highest frequency codes to the lowest. In the bottom left of the screen you can see the number of codes that have approved mappings, and how many code occurrences that corresponds to.

It is possible to add comments to mappings, which could be used to document why a particular mapping decision was made.

Best Practices

- Use someone who has experience with coding schemes.
- By clicking on a column name you can sort the columns in the Overview Table. It may be valuable to sort on “Match Score”; reviewing codes that Usagi is most confident on first may quickly knock out a significant chunk of codes. Also sorting on “Frequency” is valuable, spending more effort on frequent codes versus non-frequent is important.
- It is okay to map some codes to CONCEPT_ID = 0, some codes may not be worth it to find a good map and others may just lack a proper map.
- It is important to consider the context of a concept, specifically its parents and children.

Export the Usagi Map Created

Once you have created your map within USAGI, the best way to use it moving forward is to export it and append it to the Vocabulary SOURCE_TO_CONCEPT_MAP table.

To export your mappings go to File → Export source_to_concept_map. A pop-up will appear asking you which SOURCE_VOCABULARY_ID you would like to use, type in a short identifier. Usagi will use this identifier. as the SOURCE_VOCABULARY_ID which will allow you to identify your specific mapping in the SOURCE_TO_CONCEPT_MAP table.

After selecting the SOURCE_VOCABULARY_ID, you give your export CSV a name and save to location. The export CSV structure is in that of the SOURCE_TO_CONCEPT_MAP table. This mapping could be appended to the OMOP Vocabulary’s SOURCE_TO_CONCEPT_MAP table. It would also make sense to append a single row to the VOCABULARY table defining the SOURCE_VOCABULARY_ID you defined in the step above. Finally, it is important to note that only mappings with the “Approved” status will be exported into the CSV file; the mapping needs to be completed in USAGI in order to export it.

Updating an Usagi mapping

Often a mapping is not a one-time effort. As data is updated perhaps new source codes are added, and also the vocabulary is updated regularly, perhaps requiring an update of the mapping.

When the set of source codes is updated the following steps can be followed to support the update:

1. Import the new source code file
2. Choose File → Apply previous mapping, and select the old Usagi mapping file
3. Identify codes that haven’t inherited approved mappings from the old mapping, and map them as usual.

When the vocabulary is updated, follow these steps:

1. Download the new vocabulary files from Athena
2. Rebuild the Usagi index (Help → Rebuild index)
3. Open the mapping file
4. Identify codes that map to concepts that in the new vocabulary version no longer are Standard concepts, and find more appropriate target concepts.

7.4 Step 3: Implement the ETL

Implementation usually varies site to site and it largely depends on many factors including infrastructure, size of the database, the complexity of the ETL, and the technical expertise available. A few examples of different ETLs:

- ETL-CDMBuilder - A .NET application designed to transform multiple databases
 - <https://github.com/OHDSI/etl-cdmbuilder>
- ETL-Synthea - A SQL builder written to convert the Synthea database
 - <https://github.com/OHDSI/etl-synthea>
- ETL-LambdaBuilder - A builder using the AWS lambda functionality
 - <https://github.com/OHDSI/etl-lambdabuilder>

7.5 Step 4: Quality control

For the extract, transform, load process, quality control is iterative. The typical pattern is to write logic → implement logic → test logic → fix/write logic. There are different ways to approach data quality as detailed in chapter 16 but we recommend at least the following steps in quality control:

- Review of the ETL design document, computer code, and code mappings. Any one person can make mistakes, so always at least one other person should review what the first person did.
- Manually compare all information on a sample of persons in the source and target data.
- Compare overall counts in the source and target data.
- Replicate a study that has already been performed on the source data on the CDM version.
- Create unit tests meant to replicate a pattern in the source data that should be addressed in the ETL. For example, if your ETL specifies that patients without gender information should be dropped, create a unit test of a person without a gender and assess how the builder handles it.

7.6 Final thoughts on ETL

The ETL process is a difficult one to master for many reasons, not the least of which the fact that we are all working off of unique source data, making it hard to create a “one-size-fits-all” solution. However, there are some hard won lessons we have learned over the years.

- The 80/20 rule. If you can avoid it don’t spend too much time manually mapping source codes to concepts sets. Ideally, map the source codes that cover the majority of your data.

This should be enough to get you started and you can address any remaining codes in the future based on use cases.

- It's ok if you lose data that is not of research quality. Often these are the records that would be discarded before starting an analysis anyway, we just remove them during the ETL process instead.
- A CDM requires maintenance. Just because you complete an ETL does not mean you don't need to touch it ever again. Your raw data might change, there might be a bug in the code, there may be new vocabulary or an update to the CDM. Plan for an allocate resources to these changes so your ETL is always up-to-date.

7.7 Summary

- 
- There is a generally agreed upon process for how to approach an ETL, including
 - * Data experts and CDM experts together design the ETL
 - * People with medical knowledge create the code mappings
 - * A technical person implements the ETL
 - * All are involved in quality control
 - Tools have been developed by the OHDSI community to facilitate these steps and are freely available for use
 - There are many ETL examples and agreed upon conventions you can use as a guide

Part III

Data Analytics

Chapter 8

Data Analytics Use Cases

Chapter lead: David Madigan

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 categories:

- Characterization
- Population-level estimation
- Patient-level prediction

We describe these in detail below. Note, for all the use cases, the evidence we generate inherits the limitations of the data; we discuss these limitations at length in the book section on Evidence Quality (Chapters 15 - 19)

8.1 Characterization

Characterization attempts to answer the question

What happened to them?

We can use the data to provide answers to questions about the characteristics of the persons in a cohort or the entire 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 arthroplasty?
- What is the incidence rate of pneumonia in patients over 65 years old?

8.2 Population-level estimation

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

What are the causal effects?

We would like to understand causal effects to understand consequences of actions. For example, if we decide to take some treatment, how does that change what happens to us in the future?

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?

8.3 Patient-Level prediction

Based on the collected patient health histories in the database, we can make patient-level predictions about future health events, answering the question

What will happen to me?

The data can provide answers to questions like:

- For a specific patient newly diagnosed with major depressive disorder, what is the probability the patient will attempt suicide in the first year following diagnosis?
- 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?

Population-level estimation and patient-level prediction 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, and should be estimated using causal effect estimation methods instead.



People have a natural tendency to erroneously interpret predictive models as if they are causal models. But a predictive model can only show correlation, never causation. For example, diabetic drug use might be a strong predictor for myocardial infarction (MI) because diabetes is a strong risk factor for MI. However, that does not mean that stopping the diabetic drugs will prevent MI!

8.4 Limitations of observational research

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 treatment.
- Anything related to over-the-counter medications.
- Many outcomes and other variables are sparsely recorded if at all. These include mortality, behavioral outcomes, lifestyle, and socioeconomic status.
- Since patients tend to encounter the healthcare system only when they are unwell, measurement of the benefits of treatments can prove elusive.

8.4.1 Missing data

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 useful introduction to this topic.

8.5 Summary



- In observational research we distinguish three large categories of uses cases.
- **Characterization aims** to answer the questions “What happened to them?”
- **Population-level estimation** attempts to answer the question “What are the causal effects?”
- **Patient-level prediction** tries to answer “What will happen to me?”
- Prediction models are not causal models; There is no reason to believe that intervening on a strong predictor will impact the outcome.

Chapter 9

OHDSI Analytics Tools

Chapter leads: Martijn Schuemie & Frank DeFalco

OHDSI offers a wide range of open source tools to support various data-analytics use cases on observational patient-level data. What these tools have in common is that they can all interact with one or more databases using the Common Data Model (CDM). Furthermore, these tools standardize the analytics for various use cases; Rather than having to start from scratch, an analysis can be implemented by filling in standard templates. This makes performing analysis easier, and also improves reproducibility and transparency. For example, there appear to be a near-infinite number of ways to compute an incidence rate, but these can be specified in the OHDSI tools with a few choices, and anyone making those same choices will compute incidence rates the same way.

In this chapter we first describe various ways in which we can choose to implement an analysis, and what strategies the analysis can employ. We then review the various OHDSI tools and how they fit the various use cases.

9.1 Analysis implementation

Figure 9.1 shows the various ways in which we can choose to implement a study against a database using the CDM.

We may choose to write our analysis as custom code, and not make use of any of the tools OHDSI has to offer. One could write a de novo analysis in R, SAS, or any other language. This provides the maximum flexibility, and may in fact be the only option if the specific analysis is not supported by any of our tools. However, this path requires a lot of technical skill, time, and effort, and as the analysis increases in complexity it becomes harder to avoid errors in the code.

An alternative is to develop the analysis in R, and make use of the packages in the OHDSI Methods Library. At a minimum, one could use the SqlRender and DatabaseConnector packages described in more detail in Chapter 10 that allow the same code to be executed on various database platforms, such as PostgreSQL, SQL Server, and Oracle. Other packages such as CohortMethod and PatientLevelPrediction offer R functions for advanced analytics against the CDM that can be called on in one's

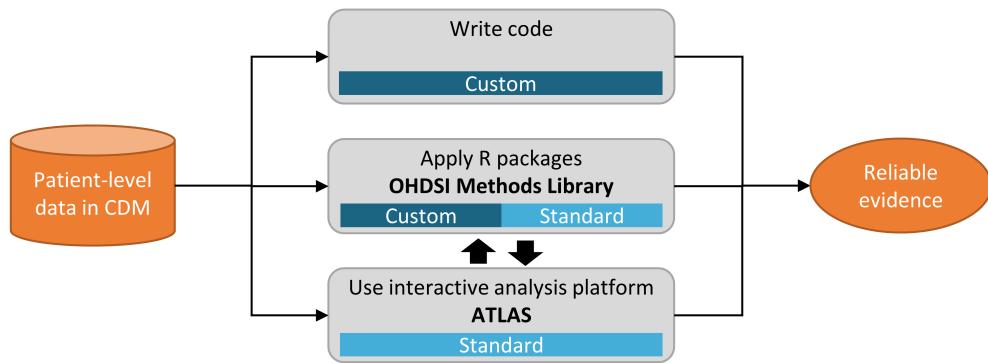


Figure 9.1: Different ways to implement an analysis against data in the CDM.

code. This still requires a lot of technical expertise, but by re-using the validated components of the Methods Library we can be more efficient and error-free than when using completely custom code.

The third approach relies on our interactive analysis platform ATLAS, a web-based tool that allows non-programmers to perform a wide range of analyses efficiently. ATLAS makes use of the Methods Libraries but provides a simple, point and click interface to design analyses and in many cases generate the necessary R code to run the analysis. The pace of development can vary between the Methods Libraries and ATLAS which can lead to limited options in the ATLAS interface where the underlying libraries have more flexibility.

ATLAS and the Methods Library are not independent. Some of the more complicated analytics that can be invoked in ATLAS are executed through calls to the packages in the Methods Library. Similarly, cohorts used in the Methods Library are often designed in ATLAS.

9.2 Analysis strategy

More or less independently of how we choose to implement our analysis is the strategy that our analytics takes in answering specific questions. Figure 9.2 highlights three strategies that are employed in OHDSI.

The first strategy views every analysis as a single individual study. The analysis must be pre-specified in a protocol, implemented as code, executed against the data, after which the result can be compiled and interpreted. For every question, all steps must be repeated. An example of such an analysis is the OHDSI study into the risk of angioedema associated with levetiracetam compared with phenytoin. (Duke et al., 2017) Here, a protocol was first written, analysis code using the OHDSI Methods Library was developed and executed across the OHDSI network, and results were compiled and disseminated in a journal publication.

The second strategy develops an application that allows users to answer a specific class of questions in real time or near-real time. Once the application has been developed, users can interactively define queries, submit them, and view the results. An example of this strategy is the cohort definition and generation tool in ATLAS. This tool allows users to specify cohort definitions of varying complexity,

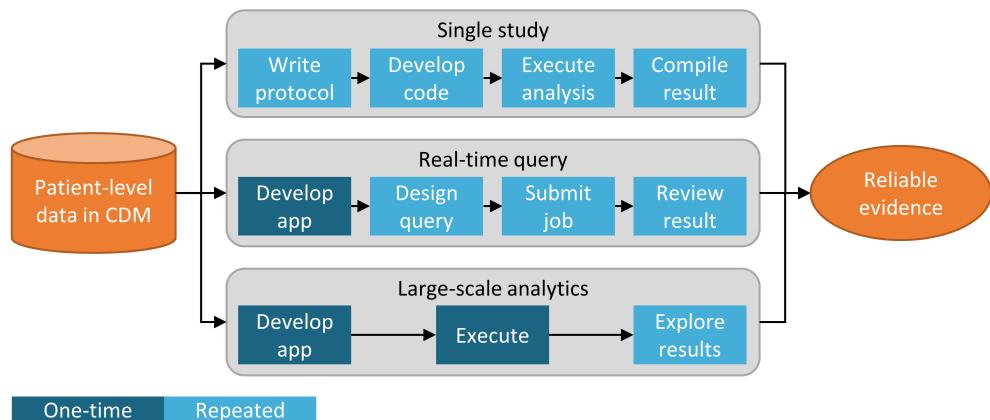


Figure 9.2: Strategies for generating evidence for (clinical) questions.

and execute the definition against a database to see how many people meet the various inclusion and exclusion criteria.

The third strategy similarly focuses on a class of questions, but then attempts to exhaustively generate all the evidence for the questions within the class. Users can then explore the evidence as needed through a variety of interfaces. One example is the OHDSI study into the effects of depression treatments (Schuemie et al., 2018b). In this study all depression treatments are compared for a large set of outcomes of interest across four large observational databases. The full set of results, including 17,718 empirically calibrated hazard ratios along with extensive study diagnostics, is available in an interactive web app¹.

9.3 ATLAS

ATLAS is a free, publically available, web-based tool developed by the OHDSI community that facilitates the design and execution of analyses on standardized, patient-level, observational data in the CDM format. ATLAS is deployed as a web application in combination with the OHDSI WebAPI and is typically hosted on Apache Tomcat. Performing real time analyses requires access to the patient-level data in the CDM and is therefore typically installed behind an organization's firewall. However, there is also a public ATLAS², and although this ATLAS instance only has access to a small simulated datasets, it can still be used for many purposes including testing and training. For example, it is possible to fully define an effect estimation or prediction study using the public instance of ATLAS, and automatically generate the R code for executing the study. That code can then be run in any environment with an available CDM without needing to install ATLAS and the WebAPI.

A screenshot of ATLAS is provided in Figure 9.3. On the left is a navigation bar showing the various functions provided by ATLAS:

Data Sources Data sources provides the capability review descriptive, standardized reporting for

¹<http://data.ohdsi.org/SystematicEvidence/>

²<http://www.ohdsi.org/web/atlas>

Figure 9.3: ATLAS user interface.

each of the data sources that you have configured within your Atlas platform. This feature uses the large-scale analytics strategy: all descriptives have been pre-computed. Data sources is discussed in Chapter 12.

Vocabulary Search Atlas provides the ability to search and explore the OMOP standardized vocabulary to understand what concepts exist within those vocabularies and how to apply those concepts in your standardized analysis against your data sources. This feature is discussed in Chapter 6.

Concept Sets Concept sets provides the ability to create collections of logical expressions that can be used to identify a set of concepts to be used throughout your standardized analyses. Concept sets provide more sophistication than a simple list of codes or values. A concept set is comprised of multiple concepts from the standardized vocabulary in combination with logical indicators that allow a user to specify that they are interested in including or excluding related concepts in the vocabulary hierarchy. Searching the vocabulary, identifying the set of concepts, and specifying the logic to be used to resolve a concept set provides a powerful mechanism for defining the often obscure medical language used in analysis plans. These concept sets can be saved within ATLAS and then used throughout your analysis as part of cohort definitions or analysis specifications.

Cohort Definitions Cohort definitions is the ability to construct a set of persons who satisfy one or more criteria for a duration of time and these cohorts can then serve as the basis of inputs for all of your subsequent analyses. This feature is discussed in Chapter 11.

Characterizations Characterizations is an analytic capability that allows you to look at one or more cohorts that you've defined and to summarize characteristics about those patient populations. This feature uses the real-time query strategy, and is discussed in Chapter 12.

Cohort Pathways Cohort pathways is an analytic tool that allows you to look at the sequence of

clinical events that occur within one or more populations. This feature uses the real-time query strategy, and is discussed in Chapter 12.

Incidence Rates Incidence rates is a tool that allows you to estimate the incidence of outcomes within target populations of interest. This feature uses the real-time query strategy, and is discussed in Chapter 12.

Profiles Profiles is a tool that allows you to explore an individual patients longitudinal observational data to summarize what is going on within a given individual. This feature uses the real-time query strategy.

Population Level Estimation Estimation is a capability to allow you to define a population level effect estimation study using a comparative cohort design whereby comparisons between one or more target and comparator cohorts can be explored for a series of outcomes. This feature can be said to implement the real-time query strategy, as no coding is required, and is discussed in Chapter 13.

Patient Level Prediction Prediction is a capability to allow you to apply machine learning algorithms to conduct patient level prediction analyses whereby you can predict an outcome within any given target exposures. This feature can be said to implement the real-time query strategy, as no coding is required, and is discussed in Chapter 14.

Jobs Select the Jobs menu item to explore the state of processes that are running through the WebAPI. Jobs are often long running processes such as generating a cohort or computing cohort characterization reports.

Configuration Select the Configuration menu item to review the data sources that have been configured in the source configuration section.

Feedback The Feedback link will take you to the issue log for Atlas so that you can log a new issue or to search through existing issues. If you have ideas for new features or enhancements, this is also a place note these for the development community.

9.3.1 Security

ATLAS and the WebAPI provide a granular security model to control access to features or data sources within the overall platform. The security system is built leveraging the Apache Shiro library. Additional information on the security system can be found in the online WebAPI security wiki.

9.3.2 Documentation

Documentation for ATLAS can be found online in the ATLAS Github repository wiki. This wiki includes information on the various application features as well as links to online video tutorials.

9.3.3 How to install

Installation of ATLAS is done in combination with the OHDSI WebAPI. Installation guides for each component are available online in the ATLAS Github repository Setup Guide and WebAPI Github repository Installation Guide.

9.4 Methods Library

The OHDSI Methods Library is the collection of open source R packages shown in Figure 9.4.

The packages offer R functions that together can be used to perform an observational study from data to estimates and supporting statistics, figures, and tables. The packages interact directly with observational data in the CDM, and can be used simply to provide cross-platform compatibility to completely custom analyses as described in Chapter 10, or can provide advanced standardized analytics for population characterization (Chapter 12), population-level causal effect estimation (Chapter 13), and patient-level prediction (Chapter 14). The Methods Library supports best practices for use of observational data as learned from previous and ongoing research, such as transparency, reproducibility, as well as measuring of the operating characteristics of methods in a particular context and subsequent empirical calibration of estimates produced by the methods.

The Methods Library has already been used in many published clinical studies (Boland et al., 2017; Duke et al., 2017; Ramcharran et al., 2017; Weinstein et al., 2017; Wang et al., 2017; Ryan et al., 2017, 2018; Vashisht et al., 2018; Yuan et al., 2018; Johnston et al., 2019), as well as methodological studies (Schuemie et al., 2014, 2016; Reps et al., 2018; Tian et al., 2018; Schuemie et al., 2018a,b; Reps et al., 2019). Great care is taken to ensure the validity of the Methods Library, as described in Chapter 18.

9.4.1 Support for large-scale analytics

One key feature incorporated in all packages is the ability to efficiently run many analyses. For example, when performing population-level estimation, the CohortMethod package allows for computing effect-size estimates for many exposures and outcomes, using various analysis settings, and the package will automatically choose the optimal path to compute all the required artifacts. Steps that can be re-used, such as extraction of covariates, or fitting a propensity model, will be executed only once. Where possible, computations will take place in parallel to maximize the use of computational resources.

This feature allows for large-scale analytics, answering many questions at once, and is also essential for including control hypotheses (e.g. negative controls) to measure the operating characteristics of our methods, and perform empirical calibration as described in Chapter 19.

9.4.2 Support for big data

The Methods Library is also designed to run against very large databases and be able to perform computations involving large amounts of data. This is achieved in three ways:

1. Most data manipulation is performed on the database server. An analysis usually only requires a small fraction of the entire data in the database, and the Methods Library, through the SqlRender and DatabaseConnector packages, allows for advanced operations to be performed on the server to preprocess and extract the relevant data.

Prediction and estimation methods	<p>Cohort Method</p> <p>New-user cohort studies using large-scale regression for propensity and outcome models</p>	<p>Self-Controlled Case Series</p> <p>Self-Controlled Case Series analysis using few or many predictors, includes splines for age and seasonality.</p>	<p>Self-Controlled Cohort</p> <p>A self-controlled cohort design, where time preceding exposure is used as control.</p>
Method characterization	<p>Patient Level Prediction</p> <p>Build and evaluate predictive models for user-specified outcomes, using a wide array of machine learning algorithms.</p>	<p>Case-control</p> <p>Case-control studies, matching controls on age, gender, provider, and visit date. Allows nesting of the study in another cohort.</p>	<p>Case-crossover</p> <p>Case-crossover design including the option to adjust for time-trends in exposures (so-called case-time-control).</p>
Supporting packages	<p>Empirical Calibration</p> <p>Use negative control exposure-outcome pairs to profile and calibrate a particular analysis design.</p>	<p>Method Evaluation</p> <p>Use real data and established reference sets as well as simulations injected in real data to evaluate the performance of methods.</p>	<p>Evidence Synthesis</p> <p>Combining study diagnostics and results across multiple sites.</p>
	<p>Database Connector</p> <p>Connect directly to a wide range of database platforms, including SQL Server, Oracle, and PostgreSQL.</p>	<p>Sql Render</p> <p>Generate SQL on the fly for the various SQL dialects.</p>	<p>Cyclops</p> <p>Highly efficient implementation of regularized logistic, Poisson and Cox regression.</p>
	<p>ParallelLogger</p> <p>Support for parallel computation with logging to console, disk, or e-mail.</p>	<p>Feature Extraction</p> <p>Automatically extract large sets of features for user-specified cohorts using data in the CDM.</p>	

Figure 9.4: Packages in the OHDSI Methods Library.

2. Large local data objects are stored in a memory-efficient manner. For the data that is downloaded to the local machine, the Methods Library uses the `ff` package to store and work with large data objects. This allows us to work with data much larger than fits in memory.
3. High-performance computing is applied where needed. For example, the `Cyclops` package implements a highly efficient regression engine that is used throughout the Methods Library to perform large-scale regressions (large number of variables, large number of observations) that would not be possible to fit otherwise.

9.4.3 Documentation

R provides a standard way of documenting package. Each package has a *package manual* that documents every function and data set in the package. All package manuals are available online through the Methods Library website ³, through the package GitHub repositories, and for those packages available through CRAN they can be found in CRAN. Furthermore, from within R the package manual can be consulted by using the question mark. For example, after loading the `DatabaseConnector` package, typing the command `?connect` brings up the documentation on the “connect” function.

In addition to the package manual, many packages provide *vignettes*. Vignettes are long-form documentation that describe how a package can be used to perform certain tasks. For example, one vignette ⁴ describes how to perform multiple analyses efficiently using the `CohortMethod` package. Vignettes can also be found through the Methods Library website , through the package GitHub repositories, and for those packages available through CRAN they can be found in CRAN.

9.4.4 System requirements

Two computing environments are relevant when discussing the system requirements: The database server, and the analytics workstation.

The database server must hold the observational healthcare data in CDM format. The Methods Library supports a wide array of database management systems including traditional database systems (PostgreSQL, Microsoft SQL Server, and Oracle), parallel data warehouses (Microsoft APS, IBM Netezza, and Amazon RedShift), as well as Big Data platforms (Hadoop through Impala, and Google BigQuery).

The analytics workstation is where the Methods Library is installed and run. This can either be a local machine, such as someone’s laptop, or a remote server running RStudio Server. In all cases the requirements are that R is installed, preferably together with RStudio. The Methods Library also requires that Java is installed. The analytics workstation should also be able to connect to the database server, specifically, any firewall between them should have the database server access ports opened the the workstation. Some of the analyses can be computationally intensive, so having multiple processing cores and ample memory can help speed up the analyses. We recommend having at least four cores and 16 gigabytes of memory.

³<https://ohdsi.github.io/MethodsLibrary>

⁴<https://ohdsi.github.io/CohortMethod/articles/MultipleAnalyses.html>

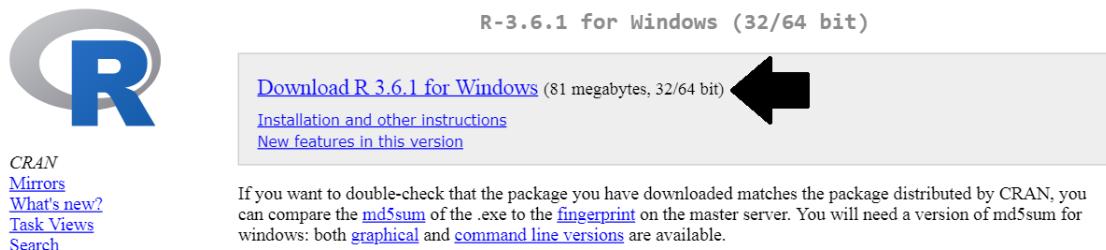


Figure 9.5: Downloading R from CRAN.

9.4.5 How to install

Here are the steps for installing the required environment to run the OHDSI R packages. Four things needs to be installed:

1. **R** is a statistical computing environment. It comes with a basic user interface that is primarily a command-line interface.
2. **RTools** is a set of programs that is required on Windows to build R packages from source.
3. **RStudio** is an IDE (Integrated Development Environment) that makes R easier to use. It includes a code editor, debugging and visualization tools. Please use it to obtain a nice R experience.
4. **Java** is a computing environment that is needed to run some of the components in the OHDSI R packages, for example those needed to connect to a database.

Below we describe how to install each of these in a Windows environment.



In Windows, both R and Java come in 32-bit and 64-bits architectures. If you install R in both architectures, you **must** also install Java in both architectures. It is recommended to only install the 64-bit version of R.

Installing R

1. Go to <https://cran.r-project.org/>, click on “Download R for Windows”, then “base”, then click the Download link indicated in Figure 9.5.
2. After the download has completed, run the installer. Use the default options everywhere, with two exceptions: First, it is better not to install into program files. Instead, just make R a subfolder of your C drive as shown in Figure 9.6. Second, to avoid problems due to differing architectures between R and Java, disable the 32-bit architecture as shown in Figure 9.7.

Once completed, you should be able to select R from your Start Menu.

Installing RTools

1. Go to <https://cran.r-project.org/>, click on “Download R for Windows”, then “Rtools”, and select the very latest version of RTools to download.
2. After downloading has completed run the installer. Select the default options everywhere.

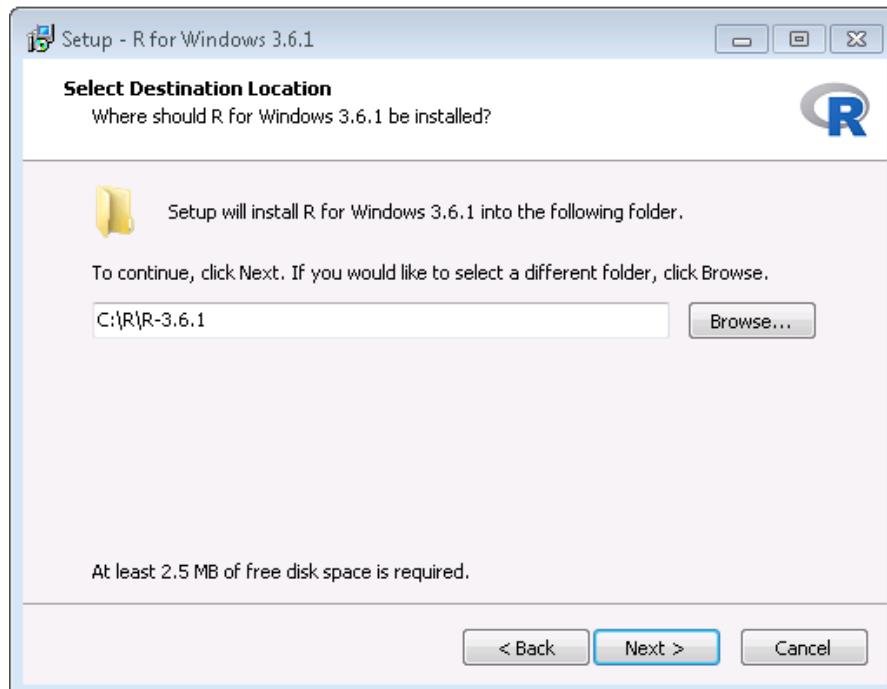


Figure 9.6: Settings the destination folder for R.

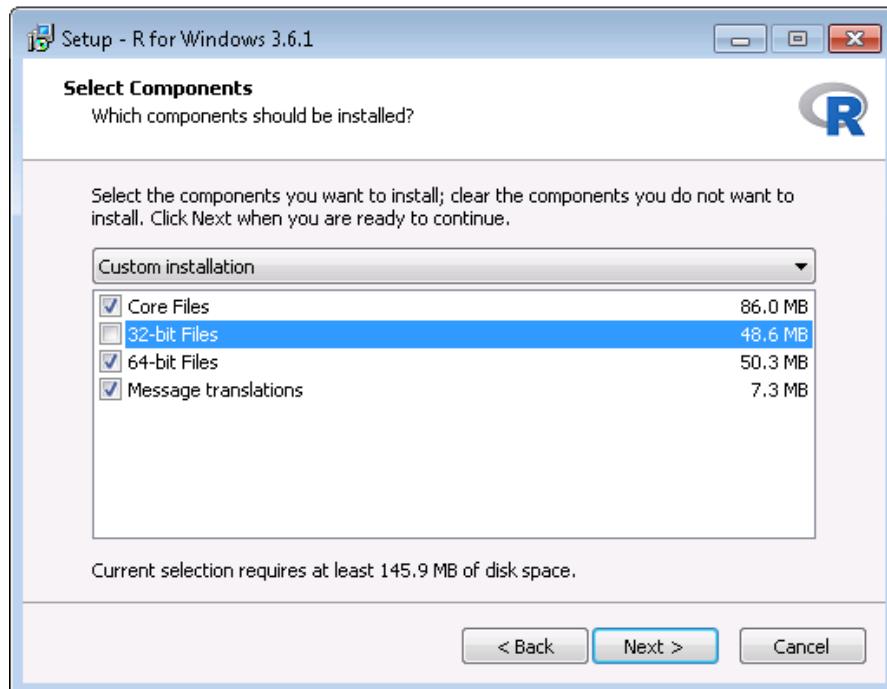


Figure 9.7: Disabling the 32-bit version of R.

Installers for Supported Platforms

Installers		Size	Date	MD5
RStudio 1.2.1335 - Windows 7+ (64-bit)		126.9 MB	2019-04-08	d0e2470f1
RStudio 1.2.1335 - Mac OS X 10.12+ (64-bit)		121.1 MB	2019-04-08	6c570b0e2
RStudio 1.2.1335 - Ubuntu 14/Debian 8 (64-bit)		92.2 MB	2019-04-08	c1b07d051

Figure 9.8: Downloading RStudio.

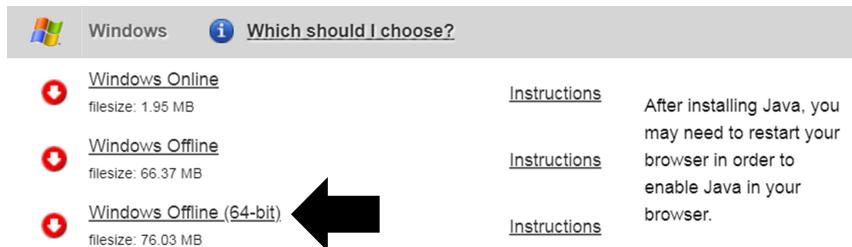


Figure 9.9: Downloading Java.

Installing RStudio

1. Go to <https://www.rstudio.com/>, select “Download RStudio” (or the “Download” button under “RStudio”), opt for the free version, and download the installer for Windows as shown in Figure 9.8.
2. After downloading, start the installer, and use the default options everywhere.

Installing Java

1. Go to <https://java.com/en/download/manual.jsp>, and select the Windows 64-bit installer as shown in Figure 9.9. If you also installed the 32-bit version of R, you *must* also install the other (32-bit) version of Java.
2. After downloading just run the installer.

Verifying the installation

You should now be ready to go, but we should make sure. Start RStudio, and type

```
install.packages("SqlRender")
library(SqlRender)
translate("SELECT TOP 10 * FROM person;", "postgresql")
```

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

This function uses Java, so if all goes well we know both R and Java have been installed correctly!

Another test is to see if source packages can be built. Run the following R code to install the

CohortMethod package from the OHDSI GitHub repository:

```
install.packages("drat")
drat::addRepo("OHDSI")
install.packages("CohortMethod")
```

9.5 Deployment strategies

Deploying the entire OHDSI tool stack, including ATLAS and the Methods Library, in an organization is a daunting task. There are many components with dependencies that have to be considered, and configurations to set. For this reason, two initiatives have developed integrated deployment strategies that allow the entire stack to be installed as one package, using some forms of virtualization: Broadsea and Amazon Web Services (AWS).

9.5.1 Broadsea

BroadSea⁵ uses Docker container technology⁶. The OHDSI tools are packaged along with dependencies into a single portable binary file called a Docker Image. This image can then be run on a Docker engine service, creating a virtual machine with all the software installed and ready to run. Docker engines are available for most operating systems, including Microsoft Windows, MacOS, and Linux. The Broadsea Docker image contains the main OHDSI tools, including the Methods Library and ATLAS.

9.5.2 Amazon AWS

Amazon has prepared two environments that can be instantiated in the AWS cloud computing environment with a click of the button: OHDSI-in-a-Box⁷ and OHDSIonAWS⁸.

OHDSI-in-a-Box is specifically created as a learning environment, and is used in most of the tutorials provided by the OHDSI community. It includes many OHDSI tools, sample data sets, RStudio and other supporting software in a single, low cost Windows virtual machine. A PostgreSQL database is used to store the CDM and also to store the intermediary results from ATLAS. The OMOP CDM data mapping and ETL tools are also included in OHDSI-in-a-Box. The architecture for OHDSI-in-a-Box is depicted in Figure 9.10.

OHDSIonAWS is a reference architecture for enterprise class, multi-user, scalable and fault tolerant OHDSI environments that can be used by organizations to perform their data analytics. It includes several sample datasets and can also automatically load your organization's real healthcare data. The data is placed in the Amazon Redshift database platform, which is supported by the OHDSI tools.

⁵<https://github.com/OHDSI/Broadsea>

⁶<https://www.docker.com/>

⁷<https://github.com/OHDSI/OHDSI-in-a-Box>

⁸<https://github.com/OHDSI/OHDSIonAWS>

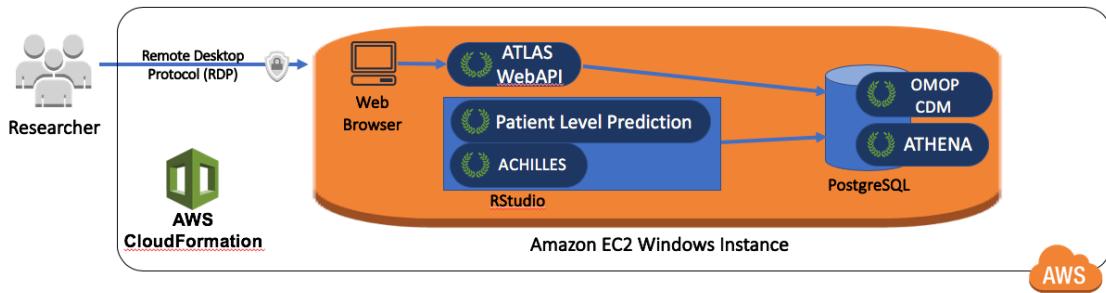


Figure 9.10: The Amazon Web Services architecture for OHDSI-in-a-Box.

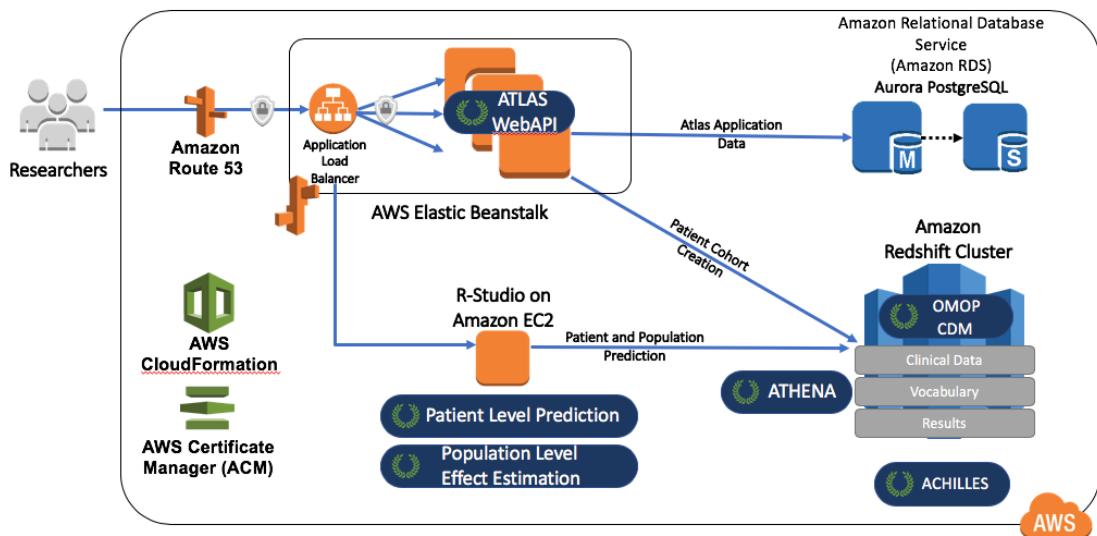


Figure 9.11: The Amazon Web Services architecture for OHDSIonAWS.

Intermediary results of ATLAS are stored in a PostgreSQL database. On the front end, users have access to ATLAS and to RStudio through a web interface (leveraging RStudio Server). In RStudio the OHDSI Methods Library has already been installed, and can be used to connect to the databases. The automation to deploy OHDSIonAWS is open-source, and can be customized to include your organization's management tools and best practices. The architecture for OHDSIonAWS is depicted in Figure 9.11.

9.6 Summary



- TODO: add

9.7 Exercises

Todo

Chapter 10

SQL and R

Chapter leads: Martijn Schuemie & Peter Rijnbeek

The Common Data Model (CDM) is a relational database model (all data is represented as records in tables that have fields), which means that the data will typically 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 greater risk of making mistakes, as the OHDSI tools are often designed to help guide the user to appropriate analysis of the data. 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 supported 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, one R package that can connect to many 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.

In this chapter we assume the reader has a basic understanding of SQL. We first review how to use SqlRender and DatabaseConnector. If the reader does not intend to use these packages these sections can be skipped. In Section 10.3 we discuss how to use SQL (in this case OHDSI SQL) to query the CDM. The following section highlights how to use the OHDSI Standardized Vocabulary when querying the CDM. We highlight the QueryLibrary, a collection of commonly-used queries against the CDM that is publicly available. We close this chapter with an example study estimating incidence rates, and implement this study using SqlRender and DatabaseConnector.

10.1 SqlRender

The SqlRender package is available on CRAN (the Comprehensive R Archive Network), and can therefore be installed using:

```
install.packages("SqlRender")
```

SqlRender supports 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). The R package comes with a package manual and a vignette that explores the full functionality. Here we describe some of the main features.

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 exchanged 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. This is the primary reason why OHDSI SQL was developed as its own, new SQL dialect. However, whenever possible we have kept to the SQL Server syntax to avoid reinventing the wheel.

Despite our best efforts, there are quite a few things to consider when writing OHDSI SQL that will run without error on all supported platforms. In what follows we discuss these considerations in detail.

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

Function	Function	Function
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 privileges on Oracle. Has no equivalent on SQLite.

Similarly, many SQL syntax structures are supported. Here is a non-exhaustive list of expressions 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 probably 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 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.qq16zlrochildren ;"

```

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.

Furthermore, 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 PostgreSQL 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

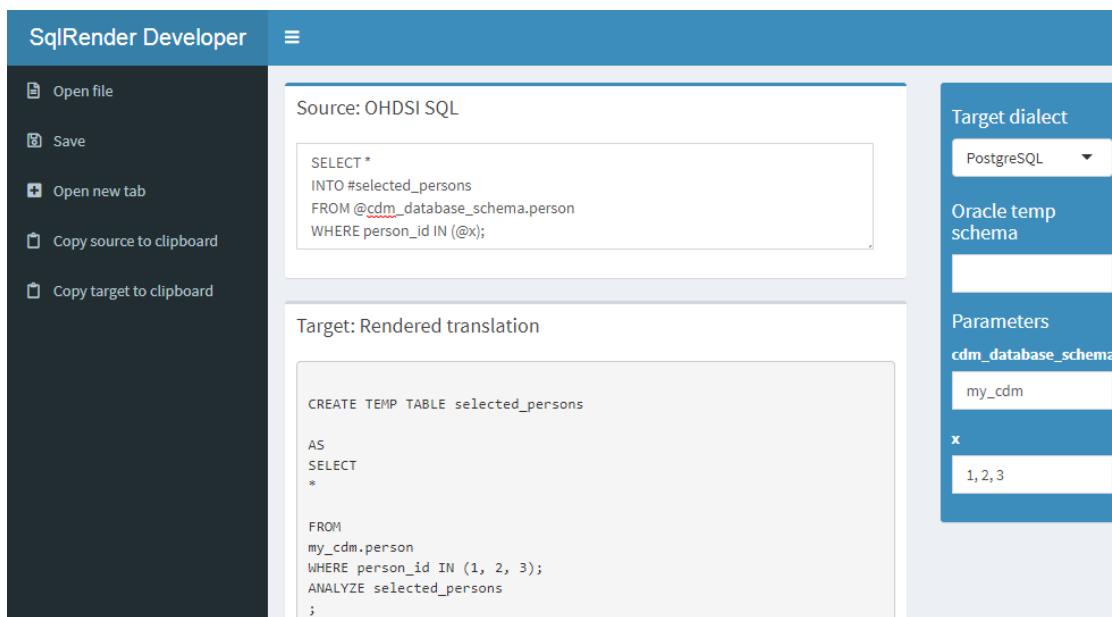


Figure 10.1: The SqlDeveloper Shiny app.

```
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:

```
launchSqlDeveloper()
```

That will open the default browser with the app shown in Figure 10.1. The app is also publicly available on the web¹.

In the app you can enter OHDSI SQL, select the target dialect as well as provide values for the parameters that appear in your SQL, and the translation will automatically appear at the bottom.

¹<http://data.ohdsi.org/SqlDeveloper/>

10.2 DatabaseConnector

DatabaseConnector is an R package for connecting to various database platforms using Java's JDBC drivers. The DatabaseConnector package is available on CRAN (the Comprehensive R Archive Network), and can therefore be installed using:

```
install.packages("DatabaseConnector")
```

DatabaseConnector supports 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). The package already contains 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:

```
connString <- "jdbc:postgresql://localhost:5432/postgres"
conn <- connect(dbms = "postgresql",
                connectionString = connString,
                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 statements 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;")
```

Both functions 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. As mentioned in Section 9.4.2, in such a case we 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")
```

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_sympuf")
```

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_sympuf`’.

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 more convenient and faster (due to some optimization) 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, which will be automatically created.

10.3 Querying the CDM

In the following examples we use OHDSI SQL to query a database that adheres to the CDM. These queries use `@cdm` to denote the database schema where the data in CDM can be found.

We can start by just querying how many people are in the database:

```
SELECT COUNT(*) AS person_count FROM @cdm.person;
```

PERSON_COUNT
26299001

Or perhaps we're interested in the average length of an observation period:

```
SELECT AVG(DATEDIFF(DAY,
                     observation_period_start_date,
                     observation_period_end_date) / 365.25) AS num_years
FROM @cdm.observation_period;
```

NUM_YEARS
1.980803

We can join tables to produce additional statistics. A join combines fields from multiple tables, typically by requiring specific fields in the tables to have the same value. For example, here we join the PERSON table to the OBSERVATION_PERIOD table on the person_id fields in both tables. In other words, the result of the join is a new table-like set that has all the fields of the two tables, but in all rows the person_id fields from the two tables must have the same value. We can now for example compute the maximum age at observation end by using the observation_period_end_date field from the OBSERVATION_PERIOD table together with the year_of_birth field of the PERSON table:

```
SELECT MAX(YEAR(observation_period_end_date) -
           year_of_birth) AS max_age
FROM @cdm.person
INNER JOIN @cdm.observation_period
ON person.person_id = observation_period.person_id;
```

MAX_AGE
90

A much more complicated query is needed to determine the distribution of age at the start of observation. In this query, we first join the PERSON to the OBSERVATION_PERIOD table to compute age at start of observation. We also compute the ordering for this joined set based on age, and store it as order_nr. Because we want to use the result of this join multiple times, we define it as a common table expression (CTE) (defined using WITH . . . AS) that we call "ages," meaning we can refer to ages as if it is an existing table. We count the number of rows in ages to produce "n," and then for each quantile find the minimum age where the order_nr is smaller than the fraction times n. For example, to find the median we use the minimum age where $order_nr < .50 * n$. The minimum and maximum age are computed separately:

```

WITH ages
AS (
    SELECT age,
        ROW_NUMBER() OVER (
            ORDER BY age
        ) order_nr
    FROM (
        SELECT YEAR(observation_period_start_date) - year_of_birth AS age
        FROM @cdm.person
        INNER JOIN @cdm.observation_period
            ON person.person_id = observation_period.person_id
        ) age_computed
    )
SELECT MIN(age) AS min_age,
    MIN(CASE
        WHEN order_nr < .25 * n
            THEN 9999
        ELSE age
        END) AS q25_age,
    MIN(CASE
        WHEN order_nr < .50 * n
            THEN 9999
        ELSE age
        END) AS median_age,
    MIN(CASE
        WHEN order_nr < .75 * n
            THEN 9999
        ELSE age
        END) AS q75_age,
    MAX(age) AS max_age
FROM ages
CROSS JOIN (
    SELECT COUNT(*) AS n
    FROM ages
) population_size;

```

MIN_AGE	Q25_AGE	MEDIAN_AGE	Q75_AGE	MAX_AGE
0	6	17	34	90

More complex computations can also be performed in R instead of using SQL. For example, we can get the same answer using this R code:

```

sql <- "SELECT YEAR(observation_period_start_date) -
        year_of_birth AS age
FROM @cdm.person
INNER JOIN @cdm.observation_period
    ON person.person_id = observation_period.person_id;"
```

```
age <- renderTranslateQuerySql(conn, sql, cdm = "cdm")
quantile(age[, 1], c(0, 0.25, 0.5, 0.75, 1))
```

```
##   0% 25% 50% 75% 100%
##    0    6   17   34   90
```

Here we compute age on the server, download all ages, and then compute the age distribution. However, this requires millions of rows of data to be downloaded from the database server, and is therefore not very efficient. You will need to decide on a case-by-case basis whether a computation is best performed in SQL or in R.

Queries can use the source values in the CDM. For example, we can retrieve the top 10 most frequent condition source codes using:

```
SELECT TOP 10 condition_source_value,
       COUNT(*) AS code_count
  FROM @cdm.condition_occurrence
 GROUP BY condition_source_value
 ORDER BY -COUNT(*);
```

CONDITION_SOURCE_VALUE	CODE_COUNT
4019	49094668
25000	36149139
78099	28908399
319	25798284
31401	22547122
317	22453999
311	19626574
496	19570098
I10	19453451
3180	18973883

Here we grouped records in the CONDITION_OCCURRENCE table by values of the condition_source_value field, and counted the number of records in each group. We retrieve the condition_source_value and the count, and reverse-order it by the count.

10.4 Using the vocabulary when querying

Many operations require the vocabulary to be useful. The Vocabulary tables are part of the CDM, and are therefore available using SQL queries. Querying the Vocabulary is already described at length in Chapter 6. Here we show how queries against the Vocabulary can be combined with queries against the CDM. Many fields in the CDM contain concept IDs which can be resolved using the CONCEPT table. For example, we may wish to count the number of persons in the database stratified by gender, and it would be convenient to resolve the GENDER_CONCEPT_ID field to a concept name:

```
SELECT COUNT(*) AS subject_count,
       concept_name
  FROM @cdm.person
 INNER JOIN @cdm.concept
    ON person.gender_concept_id = concept.concept_id
 GROUP BY concept_name;
```

SUBJECT_COUNT	CONCEPT_NAME
14927548	FEMALE
11371453	MALE

A very powerful feature of the Vocabulary is its hierarchy. A very common query looks for a specific concept *and all of its descendants*. For example, imagine we wish to count the number of prescriptions containing the ingredient ibuprofen:

```
SELECT COUNT(*) AS prescription_count
  FROM @cdm.drug_exposure
 INNER JOIN @cdm.concept_ancestor
    ON drug_concept_id = descendant_concept_id
 INNER JOIN @cdm.concept ingredient
    ON ancestor_concept_id = ingredient.concept_id
 WHERE LOWER(ingredient.concept_name) = 'ibuprofen'
   AND ingredient.concept_class_id = 'Ingredient'
   AND ingredient.standard_concept = 'S';
```

PRESCRIPTION_COUNT
26871214

10.5 QueryLibrary

QueryLibrary is a library of commonly-used SQL queries for the CDM. It is available as an online application² shown in Figure 10.2, and as an R package³.

The purpose of the library is to help new users learn how to query the CDM. The queries in the library have been reviewed and approved by the OHDSI community. The query library is primarily intended for training purposes, but it is also a valuable resource for experienced users.

The QueryLibrary makes use of SqlRender to output the queries in the SQL dialect of choice. Users can also specify the CDM database schema, vocabulary database schema (if separate), and the Oracle temp schema (if needed), so the queries will be automatically rendered with these settings.

²<http://data.ohdsi.org/QueryLibrary>

³<https://github.com/OHDSI/QueryLibrary>

The screenshot shows the QueryLibrary interface. At the top, there is a navigation bar with a logo, the title "QueryLibrary", and a menu icon. Below the navigation bar, there are two buttons: "Select" and "Execute".

The main area is titled "Select a query". It features a search bar with "Show 10 entries" and a "Search:" input field. A "Column visibility" button is also present.

A table lists two queries:

Group	Name	CDM_version	Author
drug exposure	DEX01 Counts of persons with any number of exposures to a certain drug	5.0	Patrick Ryan
drug exposure	DEX02 Counts of persons taking a drug, by age, gender, and year of exposure	5.0	Patrick Ryan

To the right of the table, there is a "Query Description" section for the first query:

DEX01: Counts of persons with any number of exposures to a certain drug

Description

This query is used to count the persons with at least one exposures to a certain drug (drug_concept_id). See [vocabulary queries](#) for obtaining valid drug_concept_id values. The input to the query is a value (or a comma-separated list of values) of a drug_concept_id. If the input is omitted, all drugs in the data table are summarized.

Query

The following is a sample run of the query. The input parameters are highlighted in blue.

```
SELECT
    c.concept_name,
    drug_concept_id,
    COUNT(person_id) AS num_persons
```

Figure 10.2: QueryLibrary: a library of SQL queries against the CDM.

10.6 Designing a simple study

10.6.1 Problem definition

Angioedema is a well-known side-effect of ACE inhibitors (ACEi). Slater et al. (1988) estimate the incidence rate of angioedema in the first week of ACEi treatment to be one case per 3,000 patients per week. Here we seek to replicate this finding, and stratify by age and gender, thus answering the question

What is the rate of angioedema in the first week following ACEi treatment initiation, stratified by age and gender?

10.6.2 Exposure

We'll define exposure as first exposure to a drug containing an ingredient in the ACEi class. By first we mean no earlier exposure to any ingredient in the class. We require 365 days of continuous observation time prior to the first exposure.

10.6.3 Outcome

We define angioedema as any occurrence of an angioedema diagnosis code during an inpatient or emergency room (ER) visit.

10.6.4 Time-at-risk

We will compute the incidence rate in the first week following treatment initiation, irrespective of whether patients were exposed for the full week.

10.7 Implementing the study using SQL and R

Although we are not bound to any of the OHDSI tool conventions, it is helpful to follow the same principles. In this case, we will use SQL to populate a cohort table, similarly to how the OHDSI tools work. The COHORT table is defined in the CDM, and has a predefined set of fields that we will also use. We first must create the COHORT table in a database schema where we have write access, which likely is not the same as the database schema that holds the data in CDM format.

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

```

cohortDbSchema <- "scratch"
cohortTable <- "my_cohorts"

sql <-
CREATE TABLE @cohort_db_schema.@cohort_table (
  cohort_definition_id INT,
  cohort_start_date DATE,
  cohort_end_date DATE,
  subject_id BIGINT
);
"
renderTranslateExecuteSql(conn, sql,
                         cohort_db_schema = cohortDbSchema,
                         cohort_table = cohortTable)

```

Here we have parameterized the database schema and table names, so we can easily adapt them to different environments. The result is an empty table on the database server.

10.7.1 Exposure cohort

Next we create our exposure cohort, and insert it into our COHORT table:

```

sql <-
INSERT INTO @cohort_db_schema.@cohort_table (
  cohort_definition_id,
  cohort_start_date,
  cohort_end_date,
  subject_id
)
SELECT 1 AS cohort_definition_id,
       cohort_start_date,
       cohort_end_date,
       subject_id
FROM (
  SELECT MIN(drug_exposure_start_date) AS cohort_start_date,
         MIN(drug_exposure_end_date) AS cohort_end_date,
         person_id AS subject_id
  FROM @cdm_db_schema.drug_exposure
  INNER JOIN @cdm_db_schema.concept_ancestor
    ON drug_concept_id = descendant_concept_id
  WHERE ancestor_concept_id IN (1335471, 1340128, 1341927,
                                 1363749, 1308216, 1310756, 1373225, 1331235, 1334456,
                                 1342439) -- ACE inhibitors
  GROUP BY person_id
) first_exposure
INNER JOIN @cdm_db_schema.observation_period
  ON subject_id = person_id
  AND observation_period_start_date < cohort_start_date

```

```

        AND observation_period_end_date > cohort_start_date
WHERE DATEDIFF(DAY,
    observation_period_start_date,
    cohort_start_date) >= 365;
"
renderTranslateExecuteSql(conn, sql,
    cohort_db_schema = cohortDbSchema,
    cohort_table = cohortTable,
    cdm_db_schema = cdmDbSchema)

```

Here we use the DRUG_EXPOSURE table, and join it to the CONCEPT_ANCESTOR table, thus allowing us to search for the ACEi ingredients and all their descendants, i.e. all drugs containing an ACEi. We take the first drug exposure per person, and then join to the OBSERVATION_PERIOD table, and because a person can have several observation periods we must make sure we only join to the period containing the drug exposure. We then require at least 365 days between the observation_period_start_date and the cohort_start_date.

10.7.2 Outcome cohort

Finally, we must create our outcome cohort:

```

sql <- "
INSERT INTO @cohort_db_schema.@cohort_table (
    cohort_definition_id,
    cohort_start_date,
    cohort_end_date,
    subject_id
)
SELECT 2 AS cohort_definition_id,
    cohort_start_date,
    cohort_end_date,
    subject_id
FROM (
    SELECT DISTINCT person_id AS subject_id,
        condition_start_date AS cohort_start_date,
        condition_end_date AS cohort_end_date
    FROM @cdm_db_schema.condition_occurrence
    INNER JOIN @cdm_db_schema.concept_ancestor
        ON condition_concept_id = descendant_concept_id
    WHERE ancestor_concept_id = 432791 -- Angioedema
) distinct_occurrence
INNER JOIN @cdm_db_schema.visit_occurrence
    ON subject_id = person_id
    AND visit_start_date <= cohort_start_date
    AND visit_end_date >= cohort_start_date
WHERE visit_concept_id IN (262, 9203,
    9201) -- Inpatient or ER;

```

```
""
renderTranslateExecuteSql(conn, sql,
    cohort_db_schema = cohortDbSchema,
    cohort_table = cohortTable,
    cdm_db_schema = cdmDbSchema)
```

Here we join the CONDITION_OCCURRENCE table to the CONCEPT_ANCESTOR table to find all occurrences of angioedema or any of its descendants. We use DISTINCT to make sure we only select one record per day, as we believe multiple angioedema diagnoses on the same day are more likely to be the same occurrence rather than multiple angioedema events. We join these occurrences to the VISIT_OCCURRENCE table to ensure the diagnosis was made in and inpatient or ER setting.

10.7.3 Incidence rate calculation

Now that our cohorts are in place, we can compute the incidence rate, stratified by age and gender:

```
sql <- "
WITH tar AS (
    SELECT concept_name AS gender,
        FLOOR((YEAR(cohort_start_date) -
            year_of_birth) / 10) AS age,
        subject_id,
        cohort_start_date,
        CASE WHEN DATEADD(DAY, 7, cohort_start_date) >
            observation_period_end_date
        THEN observation_period_end_date
        ELSE DATEADD(DAY, 7, cohort_start_date)
        END AS cohort_end_date
    FROM @cohort_db_schema.@cohort_table
    INNER JOIN @cdm_db_schema.observation_period
        ON subject_id = observation_period.person_id
        AND observation_period_start_date < cohort_start_date
        AND observation_period_end_date > cohort_start_date
    INNER JOIN @cdm_db_schema.person
        ON subject_id = person.person_id
    INNER JOIN @cdm_db_schema.concept
        ON gender_concept_id = concept_id
    WHERE cohort_definition_id = 1 -- Exposure
)
SELECT days.gender,
    days.age,
    days,
    CASE WHEN events IS NULL THEN 0 ELSE events END AS events
FROM (
    SELECT gender,
        age,
        SUM(DATEDIFF(DAY, cohort_start_date,
```

```

        cohort_end_date)) AS days
    FROM tar
    GROUP BY gender,
        age
) days
LEFT JOIN (
    SELECT gender,
        age,
        COUNT(*) AS events
    FROM tar
    INNER JOIN @cohort_db_schema.@cohort_table angioedema
        ON tar.subject_id = angioedema.subject_id
        AND tar.cohort_start_date <= angioedema.cohort_start_date
        AND tar.cohort_end_date >= angioedema.cohort_start_date
    WHERE cohort_definition_id = 2 -- Outcome
    GROUP BY gender,
        age
) events
ON days.gender = events.gender
    AND days.age = events.age;
"
```

```

results <- renderTranslateQuerySql(conn, sql,
                                      cohort_db_schema = cohortDbSchema,
                                      cohort_table = cohortTable,
                                      cdm_db_schema = cdmDbSchema,
                                      snakeCaseToCamelCase = TRUE)

```

We first create “tar,” a CTE that contains all exposures with the appropriate time-at-risk. Note that we truncate the time-at-risk at the observation_period_end_date. We also compute the age in 10-year bins, and identify the gender. The advantage of using a CTE is that we can use the same set of intermediate results several times in a query. In this case we use it to count the total amount of time-at-risk, as well as the number of angioedema events that occur during the time-at-risk.

We use `snakeCaseToCamelCase = TRUE` because in SQL we tend to use `snake_case` for field names (because SQL is case-insensitive), whereas in R we tend to use `camelCase` (because R is case-sensitive). The `results` data frame column names will now be in `camelCase`.

With the help of the `ggplot2` package we can easily plot our results:

```

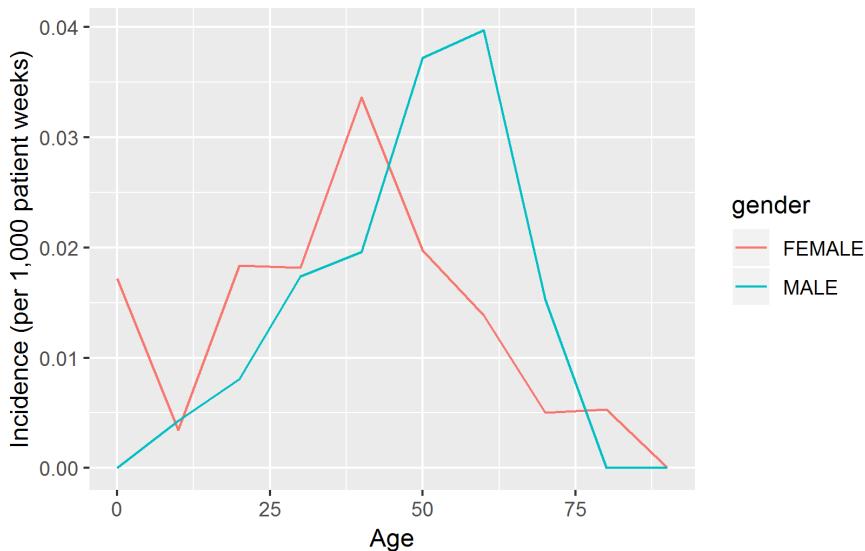
# Compute incidence rate (IR) :
results$ir <- 1000 * results$events / results$days / 7

# Fix age scale:
results$age <- results$age * 10

library(ggplot2)
ggplot(results, aes(x = age, y = ir, group = gender, color = gender)) +
    geom_line() +

```

```
xlab("Age") +
ylab("Incidence (per 1,000 patient weeks)")
```



10.7.4 Clean up

Don't forget to clean up the table we created, and to close the connection:

```
sql <- "
TRUNCATE TABLE @cohort_db_schema.@cohort_table;
DROP TABLE @cohort_db_schema.@cohort_table;
"
renderTranslateExecuteSql(conn, sql,
                          cohort_db_schema = cohortDbSchema,
                          cohort_table = cohortTable)

disconnect(conn)
```

10.7.5 Compatibility

Because we use OHDSI SQL together with DatabaseConnector and SqlRender throughout, the code we reviewed here will run on any database platform supported by OHDSI.

Note that for demonstration purposes we chose to create our cohorts using hand-crafted SQL. It would probably have been more convenient to construct cohort definition in ATLAS, and use the SQL generated by ATLAS to instantiate the cohorts. ATLAS also produced OHDSI SQL, and can therefore easily be used together with SqlRender and DatabaseConnector.

10.8 Summary



- **SQL** (Structured Query Language) is a standard language for querying databases, including those that conform to the Common Data Model (CDM).
- Different database platforms have different SQL dialects, and require different tools to query them.
- The **SqlRender** and **DatabaseConnector** R packages provide a unified way to query data in the CDM, allowing the same analysis code to be run in different environments without modification.
- By using R and SQL together we can implement custom analyses that are not supported by the OHDSI tools.
- The **QueryLibrary** provides a collection of re-usable SQL queries for the CDM.

10.9 Exercises

Prerequisites

For these exercises we assume R, R-Studio and Java have been installed as described in Section 9.4.5. Also required are the SqlRender, DatabaseConnector, and Eunomia packages, which can be installed using:

```
install.packages(c("SqlRender", "DatabaseConnector", "devtools"))
devtools::install_github("ohdsi/Eunomia")
```

The Eunomia package provides a simulated dataset in the CDM that will run inside your local R session. The connection details can be obtained using:

```
connectionDetails <- Eunomia::getEunomiaConnectionDetails()
```

The CDM database schema is “main”.

Exercise 10.1. Using SQL and R, compute how many people are in the database.

Exercise 10.2. Using SQL and R, compute how many people have at least one prescription of celecoxib.

Exercise 10.3. Using SQL and R, compute how many diagnoses of gastrointestinal haemorrhage occur during exposure to celecoxib. (Hint: the concept ID for gastrointestinal haemorrhage is 192671.)

Suggested answers can be found in Appendix D.1.

Chapter 11

Building the building blocks: cohorts

Lead: Kristin Kostka

Cohorts are used throughout OHDSI analytical tools and network studies as the primary building blocks for running high quality, systematic research. Cohort definitions vary from study to study depending on the research question of interest. Each cohort definition provides a specific way to represent a person with a condition or exposure using data in an observational health database. Thus, cohorts are an important component in documenting the methods of an observational research study.

The chapter serves to explain what is meant by creating and sharing cohort definitions, the methods for developing cohorts, and how to build your own cohorts using ATLAS (for a detailed discussion on OHDSI Analytics Tools see Chapter 9).

11.1 Theory



OHDSI Cohort: set of persons who satisfy one or more inclusion criteria for a duration of time **OHDSI Cohort Definition:** the description of inclusion criteria used for identifying a particular cohort

In many peer-reviewed scientific manuscripts, a cohort is suggested to be analogous to a codeset of specific clinical codes (e.g. ICD-9/ICD-10, NDC, HCPCS, etc). While codesets are an important piece in assembling a cohort, a cohort definition is not simply a codeset. A cohort definition requires logic for how to use the codeset for the criteria. A well documented cohort specifies how a patient enters a cohort, a patient exits a cohort and any additional inclusion criteria that impacts how to observe a patient's time-at-risk.



The term *cohort* is often interchanged with the term *phenotype*. The term *phenotype* is applied to patient characteristics inferred from electronic health record (EHR) data (Hripcak et al., 2016). The goal is to draw conclusions about a target concept based on raw EHR data, claims data, or other clinically relevant data. Thus, a *cohort* is a set of persons who satisfy one or more

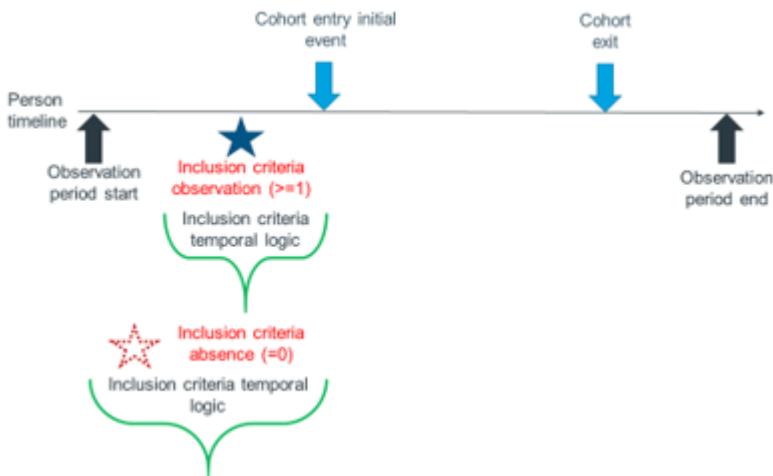


Figure 11.1: Cohort Creation

inclusion criteria (a phenotype) for a duration of time. A cohort in itself is not a phenotype but a phenotype can be used to create a cohort.

There are two main approaches to constructing a cohort: **1) rules-based design or 2) probabilistic design**. A rules-based cohort design relies heavily on the domain expertise of the individual designing the cohort to use their knowledge of the therapeutic area of interest to build rules for cohort inclusion criteria. Conversely, a probabilistic design mines already available data to identify and qualify potential cohort membership through machine-suggested patterns. The next sections will discuss these approaches in further detail.

11.1.1 Rules-based cohort design

A rules-based OHDSI cohort definition begins with clinical expertise explicitly stating one or more inclusion criteria (e.g. “people with angioedema”) in a specific duration of time (e.g. “who developed this condition within the last 6 months”).

When creating a cohort definition, you need to ask yourself the following questions:

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

To visualize the importance of these criteria, think of how this information comes together in a person’s timeline (Figure . The OBSERVATION_PERIOD table creates the window for which we see the person in the data.

Cohort entry criteria: The cohort entry event can be one or many clinical attributes which dictate an individual patient’s eligibility to be included in a cohort. Events are recorded time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements and visits. The

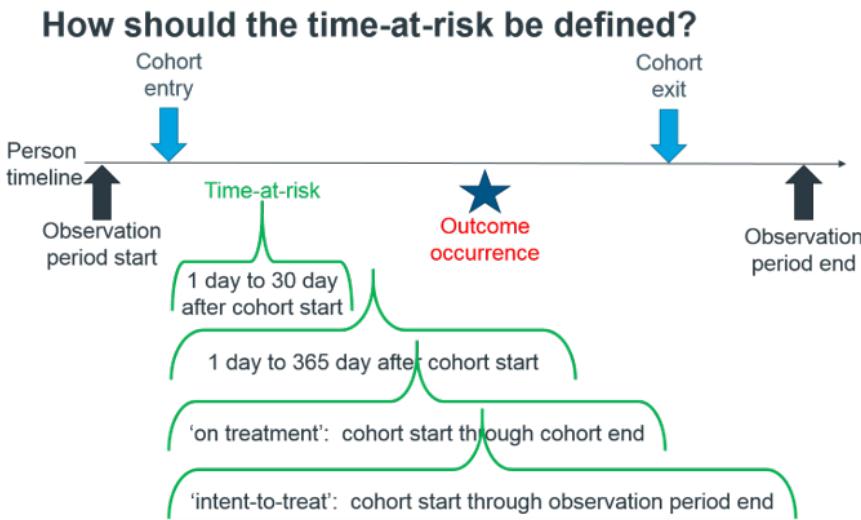


Figure 11.2: Time-at-Risk Construction

event index date is set to be equal to the event start date. Initial events defined by a domain, concept set, as well as any domain-specific attributes. We will discuss these in detail in the further section.

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

Cohort exit criteria: The cohort exit event signifies when a person no longer qualifies for cohort membership. Cohort exit can be defined in multiple ways such as the end of the observation period, a fixed time interval relative to the initial entry event, the last event in a sequence of related observations (e.g. persistent drug exposure) or through other censoring of observation period. Cohort exit strategy will impact whether a person can belong to the cohort multiple times during different time intervals.

Time-at-risk: In order to interpret risk of a specific outcome, which will be defined as a separate cohort definition, it is necessary to know the length of time that applies. A time-at-risk criteria states the period of time in which the cohort must be in the data following the cohort entry criteria. The time-at-risk will vary based on whether you're observing an acute/short term trend or a chronic/long term trend.

In traditional study design, we would categorize time-at-risk for 'on treatment' as the entirety of the time between when a person meets cohort entry through the cohort exit criteria. An 'intent-to-treat' design would include the entire time period between cohort start and observation period end (e.g. when the person leaves the data for some reason such as switching physicians, insurance carriers, etc).

The use of these criteria may present a number of unique nuances to an OHDSI cohort including:

- One person may belong to multiple cohorts
- One person may belong to the same cohort for multiple different time periods
- One person may not belong to the same cohort multiple times during the same period of time
- A cohort may have zero or more members

Throughout the Book of OHDSI, we will detail how to address these consequences in your overall study design. In each respective methodology, we will discuss how you can configure a methods package to address how one person shows up in multiple cohorts being studied.

11.1.2 Probabilistic cohort design using APHRODITE

Rules-based cohort design are a popular method for assembling cohort definitions. However, assembling necessary expert consensus to create a study cohort can be prohibitively time consuming. Probabilistic cohort design is an alternative, machine-driven method to expedite the selection of cohort attributes. In this method, supervised learning allows a phenotyping algorithm to learn from a set of labeled examples (cases) of what attributes contribute to cohort membership. This algorithm can then be used to better ascertain the defining characteristics of a phenotype and what trade offs occur in overall study accuracy when choosing to modify phenotype criteria.

To apply this approach on OMOP data, OHDSI community researchers created Automated PHenotype Routine for Observational Definition, Identification, Training and Evaluation (APHRODITE), an R-package cohort building framework that combines the ability of learning from imperfectly labeled data and the Anchor learning framework for improving selected features in the phenotype models, for use with the OHDSI/OMOP CDM (Banda et al., 2017). APHRODITE is an open-source package (<https://github.com/OHDSI/Aphrodite>) available for use which provides the OHDSI data network to the ability to start building electronic phenotype models that leverage machine learning techniques and go beyond traditional rule based approaches to cohort building.

11.2 Phenotype Algorithm Evaluation

When you build a cohort, you may start from your own knowledgebase or you may choose to look at how other studies specify a similar cohort definition. A literature review of over 33 studies found significant heterogeneity in phenotype algorithms used, validation methods, and results (Rubbo et al., 2015a). In general, the validation of a rules-based cohort definition or probabilistic algorithm can be thought of as a test of the proposed cohort compared to some form of “gold standard” reference (e.g. manual chart review of cases). Making this comparison is best understood in a tabular view (Figure 11.3).

OHDSI researchers encourage to perform a complete evaluation of the phenotype algorithm (i.e., determining sensitivity, specificity, and positive predictive value (PPV) (Swerdel et al., 2019). For a complete validation of an algorithm, we need to calculate:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}}$$

		Truth	
		Positive	Negative
Test	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

Figure 11.3: Algorithm Evaluation

$$Specificity = \frac{True\ negatives}{True\ negatives + False\ positives}$$

$$Positive\ predictive\ value = \frac{True\ positives}{True\ positives + False\ positives}$$

This framework continues to be utilized across cohort definition research to evaluate the utility of reuse of cohorts across different electronic health data. The PheEvaluator tool (Swerdel et al., 2019) is a recent addition to the OHDSI Community that provides a standard method to efficiently estimate a complete phenotype algorithm evaluation.

11.3 OHDSI Gold Standard Phenotype Library

To further assist the community in the inventory and overall evaluation of existing cohort definitions and algorithms, the OHDSI Gold Standard Phenotype Library (GSPL) Workgroup was formed. The purpose of the GSPL workgroup is to provide additional leadership to the development of community-backed cohort libraries from rules-based and probabilistic methods. The GSPL enable members of the OHDSI community to find, evaluate, and utilize community-validated cohort definitions for research and other activities. These “gold standard” definitions will reside in a library, the entries of which are held to specific standards of design and evaluation. For additional information related to the GSPL, consult the OHDSI workgroup page (<https://www.ohdsi.org/web/wiki/doku.php?id=projects:workgroups:gold-library-wg>). Research within this workgroup includes APHRODITE (Banda et al., 2017) and the PheEvaluator tool (Swerdel et al., 2019), discussed in the prior section, as well as work done to share the Electronic Medical Records and Genomics eMERGE Phenotype Library across the OHDSI network (Hripcsak et al., 2019). If phenotype curation is your interest, consider contributing to this workgroup.

11.4 Practice

Now that we’ve covered the basics, it’s time to put your cohort building skills to the test. *Note: If you’ve gotten lost on your OHDSI journey and not sure where to start, you can always return to Where to Begin ((Chapter 4) to recall the way to translate a research question into an OHDSI standard analytics approach.*



Figure 11.4: Building Blocks of Cohorts

When you are building a cohort, you should consider which of these is more important to you: *finding all the eligible patients?* vs. *Getting only the ones you are confident about?*

Your strategy to construct your cohort will depend on your the clinical stringency of how your expert consensus defines the disease. This is to say, the right cohort design will depend on the question you're trying to answer. You may opt to build a cohort definition that: uses everything you can get, uses the lowest common denominator so you can share it across OHDSI sites or is a compromise of the two. It is ultimately at the researcher's discretion what threshold of stringency is necessary to adequately study the cohort of interest.

We begin to practice our cohort skills by putting together a cohort definition using a rules-based approach. In this example, we want to find *patients who initiate ACE inhibitors monotherapy as first-line treatments for hypertension*

Recall, the components of building a cohort include:

- **Domain:** A Domain defines the set of allowable Concepts for the standardized fields in the CDM tables (refer to Chapter 5). (Ex: Condition, Drug, Procedure, Measurement)
- **Concept set:** An expression that defines one or more concepts encompassing a clinical entity of interest (Ex: Concepts for type II diabetes, concepts for antidiabetic drugs)
- **Domain-specific attribute:** Ex: DRUG_EXPOSURE: Days supply; MEASUREMENT: value_as_number, high_range
- **Temporal logic:** the time intervals within which the relationship between an inclusion criteria and an event is evaluated (Ex: Indicated condition must occur during 365d prior to or on exposure start)

As you are building your cohort definition, you may find it helpful to think of OMOP domains analogous to building blocks (see Figure 11.4 that represent cohort attributes. You can always refer to the Common Data Model chapter (Chapter 5) for help.

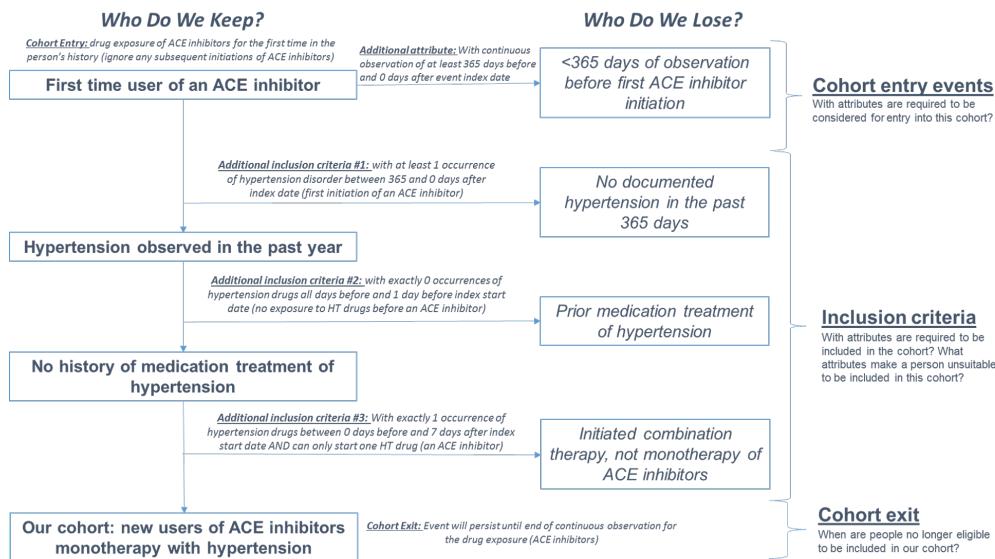


Figure 11.5: Logical Diagram of Intended Cohort

With this context in mind, we are now going to build our cohort. As we go through this exercise, we will approach building our cohort similar to standard attrition chart. Figure 11.5 shows the logical framework for how we want to build this cohort.

You can build a cohort in the user interface of ATLAS or you can write a query directly against your OMOP CDM. We will briefly discuss both in this chapter.

11.4.1 Using ATLAS

We can build a cohort using the ATLAS interface. To begin in ATLAS, click on the ‘Cohort Definition’ module (located on the left hand panel fifth selection from the top as seen in Figure 11.6).

When the module loads, click on the blue button on the right that says ‘New Cohort’ (Figure 11.7).

The next screen you will see will be an empty cohort definition. Figure 11.8 shows what you will see on your screen.

Before you do anything else, you are encouraged to change the name of the cohort from *New Cohort Definition* to your own unique name for this cohort. You may opt for a name like *New users of ACE inhibitors as first-line monotherapy for hypertension*.



ATLAS will not allow two cohorts to have the same exact names. ATLAS will give you a pop-up error message if you choose a name already used by another ATLAS cohort.

Once you have chosen a name, you can save the cohort by clicking the green floppy-disk icon. Now we can proceed with defining the initial cohort event. You will click to add to ‘Add an Initial Event’. You now have to pick which domain you are building a criteria around. You may ask yourself, *how do I know which domain is the initial cohort event?* Let’s figure that out.

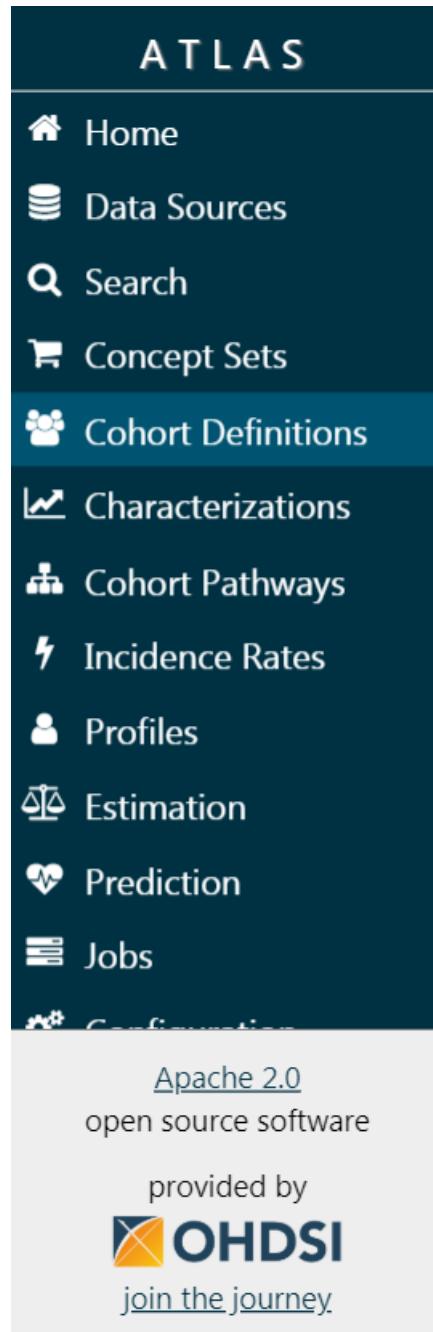


Figure 11.6: Navigating to ATLAS Cohort Definition module

The screenshot shows the ATLAS interface with the 'Cohort Definitions' section selected in the sidebar. The main area displays a list of cohort definitions, with a prominent blue 'New Cohort' button in the top right corner.

Figure 11.7: Navigating to ATLAS New Cohort button

This screenshot shows the 'New Cohort Definition' page. It includes tabs for 'Definition', 'Concept Sets', 'Generation', 'Reporting', and 'Export'. A text input field for 'enter a cohort definition description here' is present. Below it, the 'Cohort Entry Events' section allows defining events before and after an index date, with a 'Restrict initial events' button. The 'Inclusion Criteria' section has a 'New inclusion criteria' button. At the bottom, there's a 'Cohort Exit' section.

Figure 11.8: New Cohort Definition

This screenshot shows a specific cohort definition page for 'Cohort #1771427'. It features a 'Cohort Entry Events' section with event criteria and a 'Restrict initial events' button. The 'Inclusion Criteria' section includes a 'New inclusion criteria' button. On the right side, a large dropdown menu titled '+ Add Initial Event' lists various patient characteristics: 'Add Condition Era', 'Add Condition Occurrence', 'Add Death', 'Add Device Exposure', 'Add Dose Era', 'Add Drug Era', and 'Add Drug Exposure'. Each item in the list provides a brief description of its function.

Figure 11.9: Adding an Initial Event

Figure 11.10: Building a Drug Exposure Criteria

Figure 11.11: Specifying a Concept Set - Step 1

As we see in Figure 11.9, ATLAS provides descriptions below each criteria to help you. If we were building a CONDITION_OCCURRENCE based criteria, our question would be looking for patients with a specific diagnosis. If we were building a DRUG_EXPOSURE based criteria, our question would be looking for patients with a specific drug or drug class. Since we want to find *patients who initiate ACE inhibitors monotherapy as first-line treatments for hypertension*, we want to choose a DRUG_EXPOSURE criteria. You may say, *but we also care about hypertension as a diagnosis*. You are correct. Hypertension is another criteria we will build. However, eligibility to enter this cohort is predicated on being a new-user of ACE inhibitor monotherapy. The diagnosis of hypertension is what we call an *additional qualifying criteria*. We will return to this once we build this criteria. We will click to add a DRUG_EXPOSURE criteria (Figure 11.10).

The screen will update with your selected criteria but you are not done yet. You now need to tell ATLAS which concept set you want to associate with this DRUG_EXPOSURE criteria. You will need to click the down arrow to open the dialogue box to import a concept set (Figure 11.11).

Scenario 1: You have not built a concept set. If you have not assembled your concept sets to retrieve to apply to your criteria, you will need to do this before you move forward. At a very basic level, this will require you to utilize the *Search* function to find and choose the concepts you would like to

ID	Title	Created	Modified	Author
1794480	[OHDSI EU 2019] Excluded concepts of ACE inhibitors or Thiazide diuretics	03/28/2019 11:04 AM	03/28/2019 11:04 AM	anonymous
963	ACE Inhibitors			anonymous
3268	COPY OF: ACE Inhibitors			anonymous
99283	Ace Inhibitors			anonymous
142965	PheKB ACE-I ACE inhibitors			anonymous

Figure 11.12: Specifying a Concept Set - Step 2

specify. You can refer back to (see Chapter 6) on how to navigate the OMOP vocabularies to find clinical concepts of interest. This chapter will not focus on the assembly of concept sets. You are encouraged to utilize the OHDSI Resources to find ATLAS tutorials that can help you understand how to search and build a concept set.

Scenario 2: You have already built a concept set. If you have already created a concept set and saved it in ATLAS, you can click to '*Import a Concept Set*' where you will be prompted to find your concept in the concept set repository of your ATLAS (Figure 11.12).

In the above example, the user typed in the name given to this concept set '*ace inhibitors*' in the right hand search. This shortened the concept set list to only concepts with matching names. From there, the user can click on the row of the concept set to select it. (*Note: the dialogue box will disappear once you have selected a concept set.*) You are not done yet. Your question is looking for new users or the first time in someone's history they are exposed to ACE inhibitors. You need to specify this by clicking to '*Add attribute*' (Figure 11.13).

You will want to select the *First Exposure Criteria* (Figure 11.14). From there, the window will automatically close. Notice, you could specify other attributes of a criteria you build. You could specify an attribute of age at occurrence, the date of occurrence, gender or other attributes related to the drug. Criteria available for selection will look different for each domain.

Once selected, this additional attribute will show up in the same box as the initial criteria.



The current design of ATLAS may confuse some. Despite its appearance, the red X is not intended to mean "No". It is an actionable feature to allow the user to delete the criteria. If you click the red X, this criteria will go away. Thus, you need to leave the criteria with the red X to keep the criteria active.

Now you have built an initial qualifying event. To ensure you are capturing the first exposure, you will want to add a lookback window to know that you are looking at enough of the patient's history to know what comes first. You can do this by adjusting the continuous observation drop downs. You could also click the box and type in a value to these windows. To ensure this is the first exposure

The screenshot shows the ATLAS Cohort Definitions interface. On the left, a sidebar lists various features: Home, Data Sources, Search, Concept Sets, Cohort Definitions (selected), Characterizations, Cohort Pathways, Incidence Rates, Profiles, Estimation, Prediction, Jobs, Configuration (Apache 2.0, open source software, provided by OHDSI, join the journey). The main area is titled 'Cohort #1771427' and contains a search bar with the example: 'new users of ACE inhibitors as first-line mono-therapy for hypertension'. Below the search bar are tabs: Definition (selected), Concept Sets, Generation, Reporting, Export. A sub-section titled 'Cohort Entry Events' shows a dropdown menu set to 'a drug exposure of ACE Inhibitors'. To the right of the dropdown are buttons for '+ Add Initial Event', '+ Add attribute...', and 'Delete Criteria'. Below this, there are fields for 'continuous observation of at least [0] days before and [0] days after event index date' and 'Limit initial events to: earliest event per person'. A green button labeled 'Restrict initial events' is present. To the right of the entry events section, there is a list of criteria: 'Add First Exposure Criteria' (Filter Drug Exposures to the first exposure in history), 'Add Age at Occurrence Criteria' (Filter Drug Exposures by age at occurrence), 'Add Gender Criteria' (Filter Drug Exposures based on Gender), 'Add Start Date Criteria' (Filter Drug Exposures by the Drug Exposure Start Date), 'Add End Date Criteria' (Filter Drug Exposures by the Drug Exposure End Date), and 'Add Drug Type Criteria'.

Figure 11.13: Adding Attribute to Initial Criteria - Step 1

This screenshot shows the continuation of the cohort definition process. The sidebar and top navigation are identical to Figure 11.13. The main area now shows a red 'X' icon next to the 'ACE Inhibitors' dropdown in the 'Cohort Entry Events' section, indicating an error or warning. The text 'for the first time in the person's history' is displayed below the dropdown. The 'Restrict initial events' button is visible. The right-hand sidebar with criteria options is also present.

Figure 11.14: Adding Attribute to Initial Criteria - Step 2

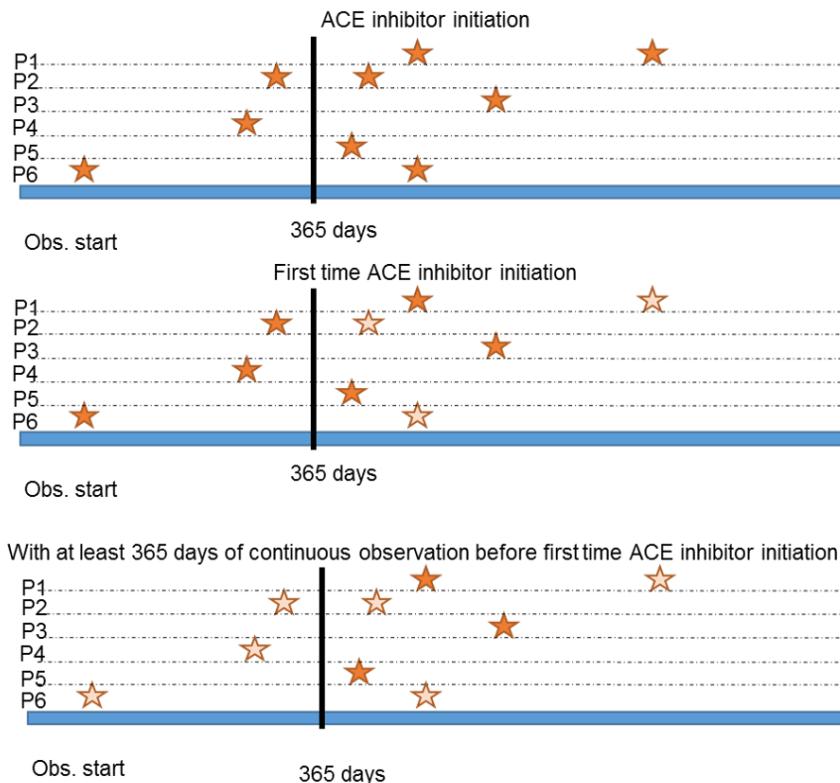
Figure 11.15: Adjusting the Observation Period

in the patient’s history, we add a lookback of 365 days. The lookback window is the discretion of your study team. You may choose differently in other cohorts. This creates, as best as we are able, a minimum period of time we see the patient to ensure we are capturing the first record. We then also opt limit it to the earliest event per person (Figure 11.15).

By now, you may be confused. *Why do I add a first ever criteria in addition to limit to the earliest event?* You can think about this logically by thinking about assembling patient timelines.

In Figure 11.16, each line represents a single patient that may be eligible to join the cohort. The filled in stars represent a time the patient fulfills the specified criteria. As additional criteria is applied, you may see some stars are a lighter shade. This means that these patients have other records that satisfy the criteria but there is another record that proceeds that. By the time we get to the last criteria, we are looking at the cumulative view of patients who have ACE inhibitors for the first time and have 365 days prior to the first time occurrence. This means that if we limit to the earliest event, it must fulfil **all** three criteria (drug exposure, first time in patient’s history and lookback window) and it is the earliest occurrence of all three criteria being met. If that still feels confusing, you are not alone. This is one of the most challenging features of ATLAS that tends to trip up researchers. When you are building your own cohorts, you may opt to engage the Researchers section of the OHDSI Forum to get a second opinion on how to construct your cohort logic.

Once we have specified a cohort entry event, you could proceed to one of two places to add your additional qualifying events: *Restrict Initial Events* and *Inclusion Criteria*. The fundamental difference between these two options is what interim information you want ATLAS to serve back to you. If you add additional qualifying criteria into the Cohort Entry Event box by selecting *Restrict Initial Events*, when you choose to generate a count in ATLAS, you will only get back the number of people who meet **ALL** of these criteria. If you opt to add criteria into the *Inclusion Criteria*, you will get an attrition chart to show you how many patients are lost by applying additional inclusion criteria. It is highly encouraged to utilize the Inclusion Criteria section so you can understand the impact of each rule on the overall success of the cohort definition. You may find a certain inclusion criteria



Only P1, P3, and P5 would be included in this study after applying both criteria

Figure 11.16: Patient Eligibility by Criteria Applied

Inclusion Criteria

New inclusion criteria

1. has hypertension diagnosis in 1 yr prior to treatment
Additional inclusion criteria #1: with at least 1 occurrence of hypertension disorder between 365 and 0 days after index date (first initiation of an ACE inhibitor)

having all of the following criteria:

with at least 1 using all occurrences of:
a condition occurrence of Hypertensive disorder

where event starts between 365 days Before and 0 days After index start date add additional constraint

restrict to the same visit occurrence
 allow events from outside observation period

+ Add criteria to group... Delete Criteria

Limit qualifying events to: earliest event per person.

Figure 11.17: Additional Inclusion Criteria 1

Inclusion Criteria

New inclusion criteria

1. has hypertension diagnosis in 1 yr prior to treatment
Additional inclusion criteria #2: with exactly 0 occurrences of hypertension drugs all days before and 1 day before index start date (no exposure to HT drugs before an ACE inhibitor)

having all of the following criteria:

with exactly 0 using all occurrences of:
a drug exposure of Hypertensive drugs

where event starts between All days Before and 1 days After index start date add additional constraint

restrict to the same visit occurrence
 allow events from outside observation period

+ Add criteria to group... Delete Criteria

Limit qualifying events to: earliest event per person.

Figure 11.18: Additional Inclusion Criteria 2

severely limits the number of people who end up in the cohort. You may choose to relax this criteria to get a larger cohort. This will ultimately be at the discretion of the expert consensus assembling this cohort.

You will now want to click ‘New Inclusion Criteria’ to add a subsequent piece of logic about membership to this cohort. The functionality in this section is identical to the way we discussed building cohort criteria above. You may specific the criteria and add specific attributes. Our first additional criteria is to subset the cohort to only patients: *With at least 1 occurrence of hypertension disorder between 365 and 0 days after index date (first initiation of an ACE inhibitor)*. Now check your logic against Figure 11.17.

You will then want to add another criteria to look for patients: *with exactly 0 occurrences of hypertension drugs all days before and 1 day before index start date (no exposure to HT drugs before an ACE inhibitor)*. Now check your logic against Figure 11.18.

You may be confused why “having no occurrences” is coded as “exactly 0 occurrences.” This is a nuance of how ATLAS consumes knowledge. ATLAS only consumes inclusion criteria. You must use logical operators to indicate when you want the absence of a specific attribute such as: “Exactly 0.” Over time you will become more familiar with the logical operators available in ATLAS criteria.

Lastly, you will want to add your another criteria to look for patients: *with exactly 1 occurrence of hypertension drugs between 0 days before and 7 days after index start date AND can only start one HT drug (an ACE inhibitor)* Now check your logic against Figure 11.19.

You have now added all of your qualifying inclusion criteria. You must now specify your cohort exit criteria. You will ask yourself, *when are people no longer eligible to be included in this cohort,* In this cohort, we are following new-users of a drug exposure. We want to look at continuous observation period as it relates to the drug exposure. As such, the exit criteria is specified to follow

Inclusion Criteria

New inclusion criteria

1. has hypertension diagnosis in 1 yr prior to treatment
Additional inclusion criteria #1: with at least 1 occurrence of hypertension disorder between 36..

2. Has no prior antihypertensive drug exposures in medical history
Additional inclusion criteria #2: with exactly 0 occurrences of hypertension drugs all days before..

3. Is only taking ACE as monotherapy, with no concomitant combination treatments
Additional inclusion criteria #3: With exactly 1 occurrence of hypertension drugs between 0 day..

Is only taking ACE as monotherapy, with no concomitant combination treatments

Additional inclusion criteria #3: With exactly 1 occurrence of hypertension drugs between 0 days before and 7 days after index start date AND can only start one HT drug (an ACE inhibitor) having all of the following criteria:

with exactly 1 using all occurrences of:
a drug exposure of Hypertensive drugs
where event starts between 0 days Before and 7 days After index start date add additional constraint
 restrict to the same visit occurrence
 allow events from outside observation period

+ Add criteria to group...
Delete Criteria
Delete

Limit qualifying events to: earliest event per person.

Figure 11.19: Additional Inclusion Criteria 3

Cohort Exit

Event Persistence:
Event will persist until end of a continuous drug exposure

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

Concept set containing the drug(s) of interest: ACE inhibitors

- Persistence window: allow for a maximum of 30 days between exposure records when inferring the era of persistence exposure
- Surveillance window: add 0 days to the end of the era of persistence exposure as an additional period of surveillance prior to cohort exit.

Censoring Events:
Exit Cohort based on the following criteria:
No censoring events selected.

+ Add Censoring Event

Figure 11.20: Cohort Exit Criteria

for the entirety of the continuous drug exposure. If there is a subsequent break in the drug exposure, the patient will exit the cohort at this time. We do this as we cannot determine what happened to the person during the break in the drug exposure. We can also set a criteria on the persistence window to specify an "allowable" gap between drug exposures. In this case, our experts leading this study concluded that a maximum of 30 days between exposure records is allowable when inferring the era of persistence exposure.

Why are gaps allowed? In some data sets, we see only portions of clinical interactions. Drug exposures, in particular, may represent a dispense of a prescription that can cover a certain period of time. Thus, we allow a certain amount of time between drug exposures as we know the patient may logically still have access to the initial drug exposure because the unit of dispense exceeded one day.

We can configure this by selecting the Event will persist *until the end of a drug exposure*. We then will add our persistence window and append the concept set for ACE inhibitors. Now check your logic against Figure 11.20.

In the case of this cohort, there are no other censoring events. However, you may build other cohorts where you need to specify this criteria. You would proceed similarly to the way we have added other attributes to this cohort definition. You have now successfully finished creating your cohort. Congratulations! Building a cohort is the most important building block of answering a question in the OHDSI tools. You can now use the Export tab to share your cohort definition to other collaborators in the form of code or JSON files to load into ATLAS. For more information on how to utilize ATLAS, you can always return to OHDSI Resources to find short videos on basic cohort building tasks in ATLAS.

11.4.2 Cohort Building at the Database Layer Using SQL

While it is encouraged to use the OHDSI analytical tools to build and share cohorts, you may not have an instance of ATLAS available in your local environment. If you do not have ATLAS, you can still build a cohort. You may query a database directly using your preferred SQL dialect. A detailed discussion of how to write SQL against the OMOP CDM is available in Chapter 10). As you become more familiar with OHDSI code, you are encouraged to utilize SQL Render to render parameterized SQL. SQL Render will easily translate your query into other SQL dialects. This makes it a lot easier to share cohort definition across other OHDSI network sites. Even without ATLAS, you can work with other OHDSI collaborators who use ATLAS to create their cohort definition. Cohorts built in ATLAS can also be exported into your preferred SQL dialect.

11.5 Summary



- An **OHDSI cohort** is set of persons who satisfy one or more inclusion criteria for a duration of time.
- The **OHDSI Cohort Definition** is the description of inclusion criteria used for identifying a particular cohort.
- Building a cohort is a fundamental piece of using the OHDSI Analytics Tools.
- There are two major approaches to building a cohort (rules-based vs probabilistic).
- The OHDSI community has a variety of resources available to support you as you’re building your own cohorts including short videos of ATLAS functionality, a ready-to-use probabilistic machine-learning package (APHRODITE) to run on your OMOP CDM and even a freely available tool to evaluate the sensitivity and specificity of your cohort (PheValuator).

11.5.1 Exercises

(Need help on syntax for how we format these... can you point me to a good example of an exercise in the BoO?)

Chapter 12

Characterization

Chapter leads: Anthony G. Sena, Daniel Prieto-Alhambra

Observational healthcare databases provide a valuable resource to understand variations in populations based on a host of characteristics. Characterizing populations through the use of descriptive statistics is an important first step in generating hypotheses about the determinants of health and disease. In this chapter we cover methods for characterization:

- **Database-level characterization:** provides a top-level set of summary statistics to understand the data profile of a database in its totality.
- **Cohort characterization:** describes a population in terms of its aggregate medical history.
- **Treatment pathways:** describes the sequence of interventions a person received for a duration of time.
- **Incidence:** measures the occurrence rate of an outcome in a population for a time at risk.

With the exception of database-level characterization, these methods aim to describe a population relative to an event referred to as the index date. This population of interest is defined as a cohort as described in chapter 11. The cohort defines the index date for each person in the population of interest. Using the index date as an anchor, we define the time preceding the index date as **baseline** time. The index date and all time after is called the **post-index** time.

Use-cases for characterization include disease natural history, treatment utilization and quality improvement. In this chapter will describe the methods for characterization. We will use a population of hypertensive persons to demonstrate how to use ATLAS and R to perform these characterization tasks.

12.1 Database Level Characterization

Before we can answer any characterization question about a population of interest, we must first understand the characteristics of the database we intend to utilize. Database level characterization seeks to describe the totality of a database in terms of the temporal trends and distributions. This quantitative assessment of a database will typically include questions such as:

- What is the total count of persons in this database?
- What is the distribution of age for persons?
- How long are persons in this database observed for?
- What is the proportion of persons having a {treatment, condition, procedure, etc} recorded/prescribed over time?

These database-level descriptive statistics also help a researcher to understand what data may be missing in a database. Chapter 16 goes into further detail on data quality.

12.2 Cohort characterization

Cohort characterization describes the baseline and post-index characteristics of people in a cohort. OHDSI approaches characterization through descriptive statistics of all conditions, drug and device exposures, procedures and other clinical observations that are present in the person's history. We also summarize the socio-demographics of members of the cohort at the index date. This approach provides a complete summary of the cohort of interest. Importantly, this enables a full exploration of the cohort with an eye towards variation in the data while also allowing for identification of potentially missing values.

Cohort characterisation methods can be used for person-level drug utilisation studies (DUS) to estimate the prevalence of indications and contraindications amongst users of a given treatment. The dissemination of this cohort characterization is a recommended best practice for observational studies as detailed in the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2008).

12.3 Treatment Pathways

Another method to characterize a population is to describe the treatment sequence during the post-index time window. For example, Hripcsak et al. (2016) utilized the OHDSI common data standards to create descriptive statistics to characterize treatment pathways for type 2 diabetes, hypertension and depression. By standardizing this analytic approach, Hripcsak and colleagues were able to run the same analysis across the OHDSI network to describe the characteristics of these populations of interest.

The pathway analysis aims to summarize the treatments (events) received by persons diagnosed with a specific condition from the first drug prescription/dispensation. In this study, treatments were described after the diagnosis of type 2 diabetes, hypertension and depression respectively. The events for each person were then aggregated to a set of summary statistics and visualized for each condition and for each database.

As an example, figure 12.1 represents a population of persons initiating treatment for hypertension. The first ring in the center shows the proportion of persons based on their first-line therapy. In this example, Hydrochlorothiazide is the most common first-line therapy for this population. The boxes that extend from the Hydrochlorothiazide section represent the 2nd and 3rd line therapies recorded for persons in the cohort.

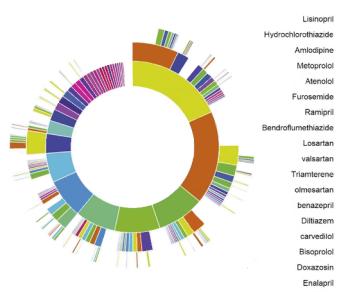


Figure 12.1: OHDSI Treatment Pathways “sunburst” visualization for hypertension

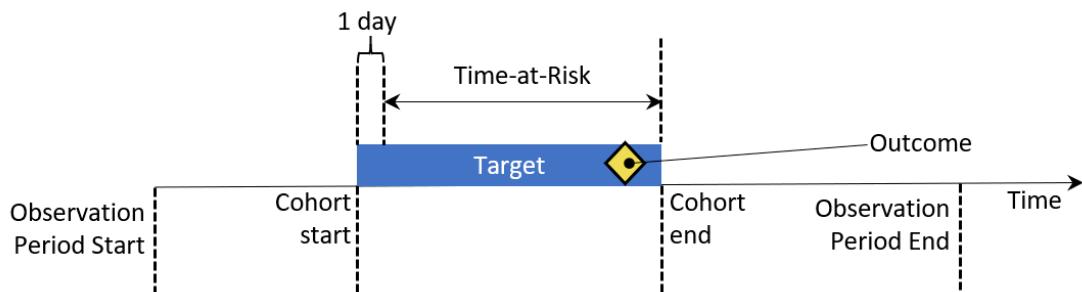


Figure 12.2: Person-level view of incidence calculation components

A pathways analysis provides important evidence about treatment utilization amongst a population. From this analysis we can describe the most prevalent first-line therapies utilized, the proportion of persons that discontinue treatment, switch treatments or augment their therapy. Using the pathway analysis, Hripcsak et al. (2016) found that metformin is the most commonly prescribed medication for diabetes thus confirming general adoption of the first-line recommendation of the American Association of Clinical Endocrinologists diabetes treatment algorithm. Additionally, they noted that 10% of diabetes patients, 24% of hypertension patients, and 11% of depression patients followed a treatment pathway that was shared with no one else in any of the data sources.

In classic DUS terminology, treatment pathway analyses include some population-level DUS estimates such as prevalence of use of one or more medications in a specified population, as well as some person-level DUS including measures of persistence and switching between different therapies.

12.4 Incidence

Incidence rates and proportions are statistics that are used in public health to assess the occurrence of a new outcome in a population during a time-at-risk. Figure 12.2 aims to show the components of an incidence calculation for a single person:

In figure 12.2, a person has a period of time where they are observed in the data denoted by their observation start and end time. Next, the person has a point in time where they enter and exit a cohort by meeting some eligibility criteria. The time at risk window then denotes when we seek to

understand the occurrence of an outcome. If the outcome falls into the time-at-risk, we count that as an incidence of the outcome.

There are two metrics for calculating incidence:

$$\text{Incidence Proportion} = \frac{\# \text{ persons in the cohort with new outcome during time at risk}}{\# \text{ persons in the cohort with time at risk}} \quad (12.1)$$

An incidence proportion provides a measure of the new outcomes per person in the population during the time-at-risk. Stated another way, this is the proportion of the population of interest that developed the outcome in a stated timeframe.

$$\text{Incidence Rate} = \frac{\# \text{ persons in the cohort with new outcome during time at risk}}{\text{person time at risk contributed by persons in the cohort}} \quad (12.2)$$

An incidence rate is a measure of the number of new outcomes during the cumulative time-at-risk for the population. When a person experiences the outcome in the time-at-risk, their contribution to the total person-time stops at the occurrence of the outcome event. The cumulative time-at-risk is referred to as **person-time** and is expressed in days, months or years.

When calculated for therapies, incidence proportions and incidence rates of use of a given therapy are classic population-level DUS.

12.5 Characterizing hypertensive persons

Per the World Health Organization's (WHO) global brief on hypertension (Organization, 2013), there are significant health and economic gains attached to early detection, adequate treatment and good control of hypertension. The WHO brief provides an overview of hypertension and characterizes the burden of the disease across different countries. The WHO provides descriptive statistics around hypertension for geographic regions, socio-economic class and gender.

Observational data sources provide a way to characterize hypertensive populations as was done by the WHO. In the subsequent sections of this chapter, we'll explore the ways that we make use of ATLAS and R to explore a database to understand its composition for studying hypertensive populations. Then, we will use these same tools to describe the natural history and treatment patterns of hypertensive populations.

12.6 Database characterization in ATLAS

Here we demonstrate how to use the data sources module in ATLAS to explore database characterization statistics created with ACHILLES to find database level characteristics related to hypertensive persons. Start by clicking on  **Data Sources** in the left bar of ATLAS to start. In the first drop

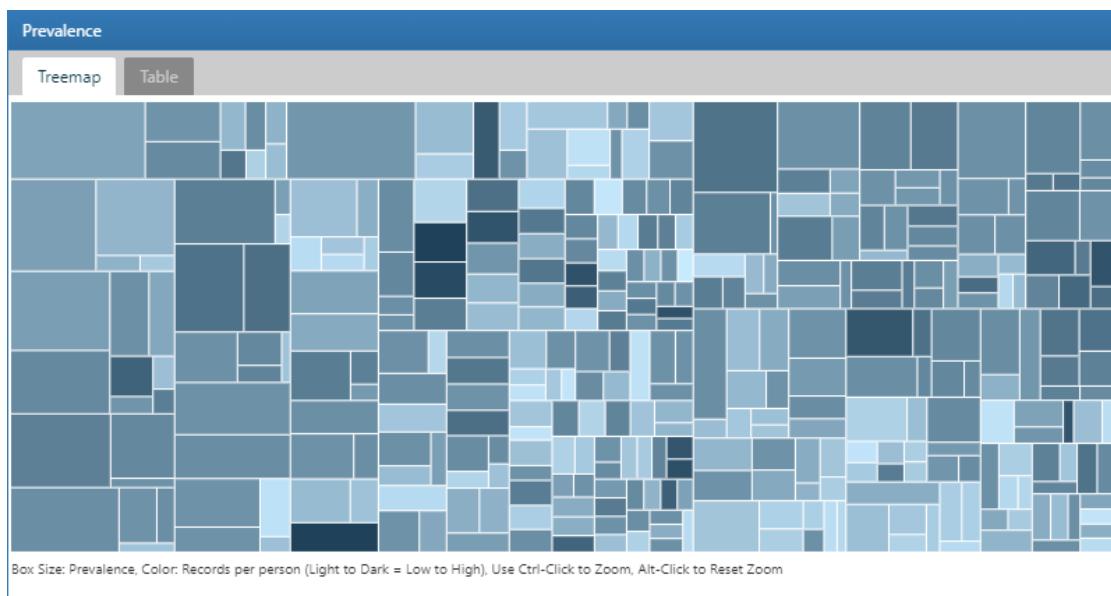


Figure 12.3: Atlas Data Sources: Condition Occurrence Treemap

down list shown in ATLAS, select the database to explore. Next, use the drop down below the database to start exploring reports. To do this, select the Condition Occurrence from the report drop down which will reveal a treemap visualization of all conditions present in the database:

To search for a specific condition of interest, click on the Table tab to reveal the full list of conditions in the database with person count, prevalence and records per person. Using the filter box on the top, we can filter down the entries in the table based on concept name containing the term “hypertension”:

We can explore a detailed drill-down report of a condition by clicking on a row. In this case, we will select “essential hypertension” to get a breakdown of the trends of the selected condition over time and by gender, the prevalence of the condition by month, the type recorded with the condition and the age at first occurrence of the diagnosis:

Now that we have reviewed the database’s characteristics for the presence of hypertension concepts and the trends over time, we can also explore drugs used to treat hypertensive persons. The process to do this follows the same steps except we use the Drug Era report to review characteristics of drugs summarized to their RxNorm Ingredient. Once we have explored the database characteristics to review items of interest, we are ready to move forward with constructing cohorts to identify the hypertensive persons to characterize.

12.7 Cohort characterization in ATLAS

Here we demonstrate how to use ATLAS to perform large-scale cohort characterization for several cohorts. Click on the **Characterizations** in the left bar of ATLAS and create a new characterization analysis. Give the analysis a name a save using the button.

Prevalence				
	Treemap	Table		
	Column visibility	Copy	CSV	Show 15 entries
Showing 1 to 15 of 47 entries (filtered from 15,907 total entries)				Filter: hypertension
Concept	Id	Name	Person Count	Records per person
320128		Essential hypertension	17,814,076	12.30% 5.80
312648		Benign essential hypertension	11,014,877	7.61% 4.35
317898		Malignant essential hypertension	1,021,441	0.70% 2.22
381290		Ocular hypertension	521,264	0.36% 2.40
441922		Transient hypertension of pregnancy	209,317	0.14% 2.45
44782429		Chronic kidney disease due to hypertension	170,534	0.12% 3.60
137940		Transient hypertension of pregnancy - delivered	153,806	0.11% 1.07
321080		Hypertension complicating pregnancy, childbirth and the puerperium	148,728	0.10% 2.15
314423		Benign essential hypertension complicating pregnancy, childbirth and the puerperium - not delivered	132,245	0.09% 3.94
44782690		Chronic kidney disease stage 5 due to hypertension	119,375	0.08% 5.20
44783618		Heritable pulmonary arterial hypertension	104,737	0.07% 3.61
319826		Secondary hypertension	96,356	0.07% 2.14
4167493		Pregnancy-induced hypertension	91,675	0.06% 2.60
321074		Pre-existing hypertension complicating pregnancy, childbirth and puerperium	74,311	0.05% 2.99
192680		Portal hypertension	71,240	0.05% 3.11

Showing 1 to 15 of 47 entries
(filtered from 15,907 total entries)

Figure 12.4: Atlas Data Sources: Conditions with “hypertension” found in the concept name

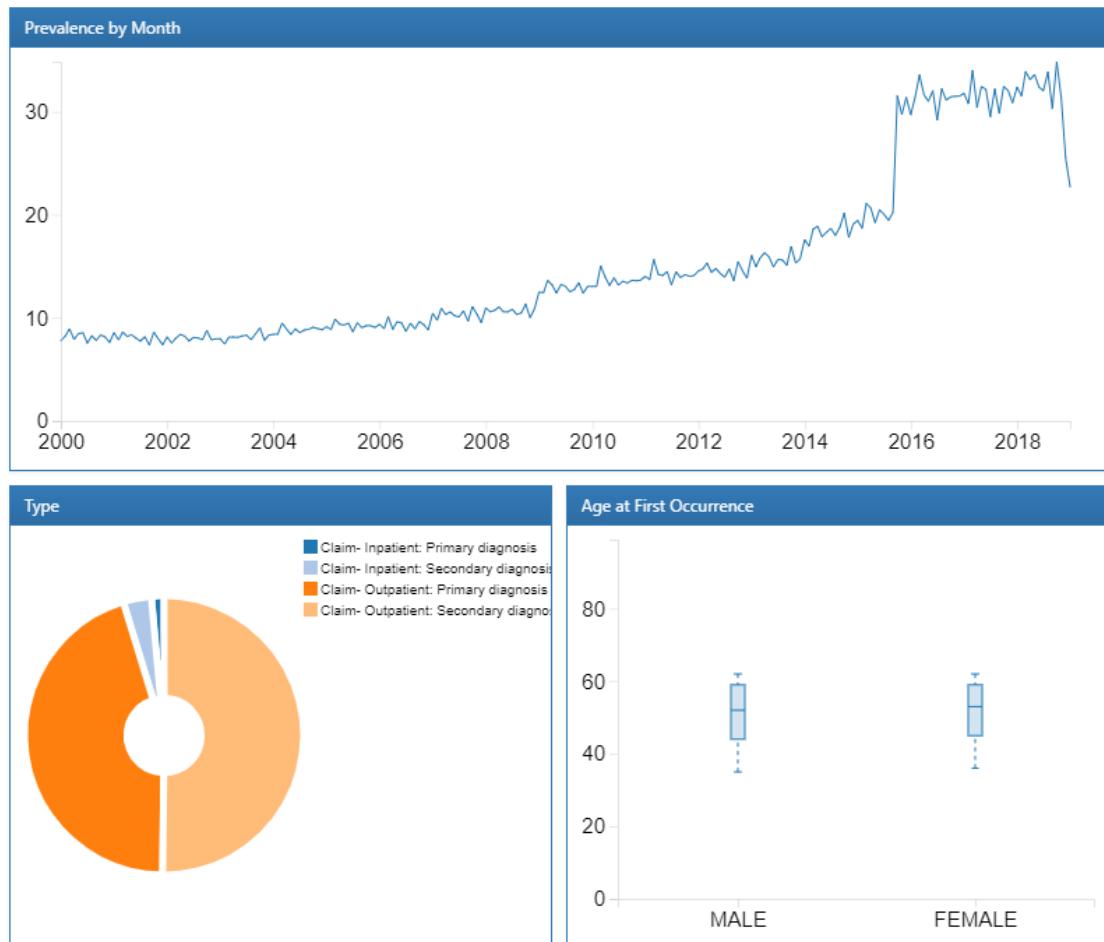


Figure 12.5: Atlas Data Sources: Essential hypertension drill down report

Cohort characterization is defined as the process of generating cohort level descriptive summary statistics from person level covariate data. Summary statistics of these person level covariates may be count, mean, sd, var, min, max, median, range, and quantiles. In addition, covariates during a period may be stratified into temporal units of time for time-series analysis such as fixed intervals of time relative to cohort_start_date (e.g. every 7 days, every 30 days etc.), or in absolute calendar intervals such as calendar-week, calendar-month, calendar-quarter, calendar-year.

Cohort definitions

Import

Show 10 entries Search:

ID	Name	Edit cohort	Remove
10447	Patients initiating first-line therapy for hypertension with >1 yr follow-up	Edit cohort	Remove
10448	Patients initiating first-line therapy for hypertension with >3 yr follow-up	Edit cohort	Remove

Showing 1 to 2 of 2 entries Previous 1 Next

Figure 12.6: Characterization design tab - cohort definition selection

12.7.1 Design

A characterization analysis requires at least one cohort and at least one feature to characterize. For this example, we will use two cohorts. The first cohort will define persons initiating a treatment for hypertension as their index date with at least one diagnosis of hypertension in the year prior. We will also require that persons in this cohort have at least one year of observation after initiating the hypertensive drug (Appendix B.6). The second cohort is identical to the first cohort described with a requirement having at least three years of observation instead of one (Appendix B.7).

12.7.1.1 Cohort definitions

We assume the cohorts have already been created in ATLAS as described in Chapter 11. Click on **Import** and select the cohorts as shown in figure 12.6. Next, we'll define the features to use for characterizing these two cohorts.

12.7.1.2 Feature Selection

ATLAS comes with nearly 100 preset feature analyses that are used to perform characterization across the clinical domains modeled in the OMOP CDM. Each of these preset feature analyses perform aggregation and summarization functions on clinical observations for the selected target cohorts. These calculations provide potentially thousands of features to describe the cohorts baseline and post-index characteristics. Under the hood, ATLAS is utilizing the OHDSI FeatureExtraction R package to perform the characterization for each cohort. We will cover the use of FeatureExtraction and R in more detail in the next section.

Feature analyses

Import

Show 25 ▾ entries Search:

ID	Name	Description	Actions
43	Drug Era Short Term	One covariate per drug in the drug_era table overlapping with any part of the short window.	Remove
49	Charlson Index	The Charlson comorbidity index (Romano adaptation) using all conditions prior to the window end.	Remove
67	Condition Occurrence Long Term	One covariate per condition in the condition_occurrence table starting in the long term window.	Remove
71	Demographics Age Group	Age of the subject on the index date (in 5 year age groups)	Remove
72	Demographics Race	Race of the subject.	Remove
73	Demographics Prior Observation Time	Number of continuous days of observation time preceding the index date.	Remove
74	Demographics Gender	Gender of the subject.	Remove
76	Condition Occurrence Medium Term	One covariate per condition in the condition_occurrence table starting in the medium term window.	Remove
77	Demographics Age	Age of the subject on the index date (in years).	Remove
79	Demographics Time In Cohort	Number of days of observation time during cohort period.	Remove
80	Demographics Index Year	Year of the index date.	Remove
81	Demographics Post Observation Time	Number of continuous days of observation time following the index date.	Remove
87	Procedure Occurrence Any Time Prior	One covariate per procedure in the procedure_occurrence table any time prior to index.	Remove
103	Visit Count Long Term	The number of visits observed in the long term window.	Remove

Figure 12.7: Characterization design tab - feature selection.

Click on **Import** to select the feature to characterize. Below is a list of features we will use to characterize these cohorts:

The figure above shows the list of features selected along with a description of what each feature will characterize for each cohort. The features that start with the name “Demographics” will calculate the demographic information for each person at the cohort start date. For the features that start with a domain name (i.e. Visit, Procedure, Condition, Drug, etc), these will characterize all recorded observations in that domain. Each domain feature has four options of time window preceding the cohort start, namely:

- **Any time prior:** uses all available time prior to cohort start that fall into the person’s observation period
- **Long term:** 365 days prior up to and including the cohort start date.
- **Medium term:** 180 days prior up to and including the cohort start date.
- **Short term:** 30 days prior up to and including the cohort start date.

Subgroup analyses

New subgroup

Female

Calculate subgroup analyses only

Female Delete

having **all** of the following criteria: **Add criteria to group...**

with the following event criteria: **Delete Criteria**

+ Add attribute...

X with a gender of: **FEMALE** **Add** **Import**

Figure 12.8: Characterization design with female sub group analysis.

Design **Executions** **Utilities**

Executions

SYNPUF 1K	Generate	View latest result	All executions (3)
SYNPUF 5%	Generate	View latest result	All executions (3)

Figure 12.9: Characterization design execution - CDM source selection.

12.7.1.3 Subgroup analysis

What if we were interested in creating different characteristics based on gender? We can use the “subgroup analyses” section to define new subgroups of interest to use in our characterization.

To create a subgroup, click on and add your criteria for subgroup membership. This step is similar to the criteria used to identify cohort enrollment. In this example, we’ll define a set of criteria to identify females amongst our cohorts:



Subgroup analyses in ATLAS are not the same as strata. Strata are mutually exclusive while subgroups may include the same persons based on the criteria chosen.

12.7.2 Executions

Once we have our characterization designed, we can execute this design against one or more databases in our environment. Navigate to the Executions tab and click on the Generate button to start the analysis on a database:

CONDITION / Condition Occurrence Long Term / stratified by Female											
Export		Export comparison		Show 10 ▾ entries					Search: <input type="text" value="card"/>		
Covariate	Explore	Concept ID	Patients initiating first-line therapy for hypertension with >1 yr follow-up				Patients initiating first-line therapy for hypertension with >3 yr follow-up				
			Count		Pct		Female		Count		
			Count		Pct		Count		Pct		
Tachycardia	Explore ▾	444070	17,322	1.04%	9,042	1.18%	6,547	0.78%	3,530	0.90%	-0.0193
Cardiomegaly	Explore ▾	314658	20,958	1.26%	8,007	1.04%	9,016	1.08%	3,465	0.89%	-0.0121
Cardiac arrhythmia	Explore ▾	44784217	30,474	1.83%	13,221	1.72%	14,540	1.74%	6,318	1.62%	-0.0052

Showing 1 to 3 of 3 entries (filtered from 206 total entries)

Previous 1 Next

Figure 12.10: Characterization results - condition occurrence long term.

Once the analysis is complete, we can view reports by clicking on the “All Executions” button and from the list of executions, select “View Reports”. Alternatively, you can click “View latest result” to view the last execution performed.

12.7.3 Results

The results provide a tabular view of the different features for each cohort selected in the design. In figure 12.10, a table provides a summary of all conditions present in the two cohorts in the preceding 365 days from the cohort start. Each covariate has a count and percentage for each cohort and the female subgroup we defined within each cohort.

We used the search box to filter the results to see what proportion of persons have a **cardiac arrhythmia** in their history in an effort to understand what cardiovascular-related diagnoses are observed in the populations. We can use the **Explore** link next to the cardiac arrhythmia concept to open a new window with more details about the concept for a single cohort as shown in figure 12.11:

Since we have characterized all condition concepts for our cohorts, the explore option enables a view of all ancestor and descendant concepts for the selected concept, in this case cardiac arrhythmia. This exploration allows us to navigate the hierarchy of concepts to explore other cardiac diseases that may appear for our hypertensive persons. Like in the summary view, the count and percentage are displayed.

We can also use the same characterization results to find conditions that are contraindicated for some anti-hypertensive treatment such as angioedema. To do this, we’ll follow the same steps above but this time search for ‘edema’ as shown in figure 12.12:

Once again, we’ll use the explore feature to see the characteristics of Edema in the hypertension population to find the prevalence of angioedema:

Here we find that a portion of this population has a record of angioedema in the year prior to starting an anti-hypertensive medication.

Exploring condition_occurrence during day -365 through 0 days relative to index: Cardiac arrhythmia							
Cohort: Patients initiating first-line therapy for hypertension with >1 yr follow-up							
Relationship type		Distance	Concept name	All stratas		Female	
				Count	Pct	Count	Pct
Explore	Ancestor	4	Disorder by body site	32	0.00%	17	0.00%
Explore	Ancestor	4	Finding of trunk structure	991	0.06%	605	0.08%
Explore	Ancestor	3	Disorder of trunk	23	0.00%	14	0.00%
Explore	Ancestor	3	Disorder of thorax	241	0.01%	104	0.01%
Explore	Ancestor	3	Disorder of body system	4,135	0.25%	1,992	0.26%
Explore	Ancestor	2	Disorder of cardiovascular system	12,979	0.78%	6,073	0.79%
Explore	Ancestor	2	Disorder of mediastinum	138	0.01%	62	0.01%
Explore	Ancestor	2	Disorder of body cavity	24	0.00%	10	0.00%
Explore	Ancestor	1	Heart disease	4,691	0.28%	1,869	0.24%
Explore	Selected	0	Cardiac arrhythmia	30,474	1.83%	13,221	1.72%

Showing 1 to 10 of 62 entries

Previous 1 2 3 4 5 6 7 Next

Figure 12.11: Characterization results - exploring a single concept.

CONDITION / Condition Occurrence Long Term / stratified by Female

CONDITION / Condition Occurrence Long Term / stratified by Female												
Export		Export comparison	Show 10 ▾ entries	Search: edema								
Covariate	Explore	Concept ID	Patients initiating first-line therapy for hypertension with >1 yr follow-up				Patients initiating first-line therapy for hypertension with >3 yr follow-up				Std diff ▾	
			Count		Pct		Count		Pct			
			Count		Pct		Count		Pct			
Edema	Explore ▾	433595	32,243	1.94%	20,200	2.63%	15,173	1.81%	9,684	2.48%	-0.0066	

Showing 1 to 1 of 1 entries (filtered from 206 total entries)

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Figure 12.12: Characterization results - exploring a contraindicated condition.

Exploring condition_occurrence during day -365 through 0 days relative to index: Edema X

Cohort: Patients initiating first-line therapy for hypertension with >1 yr follow-up

[Export](#) Show 10 entries Search: Search

Relationship type	Distance	Concept name	All stratas		Female	
			Count	Pct	Count	Pct
Explore Descendant	-2	Angioedema	2,605	0.16%	1,506	0.20%

Showing 1 to 1 of 1 entries (filtered from 56 total entries) Previous 1 Next

Figure 12.13: Characterization results - exploring a contraindicated condition details.

DEMOGRAPHICS / Demographics Age

[Export](#) [Export comparison](#) Show 10 entries Search: Search

Strata	Patients initiating first-line therapy for hypertension with >1 yr follow-up				Patients initiating first-line therapy for hypertension with >3 yr follow-up				Std diff
	Count	Avg	Std Dev	Median	Count	Avg	Std Dev	Median	
Female	768,180	49.39	9.78	51.00	390,693	49.01	9.03	51.00	-0.0291
All stratas	1,661,604	48.96	10.00	50.00	837,459	48.64	9.26	50.00	-0.0232

Showing 1 to 2 of 2 entries Previous 1 Next

Figure 12.14: Characterization results of age for each cohort and sub group.

Figure 12.15: Custom feature definition in ATLAS.

While domain covariates are computed using a binary indicator (i.e. was a record of the code present in the prior timeframe), some variables provide a continuous value such as the age of persons at cohort start. In the example above, we show the age for the 2 cohorts characterized expressed with the count of persons, mean age, median age and standard deviation.

12.7.4 Defining custom features

In addition to the preset features, ATLAS supports the ability to allow for user-defined custom features. To do this, click the **Characterization** left-hand menu item, then click the **Feature Analysis** tab and click the **New Feature Analysis** button. Provide a name for the custom feature and save it using the button.

In this example, we will define a custom feature that will identify the count of persons in each cohort that have a drug era of ACE inhibitors in their history after cohort start:

The criteria defined above assumes that it will be applied to a cohort start date. Once we have defined the criteria and saved it, we can apply it to the characterization design we created in the previous section. To do this, open the characterization design and navigate to the Feature Analysis section. Click the button and from the menu select the new custom features. They will now appear in the feature list for the characterization design. As described earlier, we can execute this design against a database to produce the characterization for this custom feature:

DRUG / Ace inhibitor exposure after index / stratified by Female												
			Export		Export comparison		Show 10 ▾ entries		Search: <input type="text"/>			
Covariate	Explore	Concept ID	Patients initiating first-line therapy for hypertension with > 1 yr follow-up				Patients initiating first-line therapy for hypertension with > 3 yr follow-up				Std diff	
			Count	Pct	Female		Count	Pct	Female			
			Count	Pct	Count	Pct	Count	Pct	Count	Pct		
Ace inhibitor exposure after index	Explore ▾	0	686,034	41.29%	289,215	17.41%	426,280	50.90%	182,219	21.76%	0.1001	

Showing 1 to 1 of 1 entries

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Figure 12.16: Custom feature results display.

12.8 Cohort characterization in R

We may also choose to characterize cohorts using R. Here we'll describe how to use the OHDSI R package FeatureExtraction to generate baseline features (covariates) for our hypertension cohorts. FeatureExtraction provides users with the ability to construct covariates in three ways:

- Choose the default set of covariates
- Choose from a set of prespecified analyses
- Create a set of custom analyses

FeatureExtraction creates covariates in two distinct ways: person-level features and aggregate features. Person-level features are useful for machine learning applications. In this section, we'll focus on using aggregate features that are useful for generating baseline covariates that describe the cohort of interest. Additionally, we'll focus on the second two ways of constructing covariates: prespecified and custom analyses and leave using the default set as an exercise for the reader.

12.8.1 Cohort instantiation

We first need to instantiate the cohort to characterize it. Instantiating cohorts is described in Chapter 11. In this example, we'll use the persons initiating a first-line therapy for hypertension with 1 year follow up (Appendix B.6). We leave characterizing the other cohorts in Appendix B as an exercise for the reader. We will assume the cohort has been instantiated in a table called `scratch.my_cohorts` with cohort definition ID equal to 1.

12.8.2 Data extraction

We first need to tell R how to connect to the server. FeatureExtraction uses the DatabaseConnector package, which provides a function called `createConnectionDetails`. Type `?createConnectionDetails` for the specific settings required for the various database man-

agement systems (DBMS). For example, one might connect to a PostgreSQL database using this code:

```
library(FeatureExtraction)
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"`.

12.8.3 Using prespecified analyses

The function `createCovariateSettings` allow the user to choose from a large set of predefined covariates. Type `?createCovariateSettings` to get an overview of the available options. For example:

```
settings <- createCovariateSettings(useDemographicsGender = TRUE,  
                                     useDemographicsAgeGroup = TRUE,  
                                     useConditionOccurrenceAnyTimePrior = TRUE)
```

This will create binary covariates for gender, age (in 5 year age groups), and each concept observed in the condition occurrence table any time prior to (and including) the cohort start date.

Many of the prespecified analyses refer to a short, medium, or long term time window. By default, these windows are defined as:

- **Long term:** 365 days prior up to and including the cohort start date.
 - **Medium term:** 180 days prior up to and including the cohort start date.
 - **Short term:** 30 days prior up to and including the cohort start date.

However, the user can change these values. For example:

```
shortTermStartDays = -14,
endDays = -1)
```

This redefines the long term window as 180 days prior up to (but not including) the cohort start date, and redefines the short term window as 14 days prior up to (but not including) the cohort start date.

Again, we can also specify which concept IDs should or should not be used to construct covariates:

```
settings <- createCovariateSettings(useConditionEraLongTerm = TRUE,
                                      useConditionEraShortTerm = TRUE,
                                      useDrugEraLongTerm = TRUE,
                                      useDrugEraShortTerm = TRUE,
                                      longTermStartDays = -180,
                                      shortTermStartDays = -14,
                                      endDays = -1,
                                      excludedCovariateConceptIds = 1124300,
                                      addDescendantsToExclude = TRUE,
                                      aggregated = TRUE)
```



The use of `aggregated = TRUE` for all of the examples above indicate to FeatureExtraction to provide summary statistics. Excluding this flag will compute covariates for each person in the cohort.

12.8.4 Creating aggregated covariates

The following code block will generate aggregated statistics for a cohort:

```
covariateSettings <- createDefaultCovariateSettings()

covariateData2 <-getDbCovariateData(connectionDetails = connectionDetails,
                                         cdmDatabaseSchema = cdmDatabaseSchema,
                                         cohortDatabaseSchema = resultsDatabaseSchema,
                                         cohortTable = "cohorts_of_interest",
                                         cohortId = 1,
                                         covariateSettings = covariateSettings,
                                         aggregated = TRUE)

summary(covariateData2)
```

And the output will look similar to the following:

```
## CovariateData object summary
##
## Number of covariates: 41330
## Number of non-zero covariate values: 41330
```

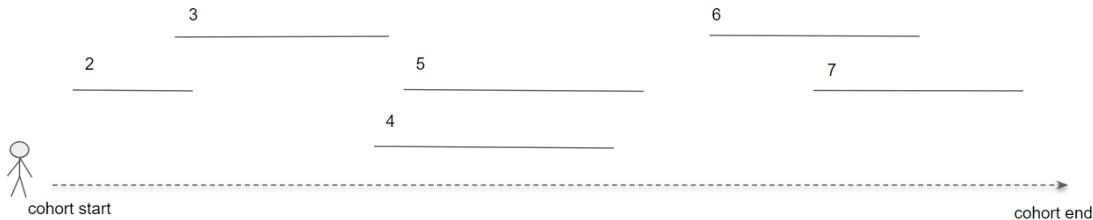


Figure 12.17: Pathways analysis in the context of a single person.

12.8.5 Output format

The two main components of the aggregated covariateData object are covariates and covariatesContinuous for binary and continuous covariates respectively:

```
covariateData2$covariates
covariateData2$covariatesContinuous
```

12.8.6 Custom covariates

FeatureExtraction also provides the ability to define and utilize custom covariates. These details are an advanced topic and covered in the user documentation: <http://ohdsi.github.io/FeatureExtraction/>.

12.9 Cohort pathways in ATLAS

The goal with a pathway analysis is to understand the sequencing of treatments along in one or more cohorts of interest. The methods applied are based on the design reported by Hripcsak et al. (2016). These methods were generalized and codified into a feature called Cohort Pathways in ATLAS.

Cohort pathways aims to provide analytic capabilities to summarize the events following the cohort start date of one or more target cohorts. To do this, we create a set of cohorts to identify the clinical events of interest for the target population called event cohort. Focusing on how this might look for a person in the target cohort:

In figure 12.17, the person is part of the target cohort with a defined start and end date. Then, the numbered line segments represent where that person also is identified in an event cohort for a duration of time. Event cohorts allow us to describe any clinical event of interest that is represented in the CDM such that we are not constrained to creating a pathway for a single domain or concept.

To start, click on  **Cohort Pathways** in the left bar of ATLAS to create a new cohort pathways study. Provide a descriptive name and press the save button .

The screenshot shows the 'Design' tab selected in the top navigation bar. Below the header, a note defines 'Cohort Pathway' as an aggregated sequence of transitions between Event Cohorts. A section titled 'Target Cohorts' indicates that each cohort will be analyzed for pathways. An 'Import' button is visible, along with a search bar and pagination controls. The main area displays a table of two cohorts:

ID	Name	Edit cohort	Remove
10447	Patients initiating first-line therapy for hypertension with >1 yr follow-up	Edit cohort	Remove
10448	Patients initiating first-line therapy for hypertension with >3 yr follow-up	Edit cohort	Remove

Showing 1 to 2 of 2 entries

Figure 12.18: Pathways analysis with target cohorts selected.

12.9.1 Design

To start, we will continue to use the cohorts initiating a first-line therapy for hypertension with 1 and 3 years follow up (Appendix B.6, B.7). Use the button to import the 2 cohorts.

Next we'll define the event cohorts by creating a cohort for each first-line hypertensive drug of interest. For this, we'll start by creating a cohort of ACE inhibitor users and define the cohort end date as the end of continuous exposure. We'll do the same for 8 other hypertensive medications and note that these definitions are found in Appendix B.8-B.16. Once complete use the **Import** button to import these into the Event Cohort section of the pathway design:

When complete, your design should look like the one above. Next, we'll need to decide on a few additional analysis settings:

- **Combination window:** This setting allows you to define a window of time, in days, in which overlap between events is considered a combination of events. For example, if two drugs represented by 2 event cohorts (event cohort 1 and event cohort 2) overlap within the combination window the pathways algorithm will combine them into “event cohort 1 + event cohort 2”.
- **Minimum cell count:** Event cohorts with less than this number of people will be censored (removed) from the output to protect privacy.
- **Max path length:** This refers to the maximum number of sequential events to consider for the analysis.

12.9.2 Executions

Once we have our pathway analysis designed, we can execute this design against one or more databases in our environment. This works the same way as we described for cohort characterization in ATLAS. Once complete, we can review the results of the analysis.

Event Cohorts

Each Event Cohort defines the step in a pathway that may occur for a person in the Target Cohort.

Import
Show **10** entries
Search:

ID	Name	Edit cohort	Remove
9174	ACE inhibitor use	Edit cohort	Remove
9175	Angiotensin receptor blocker (ARB) use	Edit cohort	Remove
9176	Thiazide or thiazide-like diuretic use	Edit cohort	Remove
9177	dihydropyridine Calcium Channel Blocker (dCCB) use	Edit cohort	Remove
9178	non-dihydropyridine Calcium Channel Blocker (ndCCB) use	Edit cohort	Remove
9179	beta blocker use	Edit cohort	Remove
9180	Diuretic-loop use	Edit cohort	Remove
9181	Diuretic-potassium sparing use	Edit cohort	Remove
9182	alpha-1 blocker use	Edit cohort	Remove

Showing 1 to 9 of 9 entries

Previous **1** Next

Figure 12.19: Event cohorts for pathway design for initiating a first-line antihypertensive therapy.

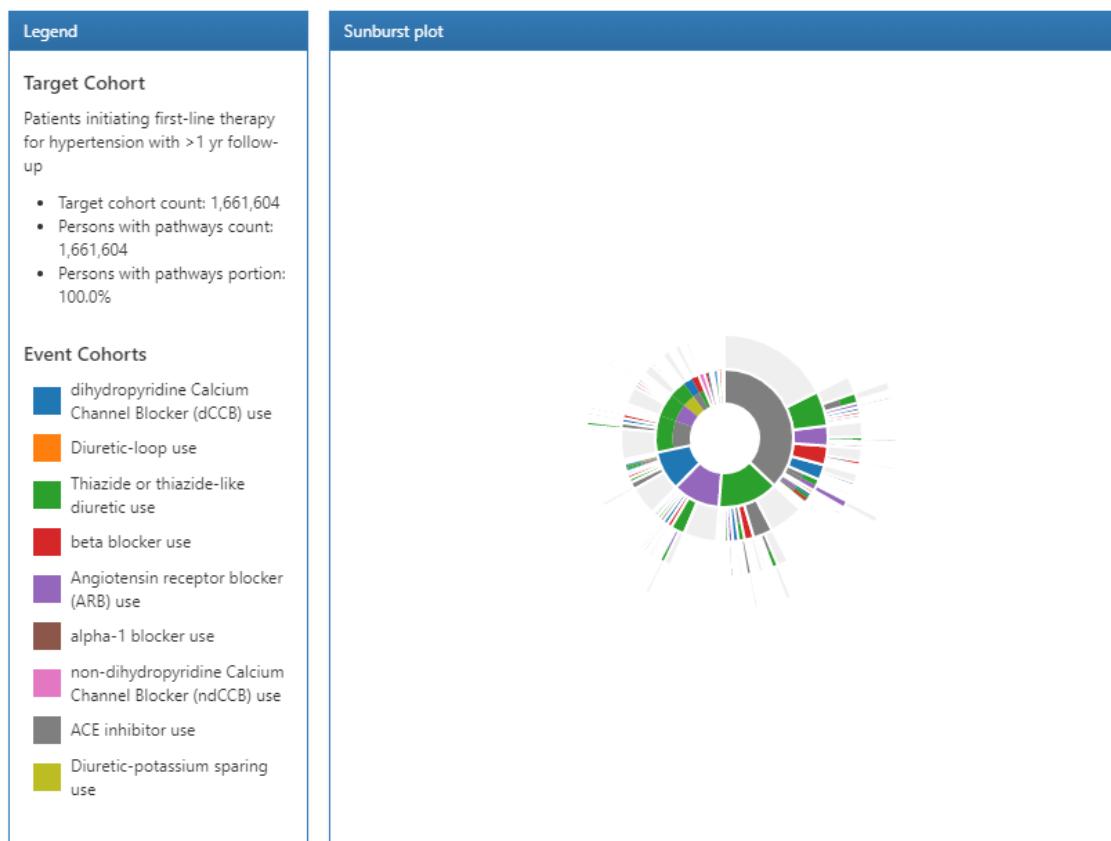


Figure 12.20: Pathways results legend and sunburst visualization.

12.9.3 Viewing Results

The results of a pathway analysis are broken into 3 sections: The legend section displays the total number of persons in the target cohort along with the number of persons that had 1 or more events in the pathway analysis. Below that summary are the color designations for each of the cohorts that appear in the sunburst plot in the center section.

The sunburst plot is a visualization that represents the various event pathways taken by persons over time. The center of the plot represents the cohort entry and the first color-coded ring shows the proportion of persons in each event cohort. In our example, the center of the circle represents hypertensive persons initiating a first line therapy. Then, the first ring in the sunburst plot shows the proportion of persons that initiated a type of first-line therapy defined by the event cohorts (i.e. ACE inhibitors, Angiotensin receptor blockers, etc). The second set of rings represents the 2nd event cohort for persons. In certain event sequences, a person may never have a 2nd event cohort observed in the data and that proportion is represented by the grey portion of the ring.

Clicking on a section of the sunburst plot will display the path details on the right. Here we can see that the largest proportion of people in our target cohort initiated a first-line therapy with ACE inhibitors and from that group, a smaller proportion started a Thiazide or thiazide diuretics.

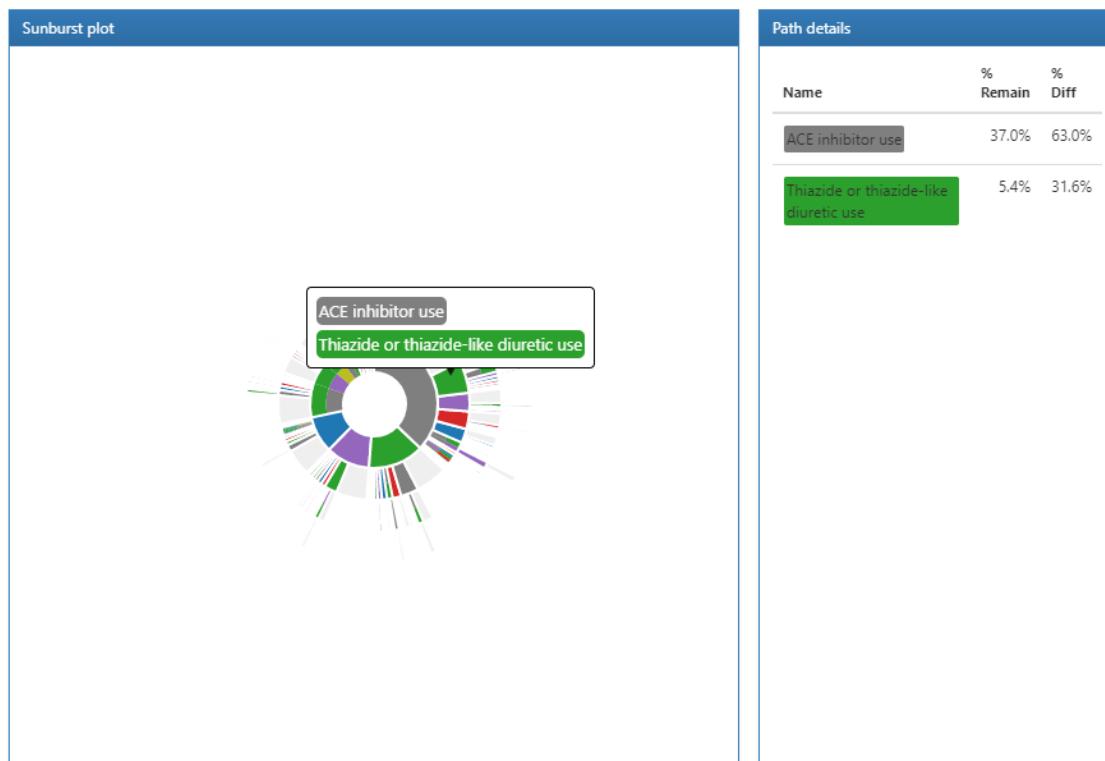


Figure 12.21: Pathways results displaying path details.

12.10 Incidence analysis in ATLAS

In an incidence calculation, we describe: amongst the persons in the target cohort, who experienced the outcome cohort during the time at risk period. Here we will design an incidence analysis to characterize angioedema and acute myocardial infarction outcomes amongst new users of ACE inhibitors (ACEi) and Thiazides and thiazide-like diuretics (THZ). We will assess these outcomes during the time-at-risk that a person was exposed to the drug. Additionally, we will add an outcome of drug exposure to Angiotensin receptor blockers (ARBs) to measure the incidence of new use of ARBs during exposure to the target cohorts (ACEi and THZ). This outcome definition provides an understanding of how ARBs are utilized amongst the target populations.

To start, click on **Incidence Rates** in the left bar of ATLAS to create a new incidence analysis. Provide a descriptive name and press the save button .

12.10.1 Design

We assume the cohorts used in this example have already been created in ATLAS as described in Chapter 11. The Appendix provides the full definitions of the target cohorts (Appendix B.2, B.5), and outcomes (Appendix B.4, B.3, B.9) cohorts.

On the definition tab, click to choose the *New users of ACE inhibitors* cohort and the *New users of*

The screenshot shows the ATLAS software interface with a navigation bar at the top containing 'Definition', 'Concept Sets', 'Generation', and 'Utilities'. Below the navigation bar, there are two main sections: 'Study Cohorts' and 'Outcome Cohorts'. The 'Study Cohorts' section contains a table with three rows, each starting with a red 'X' icon and followed by a cohort ID and description. There are green 'Add Target Cohort' and red 'Add Outcome Cohort' buttons below the table. The 'Outcome Cohorts' section also contains a table with three rows, each starting with a red 'X' icon and followed by a cohort ID and description.

Figure 12.22: Incidence Rate target and outcome definition.

Time At Risk

Time at risk defines the time window relative to the cohort start or end date with an offset to consider the person 'at risk' of the outcome.

- Time at risk starts with plus days.
- Time at risk ends with plus days.

No study window defined.

Figure 12.23: Incidence Rate target and outcome definition.

Thiazide or Thiazide-like diuretics cohort. Close the dialog to view that these cohorts are added to the design. Next we add our outcome cohorts by clicking on and from the dialog box, select the outcome cohorts of *acute myocardial infarction events*, *angioedema events* and *Angiotensin receptor blocker (ARB) use*. Again, close the window to view that these cohorts are added to the outcome cohorts section of the design.

Next, we will define the time at risk window for the analysis. As shown above, the time at risk window is defined relative to the cohort start and end dates. Here we will define the time at risk start as 1 day after cohort start for our target cohorts. Next, we'll define the time at risk to end at the cohort end date. In this case, the definition of the ACEi and THZ cohorts have a cohort end date when the drug exposure ends.

ATLAS also provides a way to stratify the target cohorts as part of the analysis specification:

To do this, click the New Stratify Criteria button and follow the same steps described in Chapter 11. Now that we have completed the design, we can move to executing our design against one or more

Stratify Criteria: You can provide optional stratification criteria to the analysis that will divide the population into unique groups based on their satisfied criteria.

The screenshot shows the 'New stratify criteria' dialog box. It has a sidebar on the left with 'New stratify criteria' and '1. Gender = Female'. The main area shows a table with a single row: 'Gender = Female'. There is a 'Copy' and 'Delete' button at the top right. Below the table, there is a text input field with placeholder text 'enter an inclusion rule description' and a dropdown menu 'having all ▾ of the following criteria:'. A blue button '+ Add criteria to group... ▾' is located to the right. A large blue box contains the text 'with the following event criteria:' and a blue button '+ Add attribute...'. Below this, there is a red 'X' icon followed by 'with a gender of: FEMALE' and buttons 'Add' and 'Import'. A red 'Delete Criteria' button is located at the bottom right of the large blue box.

Figure 12.24: Incidence Rate strata definition for females.

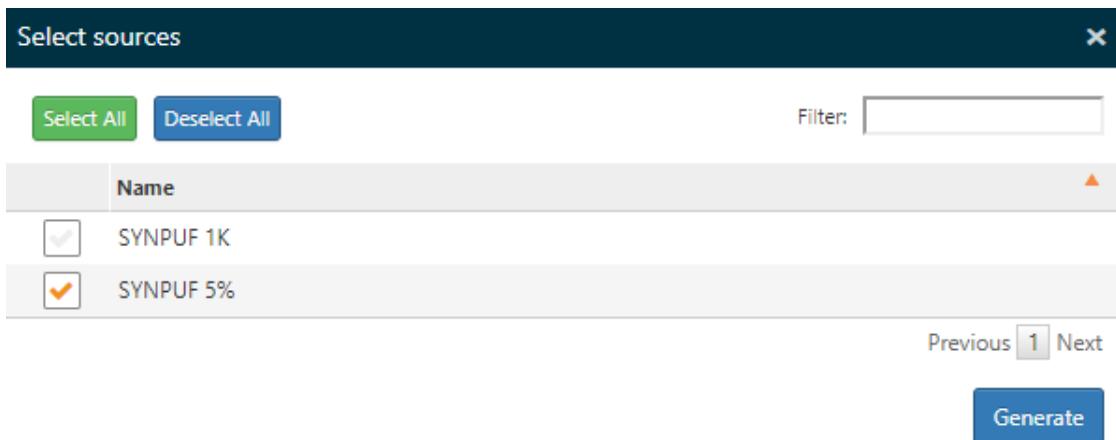


Figure 12.25: Incidence Rate analysis execution.

databases.

12.10.2 Executions

Click the Generation tab and then the button to reveal a list of databases to use to execute the analysis:

Select one or more databases and click the Generate button to start the analysis to analyze all combinations of targets and outcomes specified in the design.

12.10.3 Viewing Results

On the Generation tab, the top portion of the screen allows you to select a target and outcome to use when viewing the results. Just below this a summary of the incidence is shown for each database used in the analysis.

Select the target cohort of ACEi users and the Acute Myocardial Infarction (AMI) from the respective dropdown lists. Click the button to reveal the incidence analysis results:

A summary for the database shows the total persons in the cohort that were observed during the time-at-risk along with the total number of cases. The proportion shows the number of cases per 1000 people. The time at risk, in years, is calculated for the target cohort. The incidence rate is expressed as the number of cases per 1000 person-years.

We can also view the incidence metrics for the strata that we defined in the design. The same metrics mentioned above are calculated for each stratum. Additionally, a treemap visualization provides a representation of the proportion of each stratum represented by the boxed areas. The color represents the incidence rate as shown in the scale along the bottom.

We can gather the same information to see the incidence of new use of ARBs amongst the ACEi

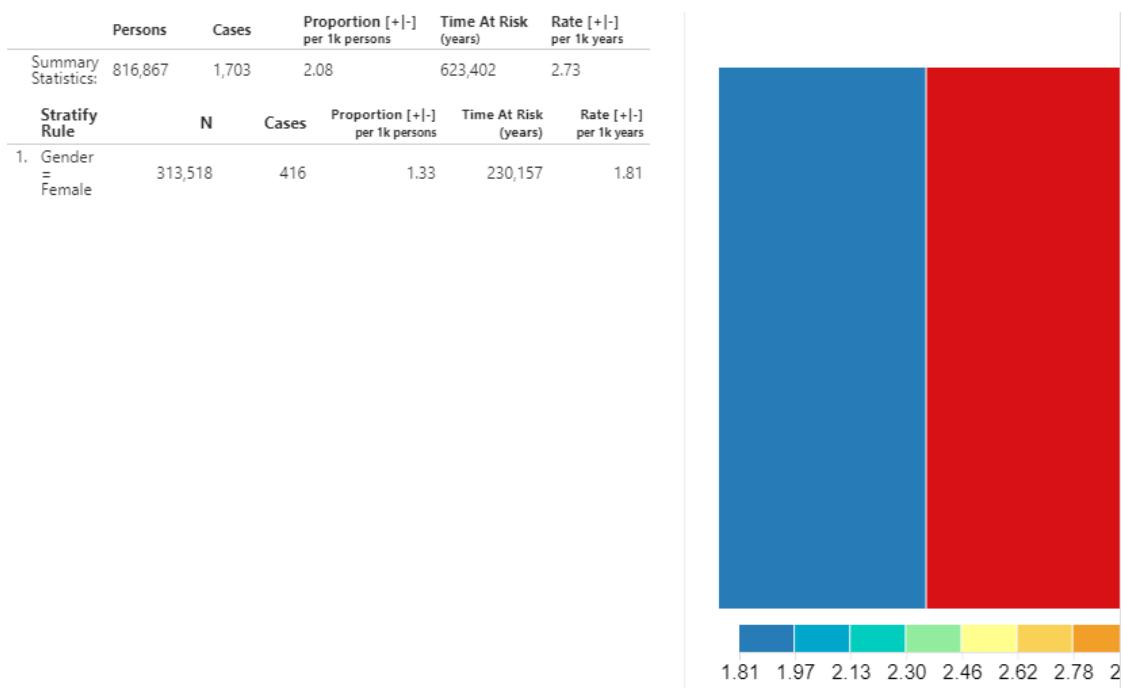


Figure 12.26: Incidence Rate analysis output - New ACEi users with AMI outcome.

population. Using the dropdown at the top, change the outcome to ARBs use and click the Reports button to reveal the details.

As shown, the metrics calculated are the same but the interpretation is different since the input (ARB use) references a drug utilization estimate instead of a health outcome.

12.11 Summary



- Characterization describes a cohort of interest during the time preceding the index date (**baseline**) and the time after index (**post-index**).
- ATLAS’ characterization module and the OHDSI Methods Library provide the capability to calculate baseline characteristics for multiple time windows.
- ATLAS’ pathways and incidence rate modules provide descriptive statistics during the post-index time period.

12.12 Exercises

1. We would like to understand how hypertensive treatments are utilized in a real world setting. To start, we would like to understand the composition of data that a source has for a hyperten-

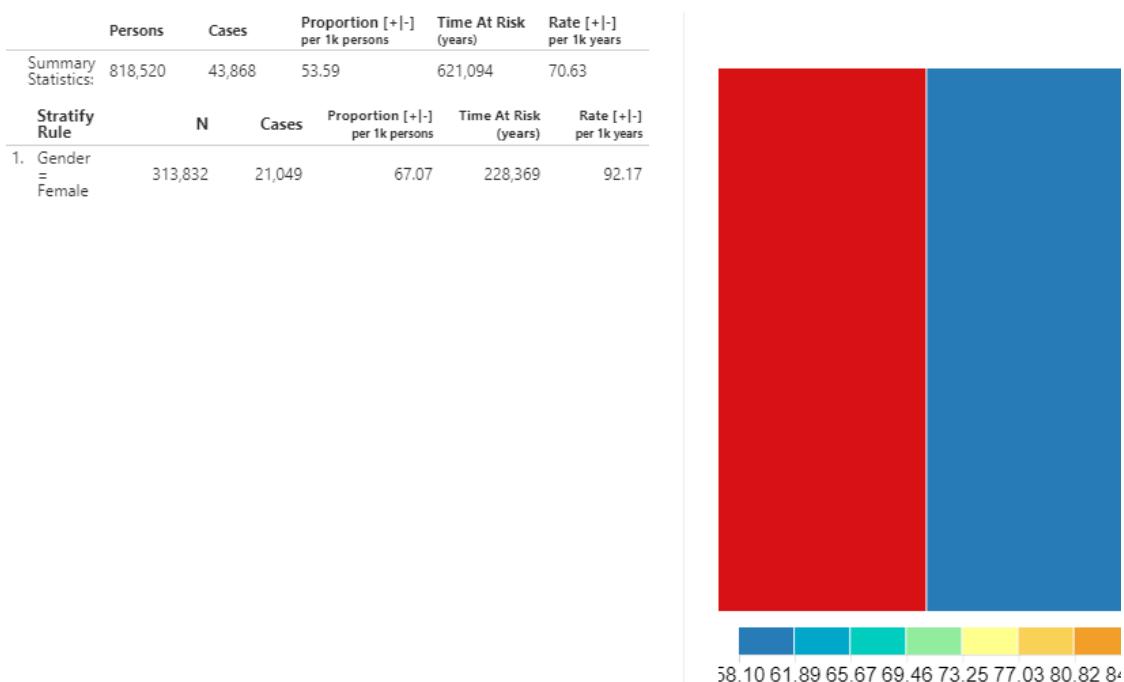


Figure 12.27: Incidence Rate - New users of ACEi receiving ARBs treatment during ACEi exposure.

sive medication such as Lisinopril. How would you use ATLAS data source module to find information on Lisinopril?

2. In the chapter we characterized new users of any hypertensive medication and utilized the cohort pathways tool in ATLAS to find that ACE Inhibitors and thiazides were the most commonly used first-line drug therapy. To better understand the disease natural history of patients initiating ACE inhibitors and Thiazides, use ATLAS to construct a cohort characterization for these populations to understand their demographics, concomitant medications and comorbid conditions.
3. How might we design a pathways analysis to characterize procedure sequences used to treat hypertension (i.e. cardiac bypass surgery, carotid artery surgery and dialysis)?
4. Using the preceding conditions found in exercise #2, construct an incidence rate analysis to find the rate of an outcome in the ACEi and THZ populations.

TODO: Define exercises using Eunomia.

Per chapter 13: Note: The excercises still have to be defined. The idea is to require readers to define a study that estimates the effect of celecoxib on GI bleed, compared to diclofenac. For this they must use the Eunomia package, which is still under development.

Chapter 13

Population-Level Estimation

Chapter leads: Martijn Schuemie, David Madigan, Marc Suchard & Patrick Ryan

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, which refers to the estimation of average causal effects of exposures (e.g. medical interventions such as drug exposures or procedures) 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:** estimating the effect of an 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 designs employ different 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.

In this chapter we first describe various population-level estimation study designs, all of which are implemented as R packages in the OHDSI Methods Library. We then detail the design of an example estimation study, followed by step-by-step guides of how to implement the design using ATLAS and R. Finally, we review the various outputs generated by the study, including study diagnostics and effect size estimates.

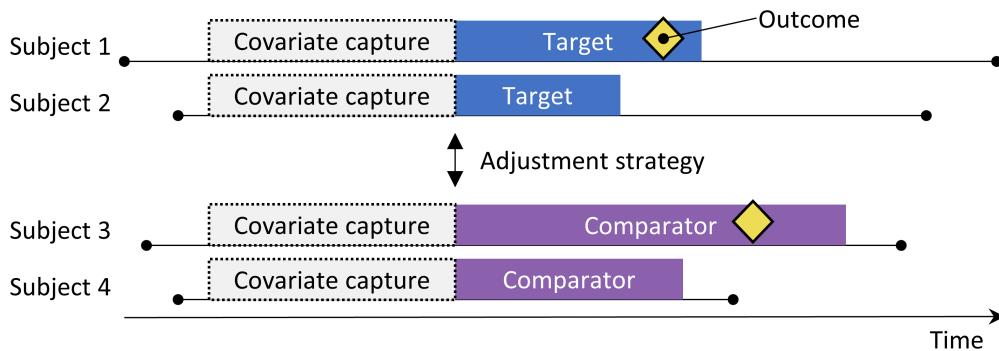


Figure 13.1: The new-user cohort design. Subjects observed to initiate the target treatment are compared to those initiating the comparator treatment. To adjust for differences between the two treatment groups several adjustment strategies can be used, such as stratification, matching, or weighting by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

13.1 The cohort method design

The 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
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, among 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 is 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 between target and comparator.



The new-user cohort method inherently is a method for comparative effect estimation, comparing one treatment to another. 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.

A key concern is that the patients receiving the target treatment may systematically differ from those receiving the comparator treatment. For example, suppose the target cohort is on average 60 years old, whereas the comparator cohort is on average 40 years old. Comparing target to comparator with respect to any age-related health outcome (e.g. stroke) might then show substantial differences. An uninformed investigator might reach the conclusion there is a causal association between the target treatment and stroke as compared to the comparator. More prosaically or commonplace, the investigator might conclude that there exist target patients that experienced stroke that would not have done so had they received the comparator. This conclusion could well be entirely incorrect! Maybe those target patients disproportionately experienced stroke simply because they are older; maybe the target patients that experienced stroke might well have done so even if they had received the comparator. In this context, age is a “confounder.”

13.1.1 Propensity scores

In a randomized trial, a (virtual) coin toss assigns patients to their respective groups. Thus, by design, the probability that a patient receives the target treatment as against the comparator treatment does not relate in any way to patient characteristics such as age. The coin has no knowledge of the patient, and, what's more, we know with certainty the exact probability that a patient receives the target exposure. As a consequence, and with increasing confidence as the number of patients in the trial increases, the two groups of patients essentially *cannot* differ systematically with respect to *any* patient characteristic. This guaranteed balance holds true for characteristics that the trial measured (such as age) as well as characteristics that the trial failed to measure.

For a given patient, the *propensity score* (PS) is the probability that that patient received the target treatment as against the comparator. (Rosenbaum and Rubin, 1983) In a balanced two-arm randomized trial, the propensity score is 0.5 for every patient. In a propensity score-adjusted observational study, we estimate the probability of a patient receiving the target treatment based on what we can observe in the data on and before the time of treatment initiation (irrespective of the treatment they actually received). This is a straightforward predictive modeling application; we fit a model (e.g. a logistic regression) that predicts whether a subject receives the target treatment, and use this model to generate predicted probabilities (the PS) for each subject. Unlike in a standard randomized trial, different patients will have different probabilities of receiving the target treatment. The PS can be used in several ways including matching target subjects to comparator subjects with similar PS, stratifying the study population based on the PS, or weighting subjects using Inverse Probability of Treatment Weighting (IPTW) derived from the PS. When matching we can select just one comparator subject for each target subject, or we can allow more than one comparator subject per target subject, a technique known as variable-ratio matching. (Rassen et al., 2012)

For example, suppose we use one-on-one PS matching, and that Jan has a prior probability of 0.4 of receiving the target treatment and in fact receives the target treatment. If we can find a patient (named Jun) that also had an a priori probability of 0.4 of receiving the target treatment but in fact received the comparator, the comparison of Jan and Jun's outcomes is like a mini-randomized trial, at least with respect to measured confounders. This comparison will yield an estimate of the Jan-Jun causal contrast that is as good as the one randomization would have produced. Estimation then proceeds as follows: for every patient that received the target, find one or more matched patients that received the comparator but had the same prior probability of receiving the target. Compare the outcome for the target patient with the outcomes for the comparator patients within each of these matched groups.

Propensity scoring controls for measured confounders. In fact, if treatment assignment is “strongly ignorable” given measured characteristics, propensity scoring will yield an unbiased estimate of the causal effect. “Strongly ignorable” essentially means that there are no unmeasured confounders, and that the measured confounders are adjusted for appropriately. Unfortunately this is not a testable assumption. See Chapter 19 for further discussion of this issue.

13.1.2 Variable selection

In the past, PS were computed based on manually selected characteristics, and although the OHDSI tools can support such practices, we prefer using many generic characteristics (i.e. characteristics that are not selected based on the specific exposures and outcomes in the study). (Tian et al., 2018) These characteristics include demographics, as well as all diagnoses, drug exposures, measurement, and medical procedures observed prior to and on the day of treatment initiation. A model typically involves 10,000 to 100,000 unique characteristics, which we fit using large-scale regularized regression (Suchard et al., 2013) implemented in the Cyclops package. In essence, we let the data appropriately weigh the characteristics.



We typically include the day of treatment initiation in the covariate capture window because many relevant data points such as the diagnosis leading to the treatment are recorded on that date. This does require us to explicitly exclude the target and comparator treatment from the set of covariates, because these are the things we are trying to predict.

Some have argued that a data-driven approach to covariate selection that does not depend on clinical expertise to specify the “right” causal structure runs the risk of erroneously including so-called instrumental variables and colliders, thus increasing variance and potentially introducing bias. (Hernan et al., 2002) However, these concerns are unlikely to have a large impact in real-world scenarios. (Schneeweiss, 2018) Furthermore, in medicine the true causal structure is rarely known, and when different researchers are asked to identify the ‘right’ covariates to include for a specific research question, each researcher invariably comes up with a different list, thus making the process irreproducible. Most importantly, our diagnostics such as inspection of the propensity model, evaluating balance on all covariates, and including negative controls would identify most problems related to colliders and instrumental variables.

13.1.3 Caliper

Since propensity scores fall on a continuum from 0 to 1, exact matching is rarely possible. Instead, the matching process finds patients that match the propensity score of a target patient(s) within some tolerance known as a “caliper.” Following Austin (2011), we use a default caliper of 0.2 standard deviations on the logit scale.

13.1.4 Overlap: preference scores

The propensity method requires that matching patients exist! As such, a key diagnostic shows the distribution of the propensity scores in the two groups. To facilitate interpretation, the OHDSI tools plot a transformation of the propensity score called the “preference score”. (Walker et al., 2013) The preference score adjusts for the “market share” of the two treatments. For example, if 10% of patients receive the target treatment (and 90% receive the comparator treatment), then patients with a preference score of 0.5 have a 10% probability of receiving the target treatment. Mathematically, the preference score is

$$\ln \left(\frac{F}{1 - F} \right) = \ln \left(\frac{S}{1 - S} \right) - \ln \left(\frac{P}{1 - P} \right)$$

Where F is the preference score, S is the propensity score, and P is the proportion of patients receiving the target treatment.

Walker et al. (2013) discuss the concept of “empirical equipoise.” They accept exposure pairs as emerging from empirical equipoise if at least half of the exposures are to patients with a preference score of between 0.3 and 0.7.

13.1.5 Balance

Good practice always checks that the PS adjustment succeeds in creating balanced groups of patients. Figure 13.18 shows the standard OHDSI output for checking balance. For each patient characteristic, this plots the standardized difference between means between the two exposure groups before and after PS adjustment. Some guidelines recommend an after-adjustment standardized difference upper bound of 0.1. (Rubin, 2001)

13.2 The self-controlled cohort design

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.

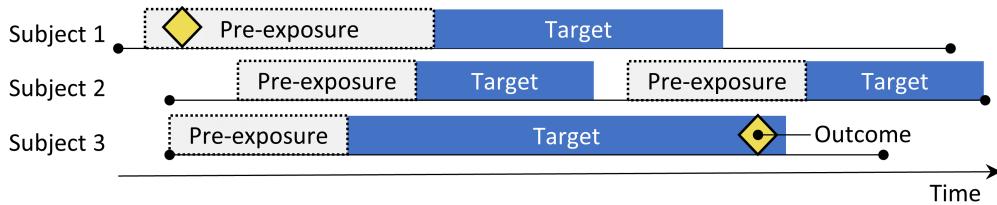


Figure 13.2: The self-controlled cohort design. The rate of outcomes during exposure to the target is compared to the rate of outcomes in the time pre-exposure.

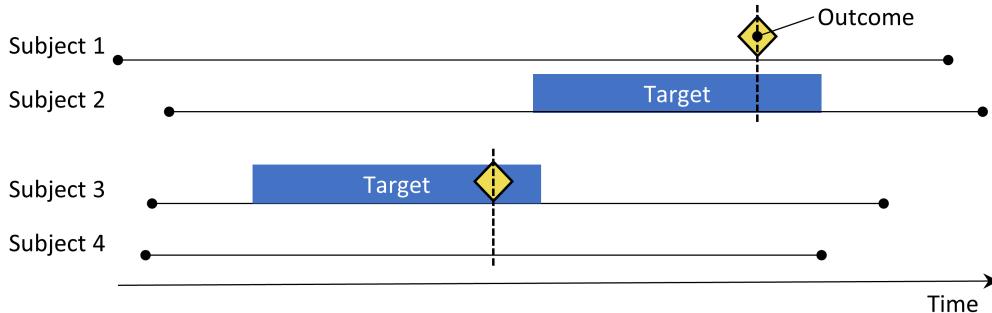


Figure 13.3: The case-control design. Subjects with the outcome ('cases') are compared to subjects without the outcome ('controls') in terms of their exposure status. Often, cases and controls are matched on various characteristics such as age and sex.

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 in the baseline risk of the outcome between different time periods.

13.3 The case-control design

Case-control studies (Vandenbroucke and Pearce, 2012) 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
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 selects controls to match 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.

13.4 The case-crossover design

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-crossover 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

Cases serve as their own controls. As self-controlled designs, they should 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

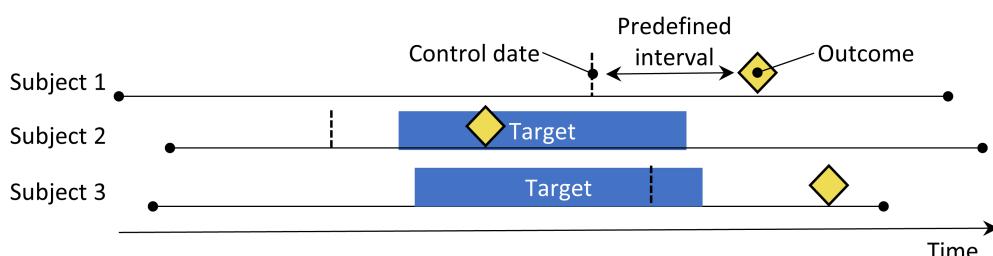


Figure 13.4: The case-crossover design. The time around the outcome is compared to a control date set at a predefined interval prior to the outcome date.

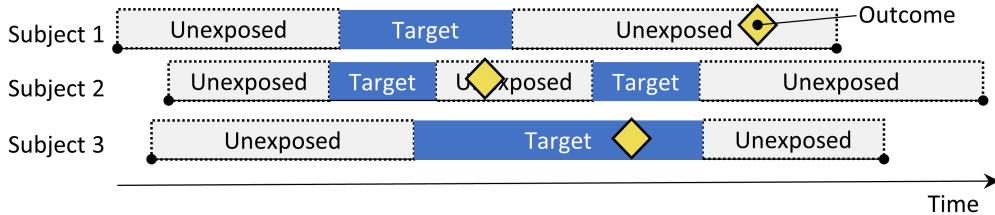


Figure 13.5: The Self-Controlled Case Series design. The rate of outcomes during exposure is compared to the rate of outcomes when not exposed.

over time (or negatively biased if there is a decrease). To address this, the case-time-control design (Suisser, 1995) was developed, which adds controls, matched for example on age and sex, to the case-crossover design to adjust for exposure trends.

13.5 The self-controlled case series design

The Self-Controlled Case Series (SCCS) design (Farrington, 1995; Whitaker et al., 2006) compares the rate of outcomes during exposure to the rate of outcomes during all unexposed time, including 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. 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)

13.6 Designing a hypertension study

13.6.1 Problem definition

ACE inhibitors (ACEi) 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 (e.g., 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 ACEi to beta-blockers for the risk of angioedema, (Magid et al., 2010; Toh et al., 2012) but beta-blockers are no longer recommended as first-line treatment of hypertension. (Whelton et al., 2018) A viable alternative treatment could be thiazides or thiazide-like diuretics (THZ), which could be just as effective in managing hypertension and its associated risks such as acute myocardial infarction (AMI), but without increasing the risk of angioedema.

The following will demonstrate how to apply our population-level estimation framework to observational healthcare data to address the following comparative estimation questions:

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

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

Since these are comparative effect estimation questions we will apply the cohort method as described in Section 13.1.

13.6.2 Target and comparator

We consider patients new-users if their first observed treatment for hypertension was monotherapy with any active ingredient in either the ACEi or THZ class. We define mono therapy as not starting on any other anti-hypertensive drug in the seven days following treatment initiation. We require patients to have at least one year of prior continuous observation in the database before first exposure and a recorded hypertension diagnosis at or in the year preceding treatment initiation.

13.6.3 Outcome

We define angioedema as any occurrence of an angioedema condition concept during an inpatient or emergency room (ER) visit, and require there to be no angioedema diagnosis recorded in the seven days prior. We define AMI as any occurrence of an AMI condition concept during an inpatient or ER visit, and require there to be no AMI diagnosis record in the 180 days prior.

13.6.4 Time-at-risk

We define time-at-risk to start on the day after treatment initiation, and stop when exposure stops, allowing for a 30-day gap between subsequent drug exposures.

13.6.5 Model

We fit a PS model using the default set of covariates, including demographics, conditions, drugs, procedures, measurements, observations, and several co-morbidity scores. We exclude ACEi and THZ from the covariates. We perform variable-ratio matching and condition the Cox regression on the matched sets.

13.6.6 Study summary

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

Choice	Value
Target cohort	New users of ACE inhibitors as first-line monotherapy for hypertension.
Comparator cohort	New users of thiazides or thiazide-like diuretics as first-line monotherapy for hypertension.
Outcome cohort	Angioedema or acute myocardial infarction.
Time-at-risk	Starting the day after treatment initiation, stopping when exposure stops.
Model	Cox proportional hazards model using variable-ratio matching.

13.6.7 Control questions

To evaluate whether our study design produces estimates in line with the truth, we additionally include a set of control questions where the true effect size is known. Control questions can be divided in negative controls, having a hazard ratio of 1, and positive controls, having a known hazard ratio greater than 1. For several reasons we use real negative controls, and synthesize positive controls based on these negative controls. How to define and use control questions is discussed in detail in Chapter 19.

The screenshot shows the 'Comparison' dialog in ATLAS. At the top, there's a back arrow and the title 'Comparison'. Below it, a message says 'Add or update the target, comparator, outcome(s) cohorts and negative control outcomes'. The 'Choose your target cohort:' section contains the text 'New users of ACE inhibitors as first-line monotherapy for hypertension' with a blue file icon and a red delete icon. The 'Choose your comparator cohort:' section contains the text 'New users of Thiazide-like diuretics as first-line monotherapy for hypertension' with a blue file icon and a red delete icon. The 'Choose your outcome cohorts:' section has a 'Add Outcome' button. Below these sections is a table with two entries:

ID	Name	Edit cohort	Remove
1770712	Angioedema outcome	Edit cohort	Remove
1770713	Acute myocardial infarction outcome	Edit cohort	Remove

At the bottom left, it says 'Showing 1 to 2 of 2 entries'. On the right, there's a 'Search:' input field, a page number '1', and 'Previous' and 'Next' buttons.

Figure 13.6: The comparison dialog

13.7 Implementing the study using ATLAS

Here we demonstrate how this study can be implemented using the Estimation function in ATLAS. Click on **Estimation** in the left bar of ATLAS, and create a new estimation study. Make sure to give the study an easy-to-recognize name. The study design can be saved at any time by clicking the button.

In the Estimation design function, there are three sections: Comparisons, Analysis Settings, and Evaluation Settings. We can specify multiple comparisons and multiple analysis settings, and ATLAS will execute all combinations of these as separate analyses. Here we discuss each section:

13.7.1 Comparative cohort settings

A study can have one or more comparisons. Click on “Add Comparison,” which will open a new dialog. Click on to select the target and comparator cohorts. By clicking on “Add Outcome” we can add our two outcome cohorts. We assume the cohorts have already been created in ATLAS as described in Chapter 11. The Appendix provides the full definitions of the target (Appendix B.2), comparator (Appendix B.5), and outcome (Appendix B.4 and Appendix B.3) cohorts. When done, the dialog should look like Figure 13.6.

Note that we can select multiple outcomes for a target-comparator pair. Each outcome will be treated independently, and will result in a separate analysis.

Negative control outcomes

Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	Exclude	Descendants	Mapped
72748	74779009	Strain of rotator cuff capsule	Condition	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
73241	197210001	Anal and rectal polyp	Condition	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
73560	55260003	Calcaneal spur	Condition	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
75911	65358001	Acquired hallux valgus	Condition	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
76786	63643000	Derangement of knee	Condition	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Figure 13.7: Negative Control concept set.

Negative control outcomes are outcomes that are not believed to be caused by either the target or the comparator, and where therefore the true hazard ratio equals 1. Ideally, we would have proper cohort definitions for each outcome cohort. However, typically, we only have a concept set, with one concept per negative control outcome, and some standard logic to turn these into outcome cohorts. Here we assume the concept set has already been created as described in Chapter 19 and can simply be selected. The negative control concept set should contain a concept per negative control, and not include descendants. Figure 13.7 shows the negative control concept set used for this study.

Concepts to include

When selecting concept to include, we can specify which covariates we would like to generate, for example to use in a propensity 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 regularized regression build a model that balances all covariates. The only reason we might want to specify particular covariates is to replicate an existing study that manually picked covariates. These inclusions can be specified in this comparison section or in the analysis section, because sometimes they pertain to a specific comparison (e.g. know confounders in a comparison), or sometimes they pertain to an analysis (e.g. when evaluating a particular covariate selection strategy).

Concepts to exclude

Rather than specifying which concepts to include, we can instead specify concepts to *exclude*. When we submit a concept set in this field, we use every covariate except for those that we submitted. When using the default set of covariates, which includes all drugs and procedures occurring on the day of treatment initiation, we must exclude the target and comparator treatment, as well as any concepts that are directly related to these. For example, if the target exposure is an injectable, we should not only exclude the drug, but also the injection procedure from the propensity model. In this example, the covariates we want to exclude are ACEi and THZ. Figure 13.8 shows we select a concept set that includes all these concepts.

After selecting the negative controls and covariates to exclude, the lower half of the comparisons

Concepts to exclude for ACEi and THZ

Concept Set Expression Included Concepts (14) Included Source Codes Explore Evidence Export Compare

Show 25 entries Search: Previous 1 Next

Showing 1 to 14 of 14 entries

	Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	<input type="checkbox"/> Exclude	<input type="checkbox"/> Descendants	<input type="checkbox"/> Mapped
1342439	38454	trandolapril	Drug	Standard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1334456	35296	Ramipril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
1331235	35208	quinapril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
1373225	54552	Perindopril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
1310756	30131	moexipril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	

Figure 13.8: The concept set defining the concepts to exclude.

dialog should look like Figure 13.9.

13.7.2 Effect estimation analysis settings

After closing the comparisons dialog we can click on “Add Analysis Settings.” In the box labeled “Analysis Name,” we can give the analysis a unique name that is easy to remember and locate in the future. For example, we could set the name to “Propensity score matching.”

Study population

There are a wide range of options to specify the study population, which is the set of subjects that will enter the analysis. Many of these overlap with options available when designing the target and comparator cohorts in the cohort definition tool. One reason for using the options in Estimation instead of in the cohort definition is re-usability; we can define the target, comparator, and outcome cohorts completely independently, and add dependencies between these at a later point in time. For example, if we wish to remove people who had the outcome before treatment initiation, we could do so in the definitions of the target and comparator cohort, but then we would need to create separate cohorts for every outcome! Instead, we can choose to have people with prior outcomes be removed in the analysis settings, and now we can reuse our target and comparator cohorts for our two outcomes of interest (as well as our negative control outcomes).

The **study start and end dates** can be used to limit the analyses to a specific period. The study end date also truncates risk windows, meaning no outcomes beyond the study end date will be considered. One reason for selecting a study start date might be that one of the drugs being studied is new and did not exist in an earlier time. Automatically adjusting for this can be done by answering “yes” to the question **“Restrict the analysis to the period when both exposures are observed?”**. Another reason to adjust study start and end dates might be that medical practice changed over time (e.g., due to a drug warning) and we are only interested in the time where medicine was practiced a specific way.

Choose your negative control outcomes:

Negative controls for ACEi and THZ



Covariate selection

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

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



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



Concepts to exclude for ACEi and THZ

Figure 13.9: The comparison window showing concept sets for negative controls and concepts to exclude.

The option “**Should only the first exposure per subject be included?**” can be used to restrict to the first exposure per patient. Often this is already done in the cohort definition, as is the case in this example. Similarly, the option “**The minimum required continuous observation time prior to index date for a person to be included in the cohort**” is often already set in the cohort definition, and can therefore be left at 0 here. Having observed time (as defined in the OBSERVATION_PERIOD table) before the index date ensures that there is sufficient information about the patient to calculate a propensity score, and is also often used to ensure the patient is truly a new user, and therefore was not exposed before.

“**Remove subjects that are in both the target and comparator cohort?**” defines, together with the option “**If a subject is in multiple cohorts, should time-at-risk be censored when the new time-at-risk starts to prevent overlap?**” what happens when a subject is in both target and comparator cohorts. The first setting has three choices:

- “**Keep All**” indicating to keep the subjects in both cohorts. With this option it might be possible to double-count subjects and outcomes.
- “**Keep First**” indicating to keep the subject in the first cohort that occurred.
- “**Remove All**” indicating to remove the subject from both cohorts.

If the options “keep all” or “keep first” are selected, we may wish to censor the time when a person is in both cohorts. This is illustrated in Figure 13.10. By default, the time-at-risk is defined relative to the cohort start and end date. In this example, the time-at-risk starts one day after cohort entry, and stops at cohort end. Without censoring the time-at-risk for the two cohorts might overlap. This is especially problematic if we choose to keep all, because any outcome that occurs during this overlap (as shown) will be counted twice. If we choose to censor, the first cohort’s time-at-risk ends when the second cohort’s time-at-risk starts.

We can choose to **remove subjects that have the outcome prior to the risk window start**, because often a second outcome occurrence is the continuation of the first one. For instance, when someone develops heart failure, a second occurrence is likely, which means the heart failure probably never

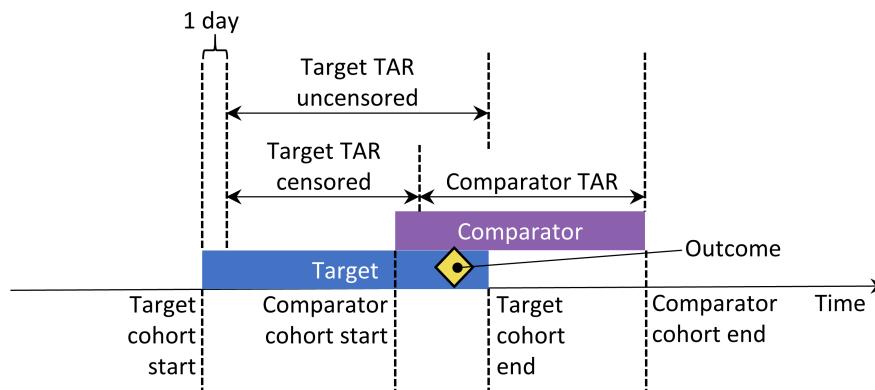


Figure 13.10: Time-at-risk (TAR) for subjects who are in both cohorts, assuming time-at-risk starts the day after treatment initiation, and stops at exposure end.

fully resolved in between. On the other hand, some outcomes are episodic, and it would be expected for patients to have more than one independent occurrence, like an upper respiratory infection. If we choose to remove people that had the outcome before, we can select **how many days we should look back when identifying prior outcomes**.

Our choices for our example study are shown in Figure 13.11. Because our target and comparator cohort definitions already restrict to the first exposure and require observation time prior to treatment initiation, we do not apply these criteria here.

Covariate settings

Here we specify the covariates to construct. These covariates are typically used in the propensity model, but can also be included in the outcome model (the Cox proportional hazards model in this case). If we **click to view details** of our covariate settings, we can select which sets of covariates to construct. However, the recommendation is to use the default set, which constructs covariates for demographics, all conditions, drugs, procedures, measurements, etc.

We can modify the set of covariates by specifying concepts to **include** and/or **exclude**. These settings are the same as the ones found in Section 13.7.1 on comparison settings. The reason why they can be found in two places is because sometimes these settings are related to a specific comparison, as is the case here because we wish to exclude the drugs we are comparing, and sometimes the settings are related to a specific analysis. When executing an analysis for a specific comparison using specific analysis settings, the OHDSI tools will take the union of these sets.

The choice to **add descendants to include or exclude** affects this union of the two settings. So in this example we specified only the ingredients to exclude when defining the comparisons. Here we set “Should descendant concepts be added to the list of excluded concepts?” to “Yes” to also add all descendants.

Figure 13.12 shows our choices for this study. Note that we have selected to add descendants to the concept to exclude, which we defined in the comparison settings in Figure 13.9.

Time at risk

 Study Population

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

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

Should only the first exposure per subject be included?

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

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

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

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

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

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

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

Figure 13.11: Study population settings.

Covariate Settings

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

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

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

No

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

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

Yes

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

Figure 13.12: Covariate settings.

Time-at-risk is defined relative to the start and end dates of our target and comparator cohorts. In our example, we had set the cohort start date to start on treatment initiation, and cohort end date when exposure stops (for at least 30 days). We set the start of time-at-risk to one day after cohort start, so one day after treatment initiation. A reason to set the time-at-risk start to be later than the cohort start is because we may want to exclude outcome events that occur on the day of treatment initiation if we do not believe it biologically plausible they can be caused by the drug.

We set the end of the time-at-risk to the cohort end, so when exposure stops. We could choose to set the end date later if for example we believe events closely following treatment end may still be attributable to the exposure. In the extreme we could set the time-at-risk end to a large number of days (e.g. 99999) after the cohort end date, meaning we will effectively follow up subjects until observation end. Such a design is sometimes referred to as an *intent-to-treat* design.

A patient with zero days at risk adds no information, so the **minimum days at risk** is normally set at one day. If there is a known latency for the side effect, then this may be increased to get a more informative proportion. It can also be used to create a cohort more similar to that of a randomized trial it is being compared to (e.g., all the patients in the randomized trial were observed for at least N days).



A golden rule in designing a cohort study is to never use information that falls after the cohort start date to define the study population, as this may introduce bias. For example, if we require everyone to have at least a year of time-at-risk, we will likely have limited our analyses to those who tolerate the treatment well. This setting should therefore be used with extreme care.

Propensity score adjustment

We can opt to **trim** the study population, removing people with extreme PS values. We can choose

⌚ Time At Risk

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

 days from

Define the time-at-risk window end:

 days from

The minimum number of days at risk?

Figure 13.13: Time-at-risk settings.

to remove the top and bottom percentage, or we can remove subjects whose preference score falls outside the range we specify. Trimming the cohorts is generally not recommended because it requires discarding observations, which reduces statistical power. It may be desirable to trim in some cases, for example when using IPTW.

In addition to, or instead of trimming, we can choose to **stratify** or **match** on the propensity score. When stratifying we need to specify the **number of strata** and whether to select the strata based on the target, comparator, or entire study population. When matching we need to specify the **maximum number of people from the comparator group to match to each person in the target group**. Typical values are 1 for one-on-one matching, or a large number (e.g. 100) for variable-ratio matching. We also need to specify the **caliper**: the maximum allowed difference between propensity scores to allow a match. The caliper can be defined on difference **caliper scales**:

- **The propensity score scale:** the PS itself
- **The standardized scale:** in standard deviations of the PS distributions
- **The standardized logit scale:** in standard deviations of the PS distributions after the logit transformation to make the PS more normally distributed.

In case of doubt, we suggest using the default values, or consult the work on this topic by Austin (2011).

Fitting large-scale propensity models can be computationally expensive, so we may want to restrict the data used to fit the model to just a sample of the data. By default the maximum size of the target and comparator cohort is set to 250,000. In most studies this limit will not be reached. It is also unlikely that more data will lead to a better model. Note that although a sample of the data may be used to fit the model, the model will be used to compute PS for the entire population.

Test each covariate for correlation with the target assignment? If any covariate has an unusually high correlation (either positive or negative), this will throw an error. This avoids lengthy calculation of a propensity model only to discover complete separation. Finding very high univariate correlation allows you to review the covariate to determine why it has high correlation and whether it should be dropped.

Figure 13.14 shows our choices for this study. Note that we select variable-ratio matching by setting the maximum number of people to match to 100.

Outcome model settings

Propensity Score Adjustment

How do you want to trim your cohorts based on the propensity score distribution?

None ▼

Do you want to perform matching or stratification?

Match on propensity score ▼

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

100 ▼

What is the caliper for matching:

0.2

What is the caliper scale:

Standardized Logit ▼

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

250000 ▼

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

Yes ▼

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

Yes ▼

Figure 13.14: Propensity score adjustment settings.

Outcome Model Settings

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

Cox proportional hazards ▾

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

Yes ▾

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

No ▾

Use inverse probability of treatment weighting?

No ▾

Figure 13.15: Outcome model settings.

First, we need to **specify the statistical model we will use to estimate the relative risk of the outcome between target and comparator cohorts**. We can choose between Cox, Poisson, and logistic regression, as discussed briefly in Section 13.1. For our example we choose a Cox proportional hazards model, which considers time to first event with possible censoring. Next, we need to specify **whether the regression should be conditioned on the strata**. One way to understand conditioning is to imagine a separate estimate is produced in each stratum, and then combined across strata. For one-to-one matching this is likely unnecessary and would just lose power. For stratification or variable-ratio matching it is required.

We can also choose to **add all covariates to the outcome model** to adjust the analysis. This can be done in addition or instead of using a propensity model. However, whereas there usually is ample data to fit a propensity model, with many people in both treatment groups, there is typically very little data to fit the outcome model, with only few people having the outcome. We therefore recommend keeping the outcome model as simple as possible and not include additional covariates.

Instead of stratifying or matching on the propensity score we can also choose to **use inverse probability of treatment weighting** (IPTW). If weighting is used it is often recommended to use some form of trimming to avoid extreme weights and therefore unstable estimates.

Figure 13.15 shows our choices for this study. Because we use variable-ratio matching, we must condition the regression on the strata (i.e. the matched sets).

13.7.3 Evaluation settings

As described in Chapter 19, negative and positive controls should be included in our study to evaluate the operating characteristics, and perform empirical calibration.

Negative control outcome cohort definition

In Section 13.7.1 we selected a concept set representing the negative control outcomes. However, we need logic to convert concepts to cohorts to be used as outcomes in our analysis. ATLAS provides standard logic with three choices. The first choice is whether to **use all occurrences** or just the

Negative Control Outcome Cohort Definition

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

First occurrence ▾

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

Yes ▾

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

Condition
Drug
Device
Measurement
Observation
Procedure
Visit

Figure 13.16: Negative control outcome cohort definition settings.

first occurrence of the concept. The second choice determines **whether occurrences of descendant concepts should be considered**. For example, occurrences of the descendant “ingrown nail of foot” can also be counted as an occurrence of the ancestor “ingrown nail.” The third choice specifies which domains should be considered when looking for the concepts.

Positive control synthesis

In addition to negative controls we can also include positive controls, which are exposure-outcome pairs where a causal effect is believed to exist with known effect size. For various reasons real positive controls are problematic, so instead we rely on synthetic positive controls, derived from negative controls as described in Chapter 19. Positive control synthesis is an advanced topic that we will skip for now.

13.7.4 Running the study package

Now that we have fully defined our study, we can export it as an executable R package. This package contains everything that is needed to execute the study at a site that has data in CDM. This includes the cohort definitions that can be used to instantiate the target, comparator and outcome cohorts, the negative control concept set and logic to create the negative control outcome cohorts, as well as the R code to execute the analysis. Before generating the package make sure to save your study, then click on the **Utilities** tab. Here we can review the set of analyses that will be performed. As mentioned before, every combination of a comparison and an analysis setting will result in a separate analysis. In our example we have specified two analyses: ACEi versus THZ for AMI, and ACEi versus THZ for angioedema, both using propensity score matching.

We must provide a name for our package, after which we can click on “Download” to download the zip file. The zip file contains an R package, with the usual required folder structure for R packages. (Wickham, 2015) To use this package we recommend using R Studio. If you are running R Studio

locally, unzip the file, and double click the .Rproj file to open it in R Studio. If you are running R Studio on an R studio server, click  **Upload** to upload and unzip the file, then click on the .Rproj file to open the project.

Once you have opened the project in R Studio, you can open the README file, and follow the instructions. Make sure to change all file paths to existing paths on your system.

A common error message that may appear when running the study is “High correlation between covariate(s) and treatment detected.” This indicates that when fitting the propensity model, some covariates were observed to be highly correlated with the exposure. Please review the covariates mentioned in the error message, and exclude them from the set of covariates if appropriate (see Section 13.1.2).

13.8 Implementing the study using R

Instead of using ATLAS to write the R code that executes the study, we can also write the R code ourselves. One reason we might want to do this is because R offers far greater flexibility than is exposed in ATLAS. If we for example wish to use custom covariates, or a linear outcome model, we will need to write some custom R code, and combine it with the functionality provided by the OHDSI R packages.

For our example study we will rely on the CohortMethod package to execute our study. CohortMethod extracts the necessary data from a database in the CDM and can use a large set of covariates for the propensity model. In the following example we first only consider angioedema as outcome. In Section 13.8.6 we then describe how this can be extended to include AMI and the negative control outcomes.

13.8.1 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.2), comparator (Appendix B.5), and outcome (Appendix B.4) cohorts. We will assume the ACEi, THZ, and angioedema cohorts have been instantiated in a table called `scratch.my_cohorts` with cohort definition IDs 1, 2, and 3 respectively.

13.8.2 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(CohortMethod)
connDetails <- createConnectionDetails(dbms = "postgresql",
                                         server = "localhost/ohdsi",
                                         user = "joe",
                                         password = "supersecret")

cdmDbSchema <- "my_cdm_data"
cohortDbSchema <- "scratch"
cohortTable <- "my_cohorts"
cdmVersion <- "5"
```

The last four lines define the `cdmDbSchema`, `cohortDbSchema`, and `cohortTable` 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"`.

Now we can tell CohortMethod to extract the cohorts, construct covariates, and extract all necessary data for our analysis:

```
cmData
```

```
## CohortMethodData object
##
## Treatment concept ID: 1
## Comparator concept ID: 2
## Outcome concept ID(s): 3
```

There are many parameters, but they are all documented in the `CohortMethod` manual. The `createDefaultCovariateSettings` function is described in the `FeatureExtraction` package. In short, we are pointing the function to the table containing our cohorts and specify which cohort definition IDs in that table identify the target, comparator and outcome. We instruct that the default set of covariates should be constructed, including covariates for all conditions, drug exposures, and procedures that were found on or before the index date. As mentioned in Section 13.1 we must exclude the target and comparator treatments from the set of covariates, and here we achieve this by listing all ingredients in the two classes, and tell `FeatureExtraction` to also exclude all descendants, thus excluding all drugs that contain these ingredients.

All data about the cohorts, outcomes, and covariates are extracted from the server and stored in the `cohortMethodData` object. This 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, as mentioned in Section 9.4.2.

We can use the generic `summary()` function to view some more information of the data we extracted:

```
summary(cmData)
```

```
## CohortMethodData object summary
##
## Treatment concept ID: 1
## Comparator concept ID: 2
## Outcome concept ID(s): 3
##
## Treated persons: 67166
## Comparator persons: 35333
##
## Outcome counts:
##           Event count Person count
## 3                 980        891
##
## Covariates:
## Number of covariates: 58349
## Number of non-zero covariate values: 24484665
```

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

```
saveCohortMethodData(cmData, "AceiVsThzForAngioedema")
```

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

Defining new users

Typically, a new user is defined as first time use of a drug (either target or comparator), and typically a washout period (a minimum number of days prior to first use) is used to increase the probability that it is truly first use. When using the CohortMethod package, you can enforce the necessary requirements for new use in three ways:

1. When defining the cohorts.
 2. When loading the cohorts using the `getDbCohortMethodData` function, you can use the `firstExposureOnly`, `removeDuplicateSubjects`, `restrictToCommonPeriod`, and `washoutPeriod` arguments.
 3. When defining the study population using the `createStudyPopulation` function (see below).

The advantage of option 1 is that the input cohorts are already fully defined outside of the Cohort-Method package, and external cohort characterization tools can be used on the same cohorts used in this analysis. The advantage of options 2 and 3 is that they save you the trouble of limiting to first use yourself, for example allowing you to directly use the DRUG_ERA table in the CDM. Option 2 is more efficient than 3, since only data for first use will be fetched, while option 3 is less efficient but allows you to compare the original cohorts to the study population.

13.8.3 Defining the study population

Typically, the exposure cohorts and outcome cohorts will be defined independently of each other. When we want to produce an effect size estimate, we need to further restrict these cohorts and put them together, for example by removing exposed subjects that had the outcome prior to exposure, and only keeping outcomes that fall within a defined risk window. For this we can use the `createStudyPopulation` function:

Note that we've set `firstExposureOnly` and `removeDuplicateSubjects` to FALSE, and `washoutPeriod` to 0 because we already applied those criteria in the cohort definitions. We specify the outcome ID we will use, and that people with outcomes prior to the risk window start date will be removed. The risk window is defined as starting on the day after the cohort start date (`riskWindowStart = 1` and `addExposureDaysToStart = FALSE`), and the risk windows ends when the cohort exposure ends (`riskWindowEnd = 0` and `addExposureDaysToEnd = TRUE`), which was defined as the end of exposure in the cohort definition. Note that the risk windows are automatically truncated at the end of observation or the study end date. We also remove subjects who have no time at risk. To see how many people are left in the study population we can always use the `getAttritionTable` function:

```
getAttritionTable(studyPop)
```

	description	targetPersons	comparatorPersons	...
## 1	Original cohorts	67212	35379	...
## 2	Removed subs in both cohorts	67166	35333	...
## 3	No prior outcome	67061	35238	...
## 4	Have at least 1 days at risk	66780	35086	...

13.8.4 Propensity scores

We can fit a propensity model using the covariates constructed by the `getDbcohortMethodData()` function, and compute a PS for each person:

```
ps <- createPs(cohortMethodData = cmData, population = studyPop)
```

The `createPs` function uses the Cyclops package to fit a large-scale regularized logistic regression. To fit the propensity model, Cyclops needs to know the hyperparameter value which specifies the variance of the prior. By default Cyclops will use cross-validation to estimate the optimal hyperparameter. However, be aware that this can take a really long time. You can use the `prior` and `control` parameters of the `createPs` function to specify Cyclops' behavior, including using multiple CPUs to speed-up the cross-validation.

Here we use the PS to perform variable-ratio matching:

```
matchedPop <- matchOnPs(population = ps, caliper = 0.2,
                         caliperScale = "standardized logit", maxRatio = 100)
```

Alternatively, we could have used the PS in the `trimByPs`, `trimByPsToEquipoise`, or `stratifyByPs` functions.

13.8.5 Outcome models

The outcome model is a model describing which variables are associated with the outcome. Under strict assumptions, the coefficient for the treatment variable can be interpreted as the causal effect. In this case we fit a Cox proportional hazards model, conditioned (stratified) on the matched sets:

```
outcomeModel <- fitOutcomeModel(population = matchedPop,
                                   modelType = "cox",
                                   stratified = TRUE)
outcomeModel

## Model type: cox
## Stratified: TRUE
## Use covariates: FALSE
## Use inverse probability of treatment weighting: FALSE
## Status: OK
##
##           Estimate lower .95 upper .95    logRr seLogRr
## treatment     4.3203     2.4531     8.0771 1.4633     0.304
```

13.8.6 Running multiple analyses

Often we want to perform more than one analysis, for example for multiple outcomes including negative controls. The CohortMethod offers functions for performing such studies efficiently. This is described in detail in the package vignette on running multiple analyses. Briefly, assuming the outcome of interest and negative control cohorts have already been created, we can specify all target-comparator-outcome combinations we wish to analyze:

```
# Outcomes of interest:
ois <- c(3, 4) # Angioedema, AMI

# Negative controls:
ncs <- c(434165, 436409, 199192, 4088290, 4092879, 44783954, 75911, 137951, 77965,
       376707, 4103640, 73241, 133655, 73560, 434327, 4213540, 140842, 81378, 432303,
       4201390, 46269889, 134438, 78619, 201606, 76786, 4115402, 45757370, 433111
       433527, 4170770, 4092896, 259995, 40481632, 4166231, 433577, 4231770, 440329,
       4012570, 4012934, 441788, 4201717, 374375, 4344500, 139099, 444132, 196168,
       432593, 434203, 438329, 195873, 4083487, 4103703, 4209423, 377572, 40480893,
       136368, 140648, 438130, 4091513, 4202045, 373478, 46286594, 439790, 81634,
       380706, 141932, 36713918, 443172, 81151, 72748, 378427, 437264, 194083,
       140641, 440193, 4115367)

tcos <- createTargetComparatorOutcomes(targetId = 1,
                                         comparatorId = 2,
                                         outcomeIds = c(ois, ncs))

tcosList <- list(tcos)
```

Next, we specify what arguments should be used when calling the various functions described previously in our example with one outcome:

```
aceI <- c(1335471,1340128,1341927,1363749,1308216,1310756,1373225,
         1331235,1334456,1342439)
thz <- c(1395058,974166,978555,907013)

cs <- createDefaultCovariateSettings(excludedCovariateConceptIds = c(aceI,
                                                                     thz),
                                       addDescendantsToExclude = TRUE)

cmdArgs <- createGetDbCohortMethodDataArgs(
  studyStartDate = "",
  studyEndDate = "",
  firstExposureOnly = FALSE,
  removeDuplicateSubjects = FALSE,
  restrictToCommonPeriod = FALSE,
  washoutPeriod = 0,
  covariateSettings = cs)

spArgs <- createCreateStudyPopulationArgs(
  firstExposureOnly = FALSE,
  restrictToCommonPeriod = FALSE,
  washoutPeriod = 0,
  removeDuplicateSubjects = "remove all",
  removeSubjectsWithPriorOutcome = TRUE,
  minDaysAtRisk = 1,
  riskWindowStart = 1,
  addExposureDaysToStart = FALSE,
  riskWindowEnd = 0,
  addExposureDaysToEnd = TRUE)

psArgs <- createCreatePsArgs()

matchArgs <- createMatchOnPsArgs(
  caliper = 0.2,
  caliperScale = "standardized logit",
  maxRatio = 100)

fomArgs <- createFitOutcomeModelArgs(
  modelType = "cox",
  stratified = TRUE)
```

We then combine these into a single analysis settings object, which we provide a unique analysis ID and some description. We can combine one or more analysis settings objects into a list:

```
cmAnalysis <- createCmAnalysis(
  analysisId = 1,
  description = "Propensity score matching",
  getDbCohortMethodDataArgs = cmdArgs,
```

```

createStudyPopArgs = spArgs,
createPs = TRUE,
createPsArgs = psArgs,
matchOnPs = TRUE,
matchOnPsArgs = matchArgs
fitOutcomeModel = TRUE,
fitOutcomeModelArgs = fomArgs)

cmAnalysisList <- list(cmAnalysis)

```

We can now run the study including all comparisons and analysis settings:

```

result <- runCmAnalyses(connectionDetails = connectionDetails,
                         cdmDatabaseSchema = cdmDatabaseSchema,
                         exposureDatabaseSchema = cohortDbSchema,
                         exposureTable = cohortTable,
                         outcomeDatabaseSchema = cohortDbSchema,
                         outcomeTable = cohortTable,
                         cdmVersion = cdmVersion,
                         outputFolder = outputFolder,
                         cmAnalysisList = cmAnalysisList,
                         targetComparatorOutcomesList = tcosList)

```

The `result` object contains references to all the artifacts that were created. For example, we can retrieve the outcome model for AMI:

```

omFile <- result$outcomeModelFile[result$targetId == 1 &
                                      result$comparatorId == 2 &
                                      result$outcomeId == 4 &
                                      result$analysisId == 1]
outcomeModel <- readRDS(file.path(outputFolder, omFile))
outcomeModel

```

```

## Model type: cox
## Stratified: TRUE
## Use covariates: FALSE
## Use inverse probability of treatment weighting: FALSE
## Status: OK
##
##           Estimate lower .95 upper .95    logRr seLogRr
## treatment   1.1338     0.5921    2.1765  0.1256    0.332

```

We can also retrieve the effect size estimates for all outcomes with one command:

```

summ <- summarizeAnalyses(result, outputFolder = outputFolder)
head(summ)

```

```

##   analysisId targetId comparatorId outcomeId      rr    ci95lb ...
## 1           1         1             2     72748 0.9734698 0.5691589 ...
## 2           1         1             2     73241 0.7067981 0.4009951 ...
## 3           1         1             2     73560 1.0623951 0.7187302 ...
## 4           1         1             2     75911 0.9952184 0.6190344 ...
## 5           1         1             2     76786 1.0861746 0.6730408 ...
## 6           1         1             2     77965 1.1439772 0.5173222 ...

```

13.9 Study outputs

Our estimates are only valid if several assumptions have been met. We use a wide set of diagnostics to evaluate whether this is the case. These are available in the results produced by the R package generated by ATLAS, or can be generated on the fly using specific R functions.

13.9.1 Propensity scores and model

We first need to evaluate whether the target and comparator cohort are to some extent comparable. For this we can compute the Area Under the Receiver Operator Curve (AUC) statistic for the propensity model. An AUC of 1 indicates the treatment assignment was completely predictable based on baseline covariates, and that the two groups are therefore incomparable. We can use the `computePsAuc` function to compute the AUC, which in our example is 0.79. Using the `plotPs` function, we can also generate the preference score distribution as shown in Figure 13.17. Here we see that for many people the treatment they received was predictable, but there is also a large amount of overlap, indicating that adjustment can be used to select comparable groups.

In general it is a good idea to also inspect the propensity model itself, and especially so if the model is very predictive. That way we may discover which variables are most predictive. Table 13.7 shows the top predictors in our propensity model. Note that if a variable is too predictive, the `CohortMethod` package will throw an informative error rather than attempt to fit a model that is already known to be perfectly predictive.

Table 13.7: Top 10 predictors in the propensity model for ACEi and THZ. Positive values mean subjects with the covariate are more likely to receive the target treatment.

Beta	Covariate
-1.42	condition_era group during day -30 through 0 days relative to index: Edema
-1.11	drug_era group during day 0 through 0 days relative to index: Potassium Chloride
0.68	age group: 05-09
0.64	measurement during day -365 through 0 days relative to index: Renin
0.63	condition_era group during day -30 through 0 days relative to index: Urticaria
0.57	condition_era group during day -30 through 0 days relative to index: Proteinuria
0.55	drug_era group during day -365 through 0 days relative to index: INSULINS AND ANALOGUES

Beta	Covariate
-0.54	race = Black or African American
0.52	(Intercept)
0.50	gender = MALE



If a variable is found to be highly predictive, there are two possible conclusions: Either we find that the variable is clearly part of the exposure itself and should be removed before fitting the model, or else we must conclude that the two populations are truly incomparable, and the analysis must be stopped.

13.9.2 Covariate balance

The goal of using PS is to make the two groups comparable (or at least to select comparable groups). We must verify whether this is achieved, for example by checking whether the baseline covariates are indeed balanced after adjustment. We can use the `computeCovariateBalance` and `plotCovariateBalanceScatterPlot` functions to generate Figure 13.18. One rule-of-thumb to use is that no covariate may have an absolute standardized difference of means greater than 0.1 after propensity score adjustment. Here we see that although there was substantial imbalance before matching, after matching we meet this criterion.

13.9.3 Follow up and power

Before fitting an outcome model, we might be interested to know whether we have sufficient power to detect a particular effect size. It makes sense to perform these power calculations once the study population has been fully defined, so taking into account loss to the various inclusion and exclusion criteria (such as no prior outcomes), and loss due to matching and/or trimming. We can view the attrition of subjects in our study using the `drawAttritionDiagram` function as shown in Figure 13.19.

Since the sample size is fixed in retrospective studies (the data has already been collected), and the true effect size is unknown, it is therefore less meaningful to compute the power given an expected effect size. Instead, the `CohortMethod` package provides the `computeMdrr` function to compute the minimum detectable relative risk (MDRR). In our example study the MDRR is 1.69.

To gain a better understanding of the amount of follow-up available we can also inspect the distribution of follow-up time. We defined follow-up time as time at risk, so not censored by the occurrence of the outcome. The `getFollowUpDistribution` can provide a simple overview as shown in Figure 13.20, which suggests the follow-up time for both cohorts is comparable.

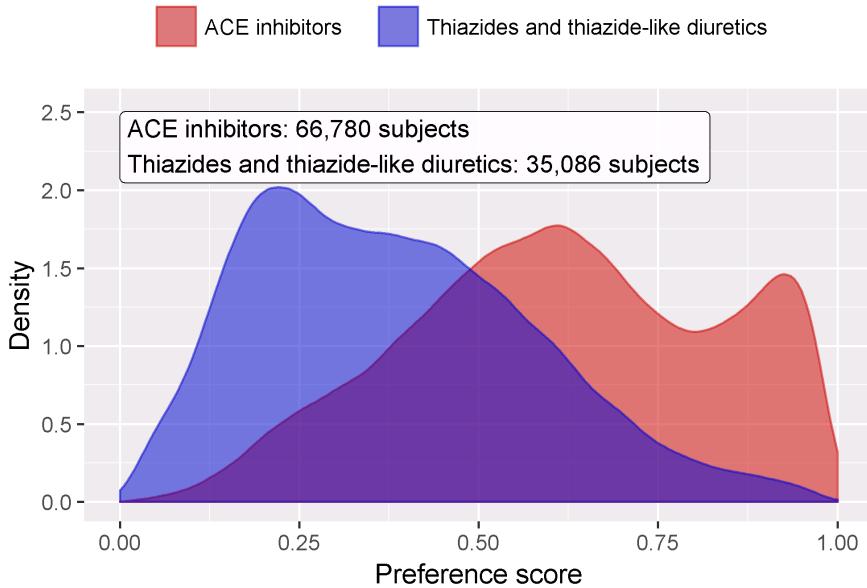


Figure 13.17: Preference score distribution.

Standardized difference of mean

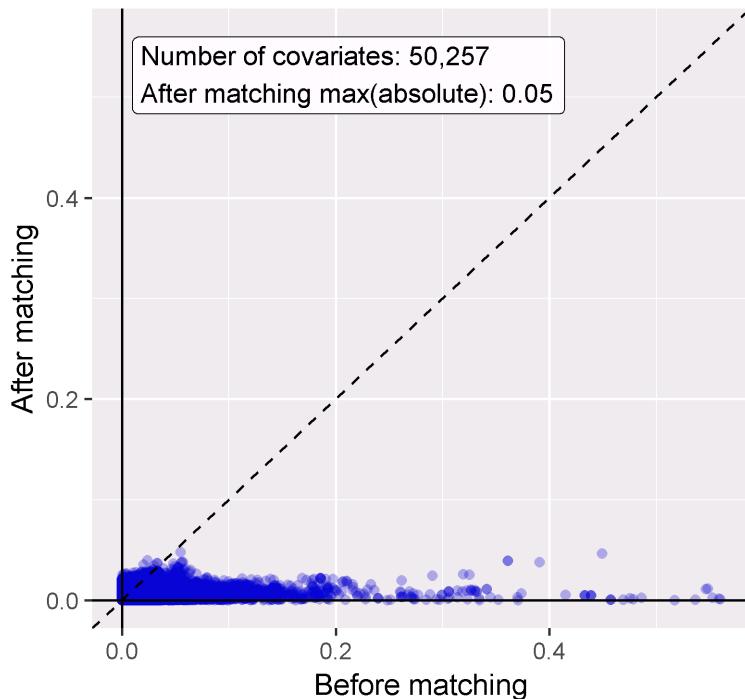


Figure 13.18: Covariate balance, showing the absolute standardized difference of mean before and after propensity score matching. Each blue dot represents a covariate.

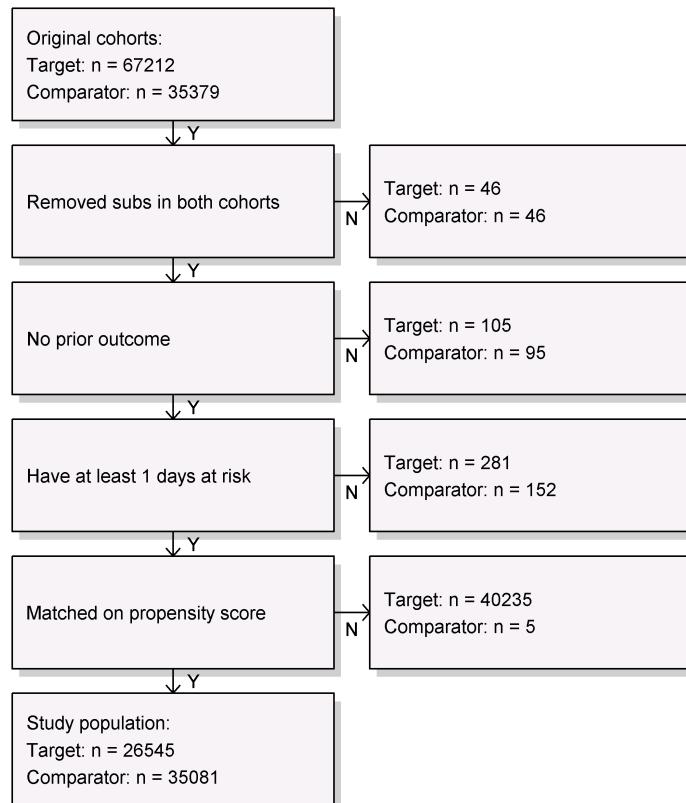


Figure 13.19: Attrition diagram. The counts shown at the top are those that meet our target and comparator cohort definitions. The counts at the bottom are those that enter our outcome model, in this case a Cox regression.

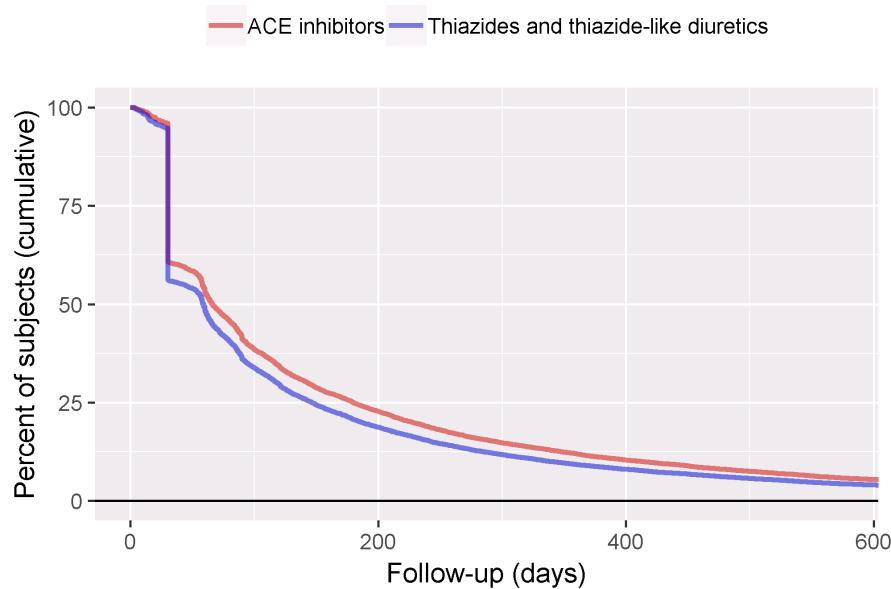


Figure 13.20: Distribution of follow-up time for the target and comparator cohorts.

13.9.4 Kaplan-Meier

One last check is to review the Kaplan-Meier plot, showing the survival over time in both cohorts. Using the `plotKaplanMeier` function we can create 13.21, which we can check for example if our assumption of proportionality of hazards holds. The Kaplan-Meier plot automatically adjusts for stratification or weighting by PS. In this case, because variable-ratio matching is used, the survival curve for the comparator groups is adjusted to mimick what the curve had looked like for the target group had they been exposed to the comparator instead.

13.9.5 Effect size estimate

We observe a hazard ratio of 4.32 (95% confidence interval: 2.45 - 8.08) for angioedema, which tells us that ACEi appears to increase the risk of angioedema compared to THZ. Similarly, we observe a hazard ratio of 1.13 (95% confidence interval: 0.59 - 2.18) for AMI, suggesting little or no effect for AMI. Our diagnostics, as reviewed earlier, give no reason for doubt. However, ultimately the quality of this evidence, and whether we choose to trust it, depends on many factors that are not covered by the study diagnostics as described in Chapter 15.

13.10 Summary

- Population-level estimation aims to infer causal effects from observational data.



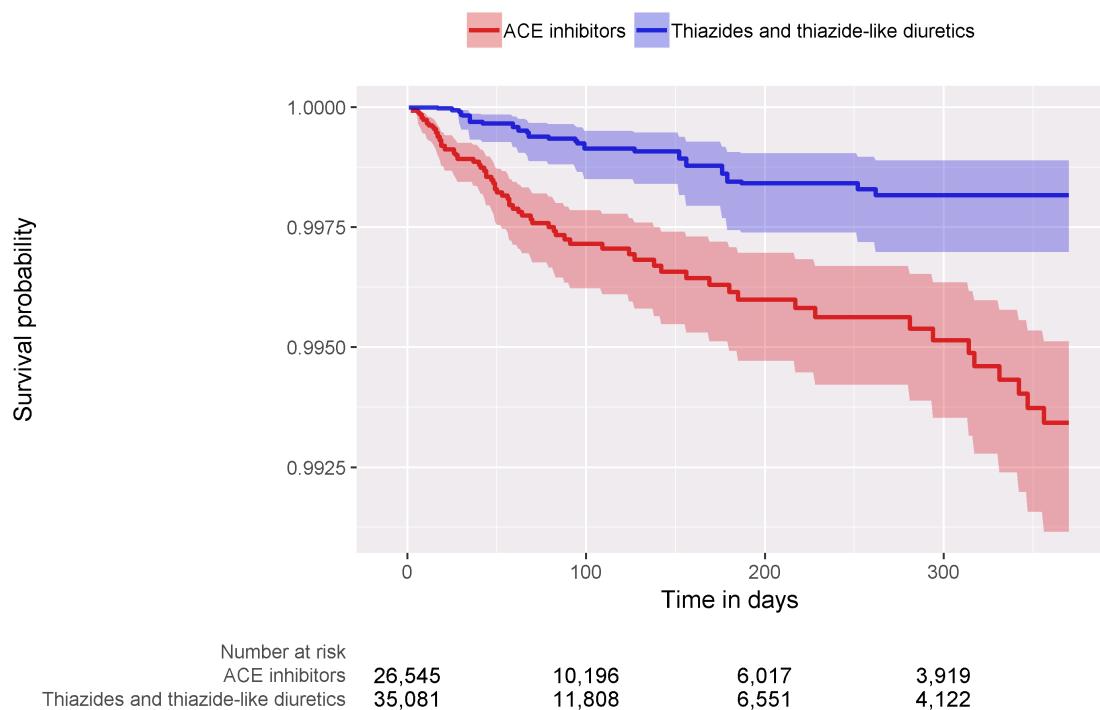


Figure 13.21: Kaplan-Meier plot.

- The **counterfactual**, what would have happened if the subject had received an alternative exposure or no exposure, cannot be observed.
- Different designs aim to construct the counterfactual in different ways.
- The various designs as implemented in the OHDSI Methods Library provide diagnostics to evaluate whether the assumptions for creating an appropriate counterfactual have been met.

13.11 Exercises

Note: The exercises still have to be defined. The idea is to require readers to define a study that estimates the effect of celecoxib on GI bleed, compared to diclofenac. For this they must use the Eunomia package, which is still under development.

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. Most currently-used models are estimated using small datasets and consider only a small set of patient characteristics. This low sample size, and thus low statistical power, forces the data analyst to make strong modelling assumptions. The selection of the 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 a huge amount of patient-specific information stored in Electronic Health Records (EHRs). This includes structured data in the form of diagnose, medication, laboratory test results, and unstructured data contained in clinical narratives. 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.

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 which 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. For example, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement¹

¹<https://www.equator-network.org/reporting-guidelines/tripod-statement/>

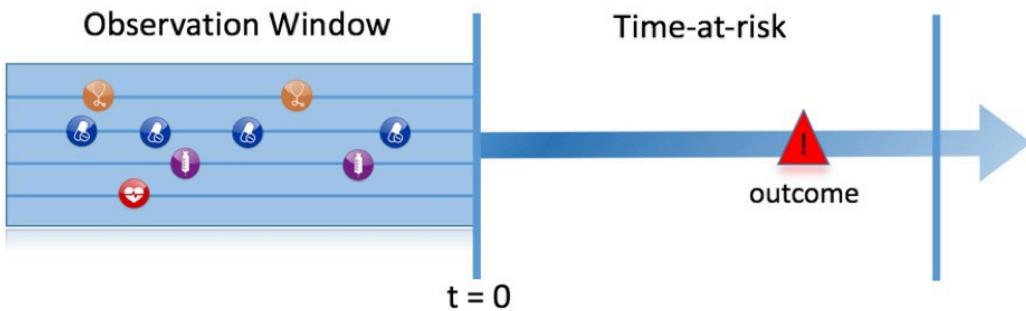


Figure 14.1: The prediction problem.

provides clear recommendations for reporting prediction model development and validation and addresses some of the concerns related to transparency.

Massive-scale, patient-specific predictive modeling has become reality due to OHDSI, where the common data model (CDM) allows for uniform and transparent analysis at an unprecedented scale. The databases available in the CDM 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.

In this chapter we describe OHDSI's standardized framework for patient-level prediction, (Reps et al., 2018) and discuss the `PatientLevelPrediction` R package that implements established best practices. We start with providing the necessary theory behind the development and evaluation of patient-level prediction and provide a high-level overview of the implemented machine learning algorithms. We then discuss an example prediction problem and provide step-by-step guidance on its definition and implementation using ATLAS or custom R code. Finally, we review two Shiny apps that allow viewing the study outputs. One app explores a single prediction model, while the other explores many models at once.

14.1 The prediction problem

Figure 14.1, illustrates the prediction problem we address. Among a population 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, the outcome we like to predict by an outcome cohort, and the time-at-risk. We define the standard prediction question as:

Among [*target cohort definition*], who will go on to have [*outcome cohort definition*] within [*time-at-risk period*]?

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, for example:

- Disease onset and progression
 - **Structure:** Among 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 fibrillation patients, who will go on to have ischemic stroke in the next three years?
- Treatment choice
 - **Structure:** Among patients with *[indicated disease]* who are treated with either *[treatment 1]* or *[treatment 2]*, which patients were treated with *[treatment 1]*?
 - **Example:** Among patients with atrial fibrillation who took either warfarin or rivaroxaban, which patients gets warfarin? (e.g. for a propensity model)
- Treatment response
 - **Structure:** Among new users of *[a treatment]*, who will experience *[some effect]* in *[time window]*?
 - **Example:** Which patients with diabetes who start on metformin stay on metformin for three years?
- Treatment safety
 - **Structure:** Among new users of *[a treatment]*, who will experience *[adverse event]* in *[time window]*?
 - **Example:** Among new users of warfarin, who will have a gastrointestinal bleed in one year?
- Treatment adherence
 - **Structure:** Among new users of *[a treatment]*, who will achieve *[adherence metric]* at *[time window]*?
 - **Example:** Which patients with diabetes who start on metformin achieve $\geq 80\%$ proportion of days covered at one year?

14.2 Data extraction

The observational data we use in OHDSI consist of time-stamped records of interactions of the patient with the healthcare system, as well as anonymized patient details such as gender and year of birth,

stored in the CDM (Chapter 5). To use this information in a prediction problem, we must convert this data into two datasets:

1. A set of **covariates** (also referred to as “features” or “independent variables”). These describe the characteristics of the patients. Covariates can include age, gender, presence of specific condition and exposure codes in a patient’s record, etc.
2. A set describing the **outcome status** (also referred to as the “labels” or “classes”). Did a patient experience the outcome of interest in the time-at-risk?

When creating a predictive model we use a process known as supervised learning - a form of machine learning - to infer the relationship between the covariates and the outcome status. Once the model is created, we can apply it to patients where we know their characteristics (their covariates), but do not know their outcome status, to create a prediction.

Converting the data in the CDM to these two datasets requires selecting a set of people, and for these people selecting a specific date. We will refer to this date as the index date. Data prior to (and on) the index date is used to construct the covariates. Covariates are typically constructed using the FeatureExtraction package, described in more detail in Chapter 12. Data after (or on) the index date is used to construct the outcome status. The group of people and their index date are defined by the **target cohort**. The outcome status is determined by the **time-at-risk**, which is usually defined relative to the target cohort start and end date, and the **outcome cohort**; If the outcome occurs within the time-at-risk, the outcome status is “positive”.

14.2.1 Data extraction example

Table 14.2 shows an example COHORT table with two cohorts. The cohort with cohort definition ID 1 is the target cohort (e.g. “people recently diagnosed with atrial fibrillation”). Cohort definition ID 2 implies the outcome cohort (e.g. “stroke”).

Table 14.2: Example COHORT table. For simplicity the cohort_end_date has been omitted.

cohort_definition_id	subject_id	cohort_start_date
1	1	2000-06-01
1	2	2001-06-01
2	2	2001-07-01

Table 14.3 provides an example CONDITION_OCCURRENCE table. Concept ID 320128 refers to “Essential hypertension”.

Table 14.3: Example CONDITION_OCCURRENCE table. For simplicity only three columns are shown.

person_id	condition_concept_id	condition_start_date
1	320128	2000-10-01

person_id	condition_concept_id	condition_start_date
2	320128	2001-05-01

Based on this example data, and assuming the time at risk is the year following the index date (the target cohort start date), we can construct the covariates and the outcome status. A covariate indicating “Essential hypertension in the year prior” will have the value 0 (not present) for person ID 1 (the condition occurred *after* the index date), and the value 1 (present) for person ID 2. Similarly, the outcome status will be 0 for person ID 1 (this person had no entry in the outcome cohort), and 1 for person ID 2 (the outcome occurred within a year following the index date).

14.2.2 Missingness

Observational healthcare data rarely reflects whether data is missing. In the prior example, we simply observed the person with ID 1 had no essential hypertension occurrence prior to the index date. This could be because the condition was not present at that time, or because it was not recorded. There is no way to distinguish between the two. For machine learning this does not matter as much as one might think. If a covariate is predictive of the outcome status it will end up in the model, else not. However, we should be aware that our interpretation of covariates should be nuanced: it is not the actual condition that is the predictor, but rather the recording of the condition in the data.

14.3 Fitting the model

When fitting a model (using supervised learning) we are trying to establish the relationship between the covariates and the observed outcome status, so that if we do not yet know the outcome status, we can predict it. If we consider the situation where we have two covariates (for example systolic and diastolic blood pressure), then we can represent each patient as a point in two dimensional space as shown in Figure 14.2. The shape of a data points corresponds to the patient’s outcome status (e.g. stroke). The idea of supervised learning is to generalize what we see and fill in where there are no current data points. A supervised learning model will try to partition the space via a decision boundary that aims to minimize the cases where the outcome status does not match the models prediction. Different supervised learning techniques lead to different decision boundaries and there are often hyper-parameters that can impact the complexity of the decision boundary.

In Figure 14.2 we can see three different decision boundaries. The boundaries are used to infer the outcome status of any new data point. If a new data point falls into the shaded area then the model will predict “has outcome”, otherwise it will predict “no outcome”. Ideally a decision boundary should perfectly partition the two classes. However, generalizability is an issue, as complex models can “overfit” the data; boundaries may be fit too closely and may not work for new data. For example, if the data contains noise, with mislabelled or incorrectly positioned data points, we would not want to fit our model to that noise. We may prefer to define a decision boundary that does not perfectly discriminate those with known outcome status, to get a model that better predicts for now, previously unseen patients. We want a model that appears to partition the labelled data well but is also as simple as possible. Techniques such as regularization aim to maximize model performance on the data with

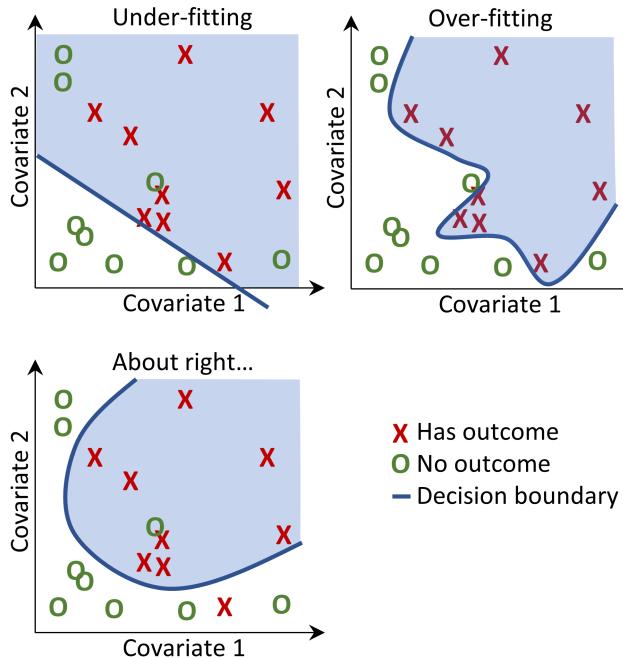


Figure 14.2: Decision boundary.

known outcome status while minimizing complexity. Complexity can also be controlled by picking classifier hyper-parameters such that a simpler decision boundary is used.

Another way to think about supervised learning is finding a function that maps from a patient's covariates to their label: $p(\text{outcome status} = 1 | \text{covariates}) = f(\text{covariates})$. Each supervised learning algorithm has a different way to learn the mapping function and the no free lunch theorem states that no one algorithm is always going to outperform the others. The performance of each type of supervised learning algorithm depends on how the labelled data points are distributed in space. Therefore we recommend trying multiple supervised learning techniques with various hyper-parameter settings when developing patient-level prediction models.

The following algorithms are available in the PatientLevelPrediction package:

14.3.1 Regularized logistic regression

LASSO (least absolute shrinkage and selection operator) 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.

Table 14.4: Hyper-parameters for the regularized logistic regression.

Parameter	Description	Typical values
Starting variance	The starting variance of the prior distribution.	0.1

Note that the variance is optimized by maximizing the out-of-sample likelihood in a cross-validation, so the starting variance has little impact on the performance of the resulting model. However, picking a starting variance that is too far from the optimal value may lead to long fitting time.

14.3.2 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.

Table 14.5: Hyper-parameters for gradient boosting machines.

Parameter	Description	Typical values
mtry	Number of features in each tree	?
ntree	Number of trees	?
maxDepth	Max levels in a tree	?
minRows	Min data points in a node	?
balance	Should class sizes be balanced?	?

14.3.3 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 implementation of Random Forest in Python.

Table 14.6: Hyper-parameters for random forests.

Parameter	Description	Typical values
mtry	Number of features in each tree	?
ntree	Number of trees	?
maxDepth	Max levels in a tree	?
minRows	Min data points in a node	?
balance	Should class sizes be balanced?	?

14.3.4 K-nearest neighbors

K-nearest neighbors (KNN) is an algorithm that uses some distance metric to find the K closest labelled data-points 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 KNN classifier.

Table 14.7: Hyper-parameters for K-nearest neighbors.

Parameter	Description	Typical values
k	Number of neighbors	?
weighted	Weight by inverse frequency?	?

14.3.5 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. Naive Bayes has no hyper-parameters.

14.3.6 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.

Table 14.8: Hyper-parameters for AdaBoost.

Parameter	Description	Typical values
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	?

14.3.7 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.

Table 14.9: Hyper-parameters for decision trees.

Parameter	Description	Typical values
maxDepth	The maximum depth of the tree	?
minSamplesSplit	?	?
minSamplesLeaf	?	?
minImpuritySplit	?	?
classWeight	“Balance”” or “None”	?

14.3.8 Multilayer Perceptron

Neural networks containing multiple layers of nodes that weight their inputs using a non-linear function. The first layer is the input layer, the last layer is the output layer, and in between are the hidden layers. Neural networks are generally trained using back-propagation, meaning the training input is propagated forward through the network to produce an output, the error between the output and the outcome status is computed, and this error is propagated backwards through the network to update the linear function weights.

Table 14.10: Hyper-parameters for Multilayer Perceptrons.

Parameter	Description	Typical values
size	The number of hidden nodes	?
alpha	The l2 regularization)	?

14.3.9 Deep Learning

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

14.3.10 Other algorithms

Other algorithms can be added to the patient-level prediction framework. This is out-of-scope for this chapter. Details can be found in the “Adding Custom Patient-Level Prediction Algorithms” vignette

in the PatientLevelPrediction package.

14.4 Evaluating prediction models

14.4.1 Evaluation Types

We can evaluate a prediction model by measuring the agreement between the model's prediction and observed outcome status, which means we need data where the outcome status is known.



For evaluation we must use a different dataset than was used to develop the model, or else we run the risk of favoring models that are over-fitted (see Section 14.3) and may not perform well for new patients.

We distinguish between

- **Internal validation:** Using different sets of data extracted from the same database to develop and evaluate the model.
- **External validation:** Developing the model in one database, and evaluating in another database.

There are two ways to perform internal validation:

- A **holdout set** approach splits the labelled data into two independent sets: a train set and a test set (the hold out set). The train set is used to learn the model and the test set is used to evaluate it. We can simply divide our patients randomly into a train and test set, or we may choose to:
 - Split the data based on time (temporal validation), for example training on data before a specific date, and evaluating on data after that date. This may inform us on whether our model generalizes to different time periods.
 - Split the data based on geographic location (spatial validation).
- **Cross validation** is useful when the data are limited. The data is split into n equally-sized sets, where n needs to be prespecified (e.g. $n = 10$). For each of these sets a model is trained on all data except the data in that set, and used to generate predictions for the held-out set. In this way, all data is used once to evaluate the model-building algorithm. In the patient-level prediction framework we use cross validation to pick the optimal hyper-parameters.

Note that some may consider bootstrapping to be another approach to internal validation, which is often used specifically to express the uncertainty around a model's prediction, typically as confidence intervals. We currently do not use bootstrapping in the patient-level prediction framework. TODO: maybe elaborate on this.

External validation is when a model trained in one database is validated on a data from another database. This is important as different databases may represent different patient populations, but also perhaps different healthcare systems and different data-capture processes. External validation can therefore inform us on how well a model will perform outside of the settings it was developed in.

14.4.2 Performance Metrics

Threshold measures

A prediction model assigns a value between 0 and 1 for each patient corresponding to the risk of the patient having the outcome during the time at risk. A value of 0 means 0% risk, a value of 0.5 means 50% risk and a value of 1 means 100% risk. Common metrics such as accuracy, sensitivity, specificity, positive predictive value can be calculated by first specifying a threshold that is used to classify patients as having the outcome or not during the time at risk. For example, given Table 14.11, if we set the threshold as 0.5, the patients 1, 3, 7 and 10 have a predicted risk greater than or equal to the threshold of 0.5 so they would be predicted to have the outcome. All other patients had a predicted risk less than 0.5, so would be predicted to not have the outcome.

Table 14.11: Example of using a threshold on the predicted probability.

Patient ID	Predicted risk	Predicted class at 0.5 threshold	Has outcome during time-at-risk	Type
1	0.8	1	1	TP
2	0.1	0	0	TN
3	0.7	1	0	FP
4	0	0	0	TN
5	0.05	0	0	TN
6	0.1	0	0	TN
7	0.9	1	1	TP
8	0.2	0	1	FN
9	0.3	0	0	TN
10	0.5	1	0	FP

If a patient is predicted to have the outcome and has the outcome (during the time-at-risk) then this is called as a true positive (TP). If a patient is predicted to have the outcome but does not have the outcome then this is called a false positive (FP). If a patient is predicted to not have the outcome and does not have the outcome then this is called a true negative (TN). Finally, if a patient is predicted to not have the outcome but does have the outcome then this is called a false negative (FN).

The following threshold based metrics are:

- accuracy: $(TP + TN)/(TP + TN + FP + FN)$
- sensitivity: $TP/(TP + FN)$
- specificity: $TN/(TN + FP)$
- positive predictive value: $TP/(TP + FP)$

Note that these values 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 positive predictive value. If the previous threshold was about right or too low, further lowering the

threshold will introduce false positives, decreasing positive predictive value. For sensitivity the denominator does not depend on the classifier threshold ($TP + FN$ is a constant). This means that lowering the classifier threshold may increase sensitivity, by increasing the number of true positive results. It is also possible that lowering the threshold may leave sensitivity unchanged, while the positive predictive value fluctuates.

Discrimination

Discrimination is the ability to assign a higher risk to patients who will experience the outcome during the time at risk. The Receiver Operating Characteristics (ROC) is determined by plotting 1 – specificity on the x-axis and sensitivity on the y-axis at all possible thresholds. An example ROC plot is presented later in this chapter in Figure 14.17. The area under the receiver operating characteristic curve (AUC) gives an overall measure of discrimination where a value of 0.5 corresponds to randomly assigning the risk and a value of 1 means perfect discrimination. In reality, most prediction models obtain AUCs between 0.6-0.8.

For rare outcomes even a model with a high AUC may not be practical, because for every positive above a given threshold there could also be many negatives (i.e. the positive predictive value will be low). Depending on the severity of the outcome and cost (health risk and/or monetary) of some intervention, a high false positive rate may be impractical. When the outcome is rare another measure known as the area under the precision-recall curve (AUPRC) is therefore recommended. The AUPRC is the area under the line generated by plotting the sensitivity on the x-axis (also known as the recall) and the positive predictive value (also known as the precision) on the y-axis.

The AUC provides a way to determine how different the predicted risk distributions are between the patients who experience the outcome during the time at risk and those who do not. If the AUC is high, then the distributions will be mostly disjointed, whereas when there is a lot of overlap, the AUC will be closer to 0.5, see Figure 14.3.

Calibration

Calibration is the ability of the model to assign the correct risk. For example, if the model assigned one hundred patients a risk of 10% then ten of the patients should experience the outcome during the time at risk. If the model assigned 100 patients a risk of 80% then eighty of the patients should experience the outcome during the time at risk. The calibration is generally calculated by partitioning the patients into deciles based on the predicted risk and in each group calculating the mean predicted risk and the fraction of the patients who experienced the outcome during the time at risk. We then plot these ten points (predicted risk on the y-axis and observed risk on the x-axis) and see whether they fall on the $x = y$ line, indicating the model is well calibrated. An example calibration plot is presented later in this chapter in Figure 14.18. We also fit a linear model using the points to calculate the intercept (which should be close to zero) and the gradient (which should be close to one). If the gradient is greater than one then the model is assigning a higher risk than the true risk and if the gradient is less than one the model is assigning a lower risk than the true risk.

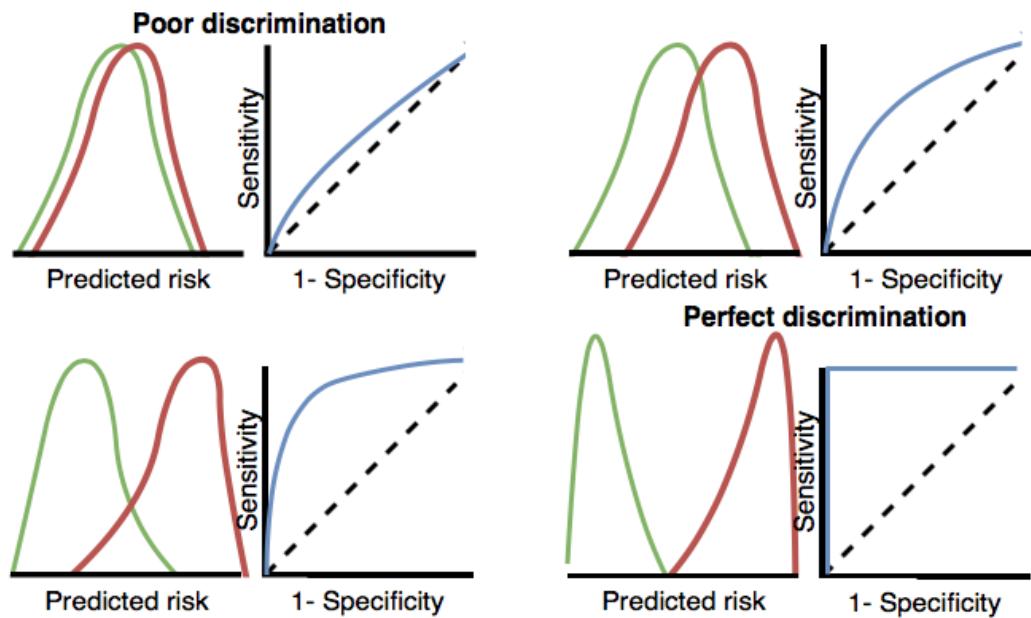


Figure 14.3: How the ROC plots are linked to discrimination. If the two classes have similar distributions of predicted risk, the ROC will be close to the diagonal, with AUC close to 0.5.

14.5 Designing a patient-level prediction Study

In this section we will demonstrate how to design a prediction study. The first step is to clearly define the prediction problem. Interestingly, in many published papers the prediction problem is poorly defined, for example 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 patient-level prediction framework we enforce proper specification of the prediction problem by requiring the key choices defined in Table 14.1 to be explicitly defined. Here we will walk through this process using a “treatment safety” type prediction problem as an example.

14.5.1 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 inhibitor in favor of another hypertension drug.

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

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

14.5.2 Study population definition

The final study population in which we will develop our model is often a subset of the target cohort, because we may for example apply criteria that are dependent on the outcome, or we want to perform sensitivity analyses with sub-populations of the target cohort. 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 the training data, but also on the time we expect to be available in the data sources we 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 look-back period. For our example, we will use a 365-day prior history as look-back 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 we 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 have to make two decisions to answer this 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 we want to avoid outcomes that were entered late in the record that actually occurred before the start of the target cohort or we want to leave a gap where interventions

to prevent the outcome could theoretically be implemented. Second, we 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 no longer observe them. For our prediction problem we decide to answer this question with “yes”, requiring a minimum 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.

14.5.3 Model development settings

To develop the prediction 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. we prefer 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 have therefore implemented many algorithms as described in Section 14.3, and allow others to be added. In this example, to keep things simple, we select just one algorithm: Gradient Boosting Machines.

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 will look for these clinical events in the year before and any time prior the index date.

14.5.4 Model evaluation

Finally, we have to define how we will evaluate our model. For simplicity, we here choose internal validation. We have to decide how we divide our dataset in a training and test dataset and how we assign patients to these two sets. Here we will use a typical 75% - 25% split. Note that for very large datasets we could use more data for training.

14.5.5 Study summary

We have now completely defined our study as shown in Table 14.12.

Table 14.12: Main design choices for our study.

Choice	Value
Target cohort	Patients who have just started on an ACE inhibitor for the first time. Patients are excluded if they have less than 365 days of prior observation time or have prior angioedema.

Choice	Value
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.

14.6 Implementing the study in ATLAS

The interface for designing a prediction study can be opened by clicking on the  Prediction button in the left hand side ATLAS menu. Create a new prediction study. Make sure to give the study an easy-to-recognize name. The study design can be saved at any time by clicking the  button.

In the Prediction design function, there are four sections: Prediction Problem Settings, Analysis Settings, Execution Settings, and Training Settings. Here we discuss each section:

14.6.1 Prediction Problem Settings

Here we select the target population cohorts and outcome cohorts for the analysis. A prediction model will be developed for all combinations of the target population cohorts and the outcome cohorts. For example, if we specify two target populations and two outcomes, we have specified four prediction problems.

To select a target population cohort we need to have previously defined it ATLAS. 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 used in this example. To add a target population to the cohort, click on the “Add Target Cohort” button. Adding outcome cohorts similarly works by clicking the “Add Outcome Cohort” button. When done, the dialog should look like Figure 14.4.

14.6.2 Analysis Settings

The analysis settings enables selection of the supervised learning algorithms, the covariates and population settings.

Model Settings

We can pick one or more supervised learning algorithms for model development. To add a supervised learning algorithms click on the “Add Model Settings” button. A dropdown containing all the models currently supported in the ATLAS interface will appear. We can select the supervised learning model

The screenshot displays the 'Prediction Problem Settings' interface in ATLAS. It is divided into two main sections: 'Target Cohorts' and 'Outcome Cohorts'.
Target Cohorts:
 - Title: 'Target Cohorts' with a paw icon.
 - Buttons: '+ Add Target Cohort' (blue), 'Remove' (grey), and 'Name' (highlighted).
 - Data: One entry: 'New users of ACE inhibitors as first-line monotherapy for hypertension' with a red 'X' icon.
 - Pagination: 'Showing 1 to 1 of 1 entries' and 'Previous [1] Next'.
Outcome Cohorts:
 - Title: 'Outcome Cohorts' with a paw icon.
 - Buttons: '+ Add Outcome Cohort' (blue), 'Remove' (grey), and 'Name' (highlighted).
 - Data: One entry: 'Angioedema outcome' with a red 'X' icon.
 - Pagination: 'Showing 1 to 1 of 1 entries' and 'Previous [1] Next'.
 The interface uses a clean, modern design with blue headers and grey backgrounds for the data tables.

Figure 14.4: Prediction problem settings.

we want to include in the study by clicking on the name in the dropdown menu. This will then show a view for that specific model, allowing the selection of the hyper-parameter values. If multiple values are provided, a grid search is performed across all possible combinations of values to select the optimal combination using cross-validation.

For our example we select gradient boosting machines, and set the hyper-parameters as specified in Figure 14.5.

Covariate Settings

We have defined a set of standard covariates that can be extracted from the observational data in the CDM format. In the covariate settings view, it is possible to select which of the standard covariates to include. We can define different types of covariate settings, and each model will be created separately with each specified covariate setting.

To add a covariate setting into the study, click on the “Add Covariate Settings”. This will open the covariate setting view.

The first part of the covariate settings view is the exclude/include option. Covariates are generally constructed for any concept. However, we may want to include or exclude specific concepts, for example if a concept is linked to the target cohort definition. To only include certain concepts, create a concept set in ATLAS and then under the **“What concepts do you want to include in baseline covariates in the patient-level prediction model? (Leave blank if you want to include everything)”** select the concept set by clicking on . We can automatically add all descendant concepts to the concepts in the concept set by answering “yes” to the question **“Should descendant concepts be added to the list of included concepts?”** The same process can be repeated for the question **“What concepts do you want to exclude in baseline covariates in the patient-level prediction model? (Leave blank if you want to include everything)”**, allowing covariates corresponding to the selected

Gradient Boosting Machine Model Settings
Use the options below to edit the model settings

The boosting learn rate (default = 0.01,0.1):

Boosting learn rate	Action
0.001	Remove
0.01	Remove
0.1	Remove
0.9	Remove

[Add](#) [Reset to default](#)

Maximum number of interactions - a large value will lead to slow model training (default = 4,6,17):

Maximum number of interactions	Action
4	Remove
7	Remove
10	Remove

[Add](#) [Reset to default](#)

The minimum number of rows required at each end node of the tree (default = 20):

Minimum number of rows	Action
20	Remove

[Add](#) [Using default](#)

The number of trees to build (default = 10,100):

Trees to build	Action
5000	Remove

[Add](#) [Reset to default](#)

The number of computer threads to use (how many cores do you have?) (default = 20):

20	Using default
----	---------------

Figure 14.5: Gradient boosting machine settings

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

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

No

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

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

No

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

Figure 14.6: Covariate inclusion and exclusion settings.

concepts to be removed. The final option “**A comma delimited list of covariate IDs that should be restricted to**” enables us to add a set of covariate IDs (rather than concept IDs) comma separated that will only be included in the model. This option is for advanced users only. Once done, the inclusion and exclusion settings should look like Figure 14.6.

The next section enables the selection of non-time bound variables.

- Gender: a binary variable indicating male or female gender
- Age: a continuous variable corresponding to age in years
- Age group: binary variables for every 5 years of age (0-4, 5-9, 10-14, ..., 95+)
- Race: a binary variable for each race, 1 means the patient has that race recorded, 0 otherwise
- Ethnicity: a binary variable for each ethnicity, 1 means the patient has that ethnicity recorded, 0 otherwise
- Index year: a binary variable for each cohort start date year, 1 means that was the patients cohort start date year, 0 otherwise. **It often does not make sense to include index year, since we would like to apply our model to the future.**
- Index month - a binary variable for each cohort start date month, 1 means that was the patients cohort start date month, 0 otherwise
- Prior observation time: [Not recommended for prediction] a continuous variable corresponding to how long in days the patient was in the database prior to the cohort start date
- Post observation time: [Not recommended for prediction] a continuous variable corresponding to how long in days the patient was in the database post cohort start date
- Time in cohort: a continuous variable corresponding to how long in days the patient was in the cohort (cohort end date minus cohort start date)
- Index year and month: [Not recommended for prediction] a binary variable for each cohort start date year and month combination, 1 means that was the patients cohort start date year and month, 0 otherwise

Once done, this section should look like Figure 14.7.

The standard covariates enable three flexible time intervals for the covariates:

- end days: when to end the time intervals relative to the cohort start date [default is 0]

Select Covariates

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

Figure 14.7: Select covariates.

Time bound covariates

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

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

Figure 14.8: Time bound covariates.

- long term [default -365 days to end days prior to cohort start date]
- medium term [default -180 days to end days prior to cohort start date]
- short term [default -30 days to end days prior to cohort start date]

Once done, this section should look like Figure 14.8.

The next option is the covariates extracted from the era tables:

- Condition: Construct covariates for each condition concept ID and time interval selected and if a patient has the concept ID with an era (i.e., the condition starts or ends during the time interval or starts before and ends after the time interval) during the specified time interval prior to the cohort start date in the condition era table, the covariate value is 1, otherwise 0.
- Condition group: Construct covariates for each condition concept ID and time interval selected and if a patient has the concept ID **or any descendant concept ID** with an era during the specified time interval prior to the cohort start date in the condition era table, the covariate value is 1, otherwise 0.
- Drug: Construct covariates for each drug concept ID and time interval selected and if a patient has the concept ID with an era during the specified time interval prior to the cohort start date in the drug era table, the covariate value is 1, otherwise 0.
- Drug group: Construct covariates for each drug concept ID and time interval selected and if a patient has the concept ID **or any descendant concept ID** with an era during the specified time interval prior to the cohort start date in the drug era table, the covariate value is 1, otherwise 0.

Overlapping time interval setting means that the drug or condition era should start prior to the cohort start date and end after the cohort start date, so it overlaps with the cohort start date. The **era start** option restricts to finding condition or drug eras that start during the time interval selected.

Once done, this section should look like Figure 14.9.

The next option selects covariates corresponding to concept IDs in each domain for the various time intervals:

Set the time bound era covariates

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

Figure 14.9: Time bound era covariates.

- Condition: Construct covariates for each condition concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the condition occurrence table, the covariate value is 1, otherwise 0.
- Condition Primary Inpatient: TODO
- Drug: Construct covariates for each drug concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the drug exposure table, the covariate value is 1, otherwise 0.
- Procedure: Construct covariates for each procedure concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the procedure occurrence table, the covariate value is 1, otherwise 0.
- Measurement: Construct covariates for each measurement concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the measurement table, the covariate value is 1, otherwise 0.
- Measurement Value: Construct covariates for each measurement concept ID with a value and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the measurement table, the covariate value is the measurement value, otherwise 0.
- Measurement range group: TODO
- Observation: Construct covariates for each observation concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the observation table, the covariate value is 1, otherwise 0.
- Device: Construct covariates for each device concept ID and time interval selected and if a patient has the concept ID recorded during the specified time interval prior to the cohort start date in the device table, the covariate value is 1, otherwise 0.
- Visit Count: Construct covariates for each visit and time interval selected and count the number of visits recorded during the time interval as the covariate value
- Visit Concept Count: Construct covariates for each visit, domain and time interval selected and count the number of records per domain recorded during the visit type and time interval as the covariate value

The distinct count option counts the number of records per domain and time interval [TODO].

Once done, this section should look like Figure 14.10.

The final option is whether to include commonly used risk scores as covariates. Once done, the risk score settings should look like Figure 14.11.

Set the time bound covariates

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

Figure 14.10: Time bound covariates.

Set the index score covariates

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

Figure 14.11: Risk score covariate settings.

Population Settings

The population settings is where addition inclusion criteria can be applied to the target population and is also where the time-at-risk is defined. To add a population setting into the study, click on the “Add Population Settings” button. This will open up the population setting view.

The first set of options enable the user to specify the time-at-risk period. This is the time interval where we look to see whether the outcome of interest occurs. If a patient has the outcome during the time-at-risk period then we will classify them as “Has outcome”, otherwise they are classified as “No outcome”. “**Define the time-at-risk window start, relative to target cohort entry:**” defines the start of the time-at-risk, relative to the target cohort start or end date. Similarly, “**Define the time-at-risk window end:**” defines the end of the time-at-risk.

“**Minimum lookback period applied to target cohort**” specifies the minimum baseline period; the minimum number of days prior to the cohort start date that a patient is continuously observed. The default is 365 days. Expanding the minimum look-back will give a more complete picture of a patient (as they must have been observed for longer) but will filter patients who do not have the minimum number of days prior observation.

If “**Should subjects without time at risk be removed?**” is set to yes, then a value for “**Minimum time at risk:**” is also required. This allows removing people who are lost to follow-up (i.e. that have left the database during the time-at-risk period). For example, if the time-at-risk period was 1 day from cohort start until 365 days from cohort start, then the full time-at-risk interval is 364 days (365-1). If we only want to include patients who are observed the whole interval, then we set the minimum time at risk to be 364. If we are happy as long as people are in the time-at-risk for the first 100 days, then we select minimum time at risk to be 100. In this case as the time-at-risk start as 1 day from the cohort start, a patient will be include if they remain in the database for at least 101 days from the cohort start date. If we set “Should subjects without time at risk be removed?” to ‘No’, then this will keep all patients, even those who drop out from the database during the time-at-risk.

The option “**Include people with outcomes who are not observed for the whole at risk period?**” is related to the previous option. If set to “yes”, then people who experience the outcome during the time-at-risk are always kept, even if they are not observed for the specified minimum amount of time.

The option “**Should only the first exposure per subject be included?**” is only useful if our target cohort contains patients multiple times with different cohort start dates. In this situation, picking “yes” will result in only keeping the earliest target cohort date per patient in the analysis. Otherwise a patient can be in the dataset multiple times.

Setting “**Remove patients who have observed the outcome prior to cohort entry?**” to “yes” will remove patients who have the outcome prior to the time-at-risk start date, so the model is for patients who have never experience the outcome before. If “no” is selected, then patients could have had the outcome prior. Often, having the outcome prior is very predictive of having the outcome during the time-at-risk.

Once done, the population settings dialog should look like Figure 14.12.

Now that we are finished with the Analysis Settings, the entire dialog should look like Figure 14.13.

Population Settings
Add or update the population settings

Define the time-at-risk window start, relative to target cohort entry:
 days from

Define the time-at-risk window end:
 days from

Minimum lookback period applied to target cohort:

Should subjects without time at risk be removed?
 Yes Minimum time at risk: days

Include people with outcomes who are not observed for the whole at risk period?
 Yes

Should only the first exposure per subject be included?
 Yes

Remove patients who have observed the outcome prior to cohort entry?
 No

Figure 14.12: Population settings.

14.6.3 Execution settings

There are three options:

- “**Perform sampling**”: here we choose whether to perform sampling (default = “no”). If set to “yes”, another option will appear: “**How many patients to use for a subset?**”, where the sample size can be specified. Sampling can be an efficient means to determine if a model for a large population (e.g. 10 million patients) will be predictive, by creating and testing the model with a sample of patients. For example, if the AUC is close to 0.5 in the sample, we might abandon the model.
- “**Minimum covariate occurrence: If a covariate occurs in a fraction of the target population less than this value, it will be removed:**”: here we choose then minimum covariate occurrence (default = 0.001). A minimum threshold value for covariate occurrence is necessary to remove rare events that are not representative of the overall population.
- “**Normalize covariate**”: here we choose whether to normalize covariates (default = “yes”). Normalization of the covariates is usually necessary for successful implementation of a LASSO model.

For our example we make the choices shown in Figure 14.14.

14.6.4 Training settings

There are four options:

- “**Specify how to split the test/train set:**” Select whether to differentiate the train/test data by person (stratified by outcome) or by time (older data to train the model, later data to evaluate

Analysis Settings

Model Settings

Show 10 entries Filter:

Remove	Model	Options
	GradientBoostingMachineSettings	{"ntrees":5000,"nthread":20,"maxDepth":4,7,10,"minRows":20,"learnRate": [0.001,0.01,0.1,0.9],"seed":null}

Showing 1 to 1 of 1 entries Previous Next

Covariate Settings

Show 10 entries Filter:

Remove	Options
	DemographicsGender, DemographicsAgeGroup, DemographicsRace, DemographicsEthnicity, DemographicsIndexMonth, ConditionGroupEraLongTerm (+12 more covariate settings)

Showing 1 to 1 of 1 entries Previous Next

Population Settings

Show 10 entries Filter:

Remove	Risk Window Start	Risk Window End	Washout Period	Include All Outcomes	Remove Subjects With Prior Outcome	Minimum Time At Risk
	1d from cohort start date	365d from cohort start date	365d	true	false	364d

Showing 1 to 1 of 1 entries Previous Next

Figure 14.13: Analysis settings.

Execution Settings

Perform sampling:

How many patients to use for a subset? patients

Minimum covariate occurrence: If a covariate occurs in a fraction of the target population less than this value, it will be removed:

Normalize covariates:

Figure 14.14: Execution settings.

The screenshot shows the 'Training Settings' interface. At the top, it says 'Specify how to split the test/train set:'. Below this, there is a dropdown menu set to 'Person'. Next is a text input field containing '25'. Then, there is a dropdown menu set to '3 folds'. Finally, there is a text input field containing '123'.

Figure 14.15: Training settings.

the model).

- “**Percentage of the data to be used as the test set (0-100%)**”: Select the percentage of data to be used as test data (default = 25%).
- “**The number of folds used in the cross validation**”: Select the number of folds for cross-validation used to select the optimal hyper-parameter (default = 3).
- “**The seed used to split the test/train set when using a person type testSplit (optional)**”: Select the random seed used to split the train/test set when using a person type test split.

For our example we make the choices shown in Figure 14.15.

14.6.5 Importing and exporting a study

To export a study, click on the “Export” tab under “Utilities”. ATLAS will produce JSON that can be directly copied and pasted into a file that contains all of the data, such as the study name, cohort definitions, models selected, covariates, settings, needed to run the study.

To import a study, click on the “Import” tab under “Utilities”. Paste the contents of a patient-level prediction study JSON into this window, then click on the Import button below the other tab buttons. Note that this will overwrite all previous settings for that study, so this is typically done using a new, empty study design.

14.6.6 Downloading the study package

Click on the “Review & Download” tab under “Utilities”. In the “Download Study Package” section, enter a descriptive name for the R package, noting that any illegal characters in R will automatically be removed from the file name by ATLAS. Click on **Download** to download the R package to a local folder.

14.6.7 Running the study

To run the R package requires having R, RStudio, and Java installed as described in Section 9.4.5. Also required is the PatientLevelPrediction package, which can be installed in R using:

```
install.packages("drat")
drat::addRepo("OHDSI")
install.packages("PatientLevelPrediction")
```

Some of the machine learning algorithms require additional software to be installed. For a full description of how to install the PatientLevelPrediction package, see the “Patient-Level Prediction Installation Guide” vignette.

To use the study R package we recommend using R Studio. If you are running R Studio locally, unzip the file generated by ATLAS, and double click the .Rproj file to open it in R Studio. If you are running R Studio on an R studio server, click  **Upload** to upload and unzip the file, then click on the .Rproj file to open the project.

TODO: full instructions for running the package should be in the package README, not in the book.

After running the R package analysis we can view the results in an interactive shiny app by running:

```
PatientLevelPrediction::viewMultiplePlp(outputFolder)
```

14.7 Implementing the study in R

An alternative to implementing our study design using ATLAS is to write the study code ourselves in R. We can make use of the functions provided in the PatientLevelPrediction package. The package enables data extraction, model building, and model evaluation using data from databases that are translated into the OMOP CDM.

14.7.1 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.

14.7.2 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

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 washout period 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.

14.7.3 Additional inclusion criteria

The final study population is obtained by applying additional constraints on the two earlier defined cohorts, e.g., a minimum 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"
)

```

14.7.4 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 gradient boosting machine: `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 best cross-validation performance will then be chosen for the final model. For our problem we choose to build a gradient boosting machine with several hyper-parameter values:

```

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 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.

We can save the model using:

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

We 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:

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

14.7.5 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 which we can view all performance measures created by the framework, including interactive plots, as shown in Figure 14.16.

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

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

The plots are described in more detail in Section 14.4.2.

14.7.5.1 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 performed 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")

population <- createStudyPopulation(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. Assuming we ran `result <- runPlp(...)` then we can extract the data required for the model and evaluated it on new data. Assuming the validation cohorts are in the table `mainschema.dob.cohort` with IDs 1 and 2 and the CDM data is in the schema `cdmschema.dob`:

```
valResult <- externalValidatePlp(
  plpResult = result,
  connectionDetails = connectionDetails,
  validationSchemaTarget = 'mainschema.dob',
  validationSchemaOutcome = 'mainschema.dob',
  validationSchemaCdm = 'cdmschema dbo',
  databaseNames = 'new database',
  validationTableTarget = 'cohort',
  validationTableOutcome = 'cohort',
  validationIdTarget = 1,
  validationIdOutcome = 2
)
```

If we have multiple databases to validate the model on then we can run:

```
valResults <- externalValidatePlp(
  plpResult = result,
  connectionDetails = connectionDetails,
```

```

validationSchemaTarget = list('mainschema.dob',
                             'difschema.dob',
                             'anotherschema.dob'),
validationSchemaOutcome = list('mainschema.dob',
                               'difschema.dob',
                               'anotherschema.dob'),
validationSchemaCdm = list('cdms1schema dbo',
                           'cdm2schema dbo',
                           'cdm3schema dbo'),
databaseNames = list('new database 1',
                      'new database 2',
                      'new database 3'),
validationTableTarget = list('cohort1',
                            'cohort2',
                            'cohort3'),
validationTableOutcome = list('cohort1',
                            'cohort2',
                            'cohort3'),
validationIdTarget = list(1,3,5),
validationIdOutcome = list(2,4,6)
)

```

14.8 Single model viewer app

Exploring the performance of a prediction model is easiest with the `viewPlp` function. This requires a results object as the input. If developing models in R we can use the result of `runPLP` as the input. If using the ATLAS-generated study package, then we need to load one of the models (in this example we will load `Analysis_1`):

```

plpResult <- loadPlpResult(file.path(outputFolder,
                                      'Analysis_1',
                                      'plpResult'))

```

Here “`Analysis_1`” corresponds to the analysis we specified earlier.

We can then launch the shiny app by running:

```
viewPlp(plpResult)
```

The Shiny app opens with a summary of the performance metrics on the test and train sets, see Figure 14.16. The results show that the AUC on the train set was 0.78 and this dropped to 0.74 on the test set. The test set AUC is the more accurate measure. Overall, the model appears to be able to discriminate those who will develop the outcome in new users of ACE inhibitors but it slightly overfit as the performance on the train set is higher than the test set. The ROC plot is presented in Figure 14.17.

The screenshot shows a Shiny application window titled "c/rwd - Shiny". The URL is "http://127.0.0.1:4888". The top navigation bar includes tabs for "PatientLevelPrediction Explorer", "Internal Validation", and "External Validation". Below this is a secondary navigation bar with tabs: "Evaluation Summary" (which is active, indicated by a dashed border), "Characterization", "ROC", "Calibration", "Demographics", "Preference", "Box Plot", and "Settings".

The main content area is titled "Evaluation Summary". It features a table with 11 rows, each containing a metric name and its corresponding test and train values. The table has three columns: "Metric", "test", and "train". The metrics listed are AUC, AUC_lb95ci, AUC_ub95ci, AUPRC, BrierScaled, BrierScore, CalibrationIntercept.intercept, CalibrationSlope.Gradient, outcomeCount, populationSize, and Incidence.

Metric	test	train
1 AUC	0.72130	0.75348
2 AUC_lb95ci	0.70057	0.74215
3 AUC_ub95ci	0.74203	0.76482
4 AUPRC	0.10971	0.13571
5 BrierScaled	0.03755	0.04902
6 BrierScore	0.03355	0.03304
7 CalibrationIntercept.intercept	-0.00089	-0.00813
8 CalibrationSlope.Gradient	1.02041	1.22457
9 outcomeCount	601.00000	1802.00000
10 populationSize	16685.00000	50054.00000
11 Incidence	3.60204	3.60011

At the bottom, it says "Showing 1 to 11 of 11 entries" and has buttons for "Previous", "1", and "Next".

Figure 14.16: Summary evaluation statistics in the Shiny app.

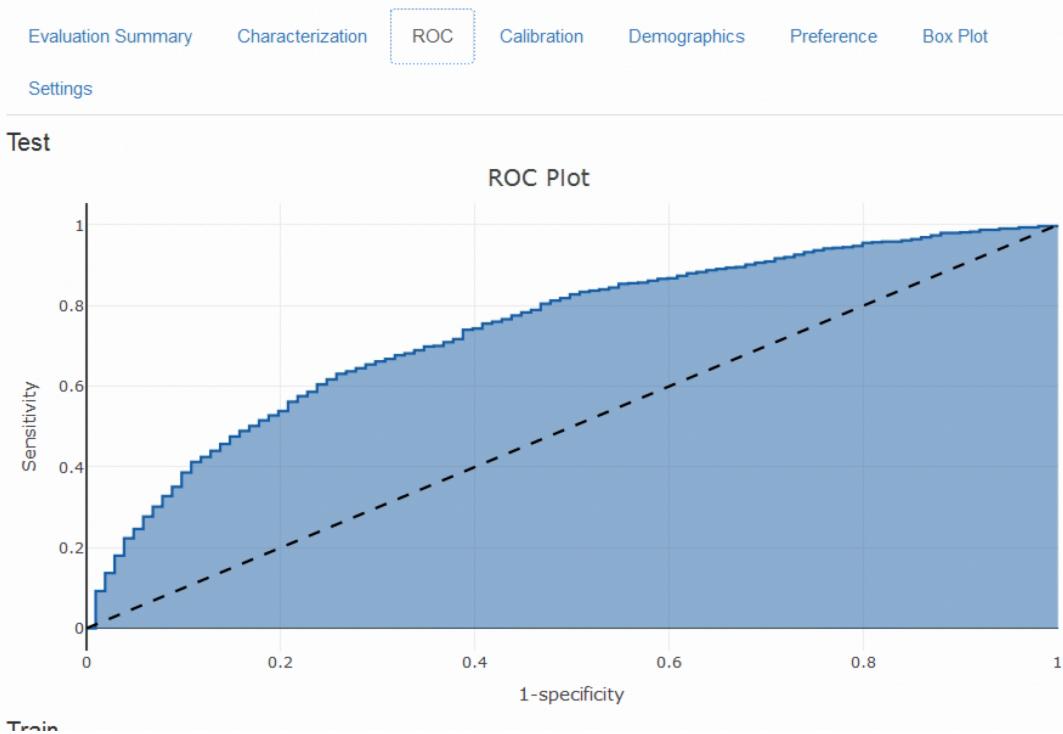


Figure 14.17: The ROC plot.

The calibration plot in Figure 14.18 shows that generally the observed risk matches the predicted risk as the dots are around the diagonal line. The demographic calibration plot in Figure 14.19 however shows that the model is not well calibrated for the younger patients, as the blue line (the predicted risk) differs from the red line (the observed risk) for those aged below 40. This may indicate we need to remove the under 40s from the target population (as the observed risk for the younger patients is nearly zero).

Finally, the attrition plot shows the loss of patients from the labelled data based on inclusion/exclusion criteria, see Figure 14.20. The plot shows that we lost a large portion of the target population due to them not being observed for the whole time at risk (1 year follow up). Interestingly, not as many patients with the outcome lacked the complete time at risk.

14.9 Multiple model viewer app

The study package as generated by ATLAS allows generating and evaluating many different prediction models, for different prediction problems. Therefore, specifically for the output generated by the study package an additional Shiny app has been developed for viewing multiple models. To start this app, run `viewMultiplePlp(outputFolder)` where `outputFolder` is the path containing the analysis results as specified when running the `execute` command (and should for example contain a sub-folder named “Analysis_1”).

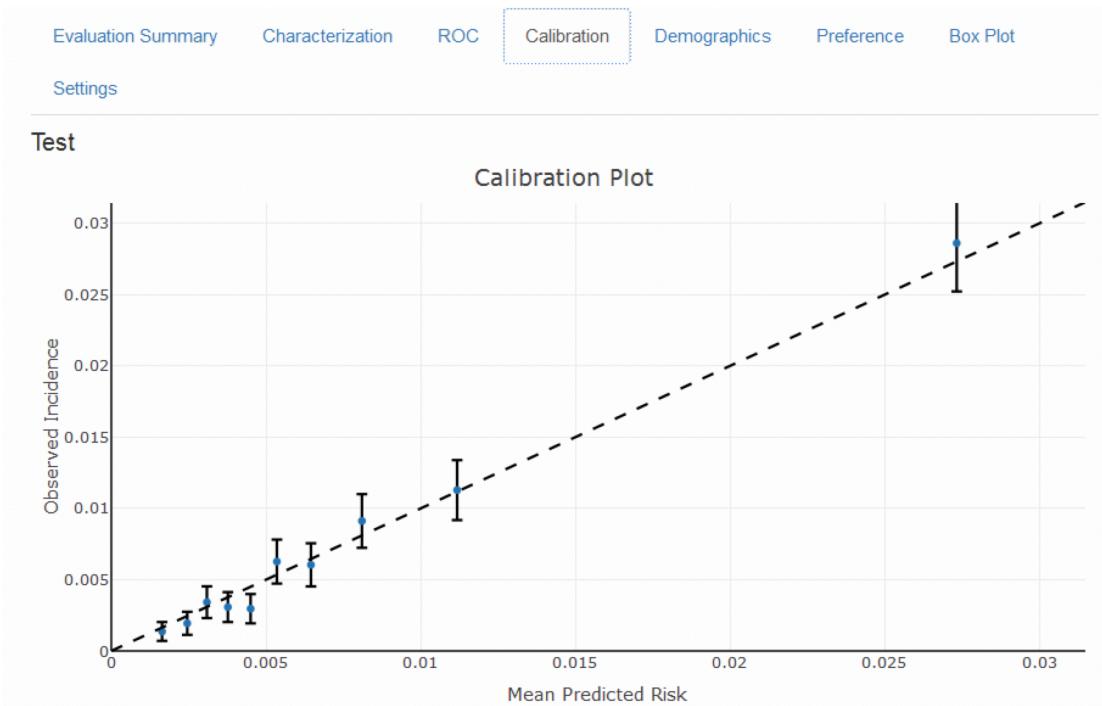


Figure 14.18: The calibration of the model

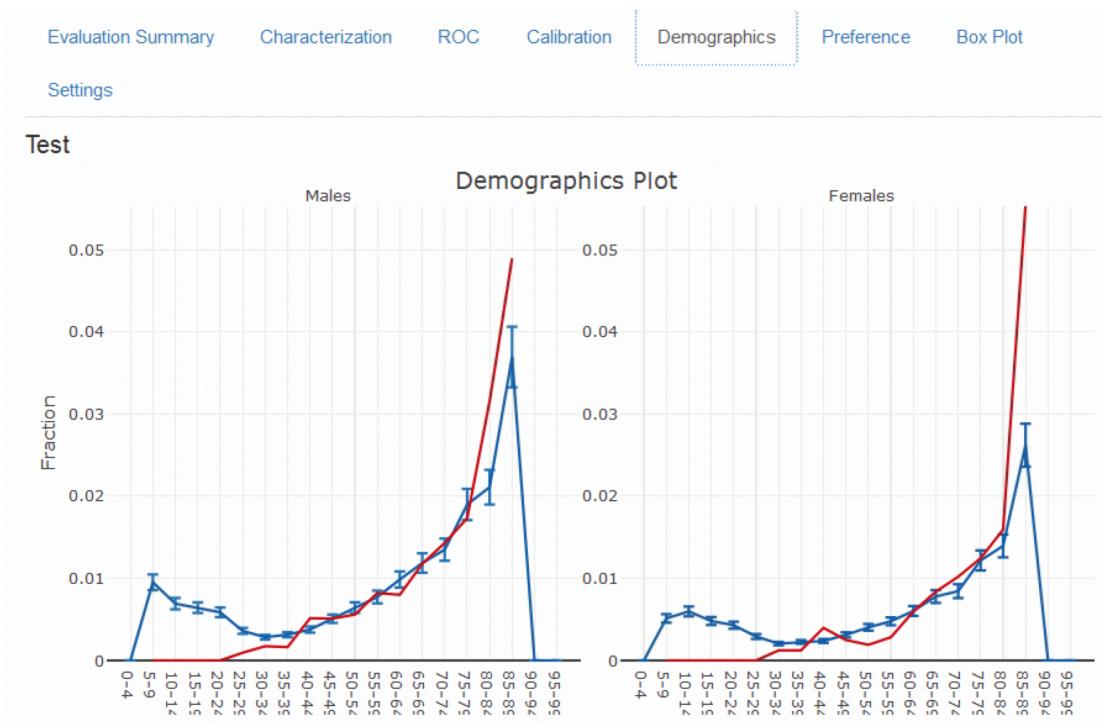


Figure 14.19: The demographic calibration of the model

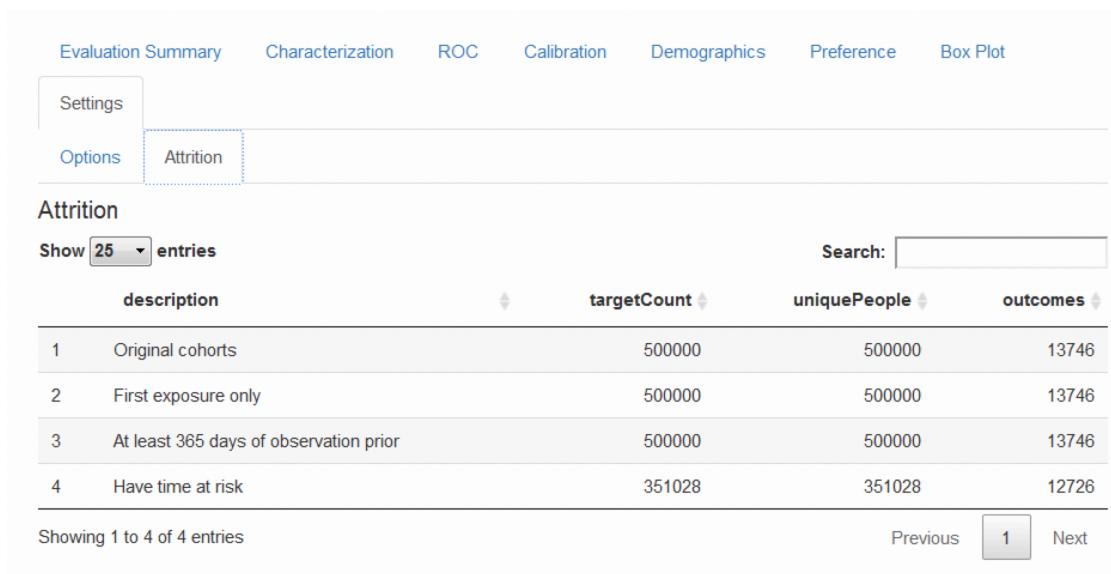


Figure 14.20: The attrition plot for the prediction problem

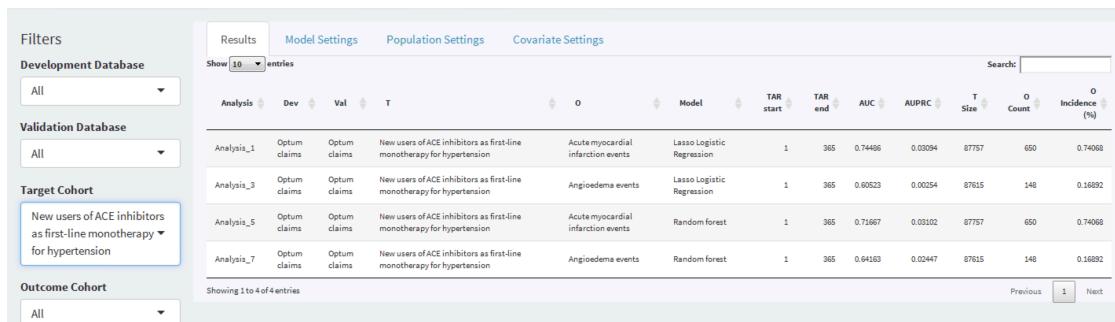


Figure 14.21: The shiny summary page containing key hold out set performance metrics for each model trained

14.9.1 Viewing the model summary and settings

The interactive shiny app will start at the summary page as shown in Figure 14.21.

This summary page table contains:

- basic information about the model (e.g., database information, classifier type, time at risk settings, target population and outcome names)
- hold out target population count and incidence of outcome
- discrimination metrics: AUC, AUPRC

To the left of the table is the filter option, where we can specify the development/validation databases to focus on, the type of model, the time at risk settings of interest and/or the cohorts of interest. For example, to pick the models corresponding to the target population “New users of ACE inhibitors as first line monotherapy for hypertension”, select this in the *Target Cohort* option.

The screenshot shows a user interface for model settings. At the top, there are tabs: 'Results' (selected), 'Model Settings' (highlighted in blue), 'Population Settings', and 'Covariate Settings'. Below the tabs, the title 'Model Settings: help' is displayed. A dropdown menu 'Show 10 entries' is visible. The main content is a table with columns 'Setting' and 'Value'. The table contains three rows:

Setting	Value
1 Model	lr_lasso
2 variance	0.01
3 seed	50975614

At the bottom left of the table area, it says 'Showing 1 to 3 of 3 entries'.

Figure 14.22: To view the model settings used when developing the model.

To explore a model click on the corresponding row, a selected row will be highlighted. With a row selected, we can now explore the model settings used when developing the model by clicking on the *Model Settings* tab:

Similarly, we can explore the population and covariate settings used to generate the model in the other tabs.

14.9.2 Viewing model performance

Once a model row had been selected we can also view the model performance. Click on **Performance** to open the threshold performance summary shown in Figure 14.23.

This summary view shows the selected prediction question in the standard format, a threshold selector and a dashboard containing key threshold based metrics such as positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity (see Section 14.4.2). In Figure 14.23 we see that at a threshold of 0.00482 the sensitivity is 83.4% (83.4% of patients with the outcome in the following year have a risk greater than or equal to 0.00482) and the PPV is 1.2% (1.2% of patients with a risk greater than or equal to 0.00482 have the outcome in the following year). As the incidence of the outcome within the year is 0.741%, identifying patients with a risk greater than or equal to 0.00482 would find a subgroup of patients that have nearly double the risk of the population average risk. We can adjust the threshold using the slider to view the performance at other values.

To look at the overall discrimination of the model click on the “Discrimination” tab to view the ROC plot, precision-recall plot, and distribution plots. The line on the plots corresponds to the selected threshold point. Figure 14.24 show the ROC and precision-recall plots. The ROC plot shows the model was able to discriminate between those who will have the outcome within the year and those who will not. However, the performance looks less impressive when we see the precision-recall plot, as the low incidence of the outcome means there is a high false positive rate.

Figure 14.25 shows the prediction and preference score distributions.

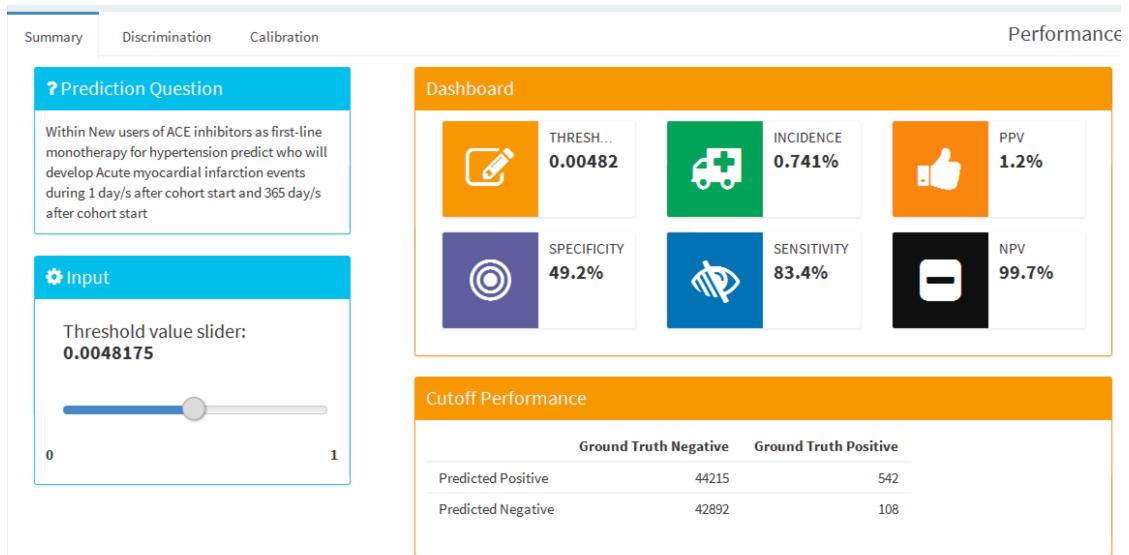


Figure 14.23: The summary performance measures at a set threshold.

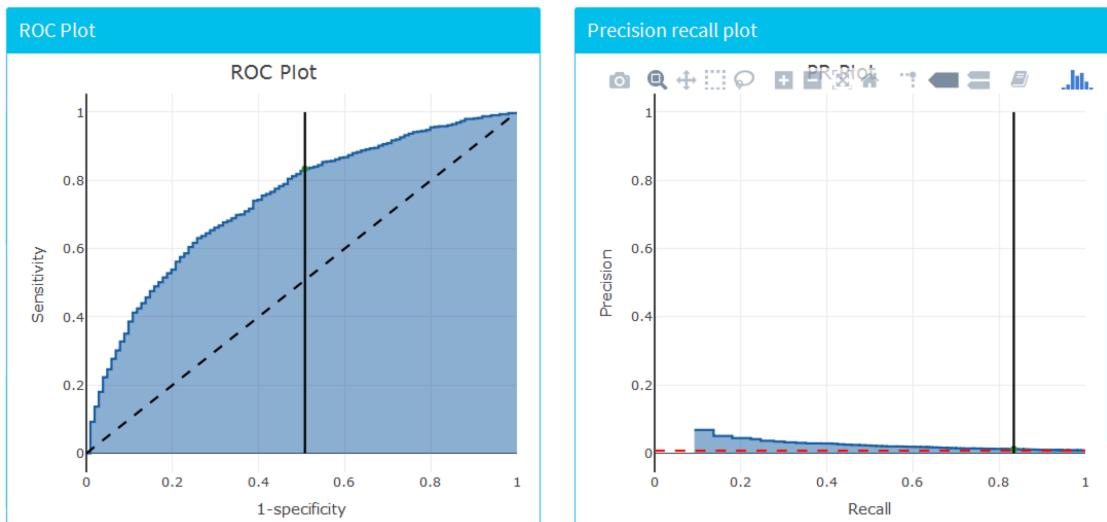


Figure 14.24: The ROC and precision-recall plots used to access the overall discrimination ability of the model.

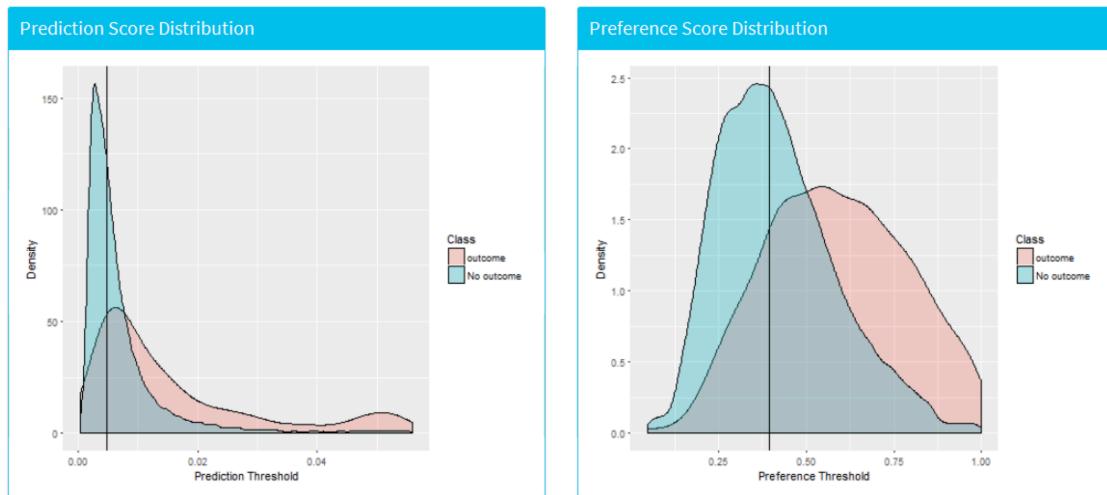


Figure 14.25: The predicted risk distribution for those with and without the outcome. The more these overlap the worse the discrimination

Finally, we can also inspect the calibration of the model by clicking on the “Calibration” tab. This displays the calibration plot and the demographic calibration shown in Figure 14.26.

We see that the average predicted risk appears to match the observed fraction who experienced the outcome within a year, so the model is well calibrated. Interestingly, the demographic calibration shows that the blue line is higher than the red line for young patients, so we are predicting a higher risk for young age groups. Conversely, for the patients above 80 the model is predicting a lower risk than the observed risk. This may prompt us to develop separate models for the younger or older patients.

14.9.3 Viewing the model

To inspect the final model, select the Model option from the left hand menu. This will open a view containing plots for each variable in the model, shown in Figure 14.27, and a table summarizing all the candidate covariates, shown in Figure 14.28. The variable plots are separated into binary variables and continuous variables. The x-axis is the prevalence/mean in patients without the outcome and the y-axis is the prevalence/mean in patients with the outcome. Therefore, any variable’s dot falling above the diagonal is more common in patients with the outcome and any variable’s dot falling below the diagonal is less common in patients with the outcome.

The table in Figure 14.28 displays the name, value (coefficient if using a general linear model, or variable importance otherwise) for all the candidate covariates, outcome mean (the mean value for those who have the outcome) and non-outcome mean (the mean value for those who do not have the outcome).

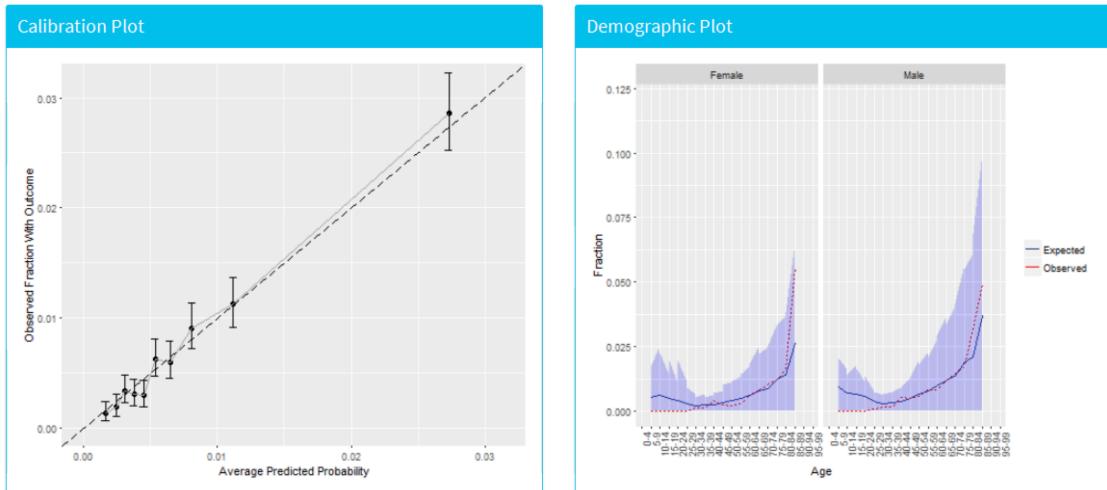


Figure 14.26: The risk stratified calibration and demographic calibration

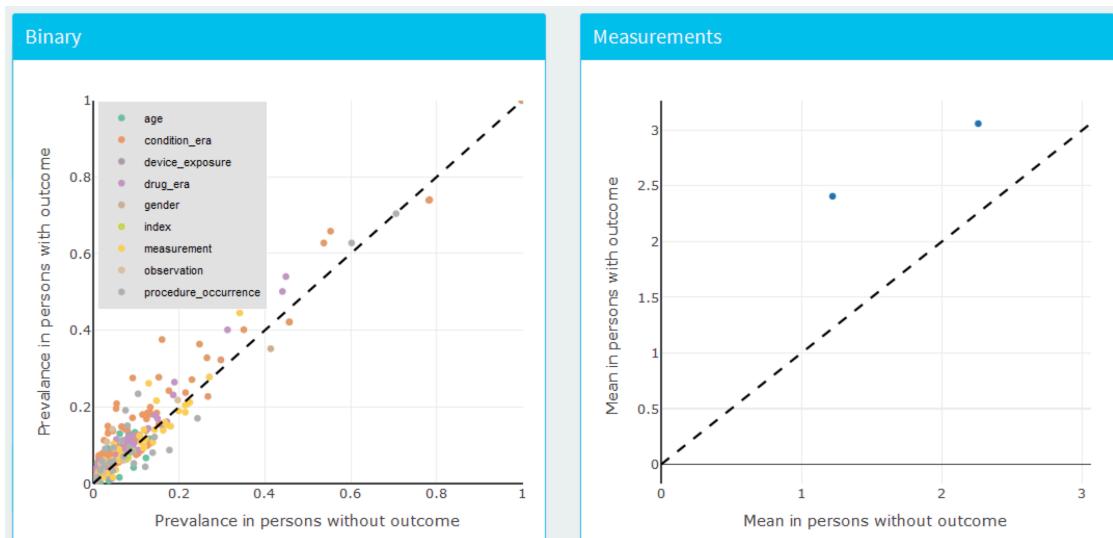


Figure 14.27: Model summary plots. Each dot corresponds to a variable included in the model.

Model Table				
	Covariate Name	Value	Outcome Mean	Non-outcome Mean
1	age group: 00-04	0	0.0004	0.0001
2	age group: 05-09	0	0	0.0003
3	index month: 1	0	0.1307	0.1096
4	observation during day -365 through 0 days relative to index: Domain	0	0.1188	0.0514
5	Charlson index - Romano adaptation	0	2.4783	1.3817
6	Diabetes Comorbidity Severity Index (DCSI)	0.1478	2.4056	1.2207
7	CHADS2VASc	0.9279	3.0573	2.2576
8	visit_occurrence concept count during day -365 through 0 concept_count relative to index	0	19.5263	13.8837
9	age group: 10-14	0	0	0.001
10	index month: 2	0	0.0934	0.0909

Showing 1 to 10 of 67,897 entries

Previous 1 2 3 4 5 ... 6790 Next

Figure 14.28: Model details table.



Predictive models are not causal models, and predictors should not be mistaken for causes. There is no guarantee that modifying any of the variables in Figure 14.28 will have an effect on the risk of the outcome.

14.10 Additional Patient-level Prediction Features

14.10.1 Journal paper generation

We have added functionality to automatically generate a word document we can use as start of a journal paper. It contains many of the generated study details and results. If we have performed external validation these results will can be added as well. Optionally, we can add a “Table 1” that contains data on many covariates for the target population. We 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.

14.11 Summary



- ToDo

14.12 Exercises

ToDo

Part IV

Evidence Quality

Chapter 15

Evidence Quality

Chapter lead: Jon Duke

15.1 Understanding Evidence Quality

How do we know if the results of a study are reliable? Can they be trusted for use in clinical settings? What about in regulatory decision-making? Can they serve as a foundation for future research? Each time a new study is published or disseminated, readers must consider these questions, regardless of whether the work was a randomized controlled trial, an observational study, or other type of analysis.

One of the concerns that is often raised around observational studies and the use of “real world data” is the topic of data quality (Botsis et al., 2010; Hersh et al., 2013; Sherman et al., 2016). Commonly noted is that data used in observational research were not originally gathered for research purposes and thus may suffer from incomplete or inaccurate data capture as well inherent biases. These concerns have given rise to a growing body of research around how to measure, characterize, and ideally improve data quality (Kahn et al., 2012; Liaw et al., 2013; Weiskopf and Weng, 2013a). The OHDSI community is a strong advocate of such research and community members have led and participated in many studies looking at data quality in the OMOP CDM and the OHDSI network (Huser et al., 2016; Kahn et al., 2015; Callahan et al., 2017; Yoon et al., 2016).

Given the findings of the past decade in this area, it has become apparent that data quality is not perfect and never will be. This notion is nicely reflected in this quote from Dr Clem McDonald, a pioneer in the field of medical informatics:

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

Thus, as a community we must ask the question—*given imperfect data, how can we achieve the most reliable evidence?* The OHDSI community is seeking to address this question through a holistic focus on “evidence quality”. Evidence quality considers not only the quality of observational data but also the validity of the methods, software, and clinical definitions used in our observational analyses.

In the following chapters, we will explore four components of evidence quality:

Component of Evidence Quality	What it Measures
Data Quality	Are the data completely captured with plausible values in a manner that is conformant to agreed structure and conventions?
Clinical Validity	To what extent does the analysis conducted match the clinical intention?
Software Validity	Can we trust that the process transforming and analyzing the data does what it is supposed to do?
Method Validity	Is the methodology appropriate for the question, given the strengths and weaknesses of the data?

15.2 Communicating Evidence Quality

An important aspect of evidence quality is the ability to express the uncertainty that comes from the data being imperfect. Thus, our efforts around evidence quality include not only concepts but also specific tools and community processes. The overarching goal of OHDSI's work around evidence quality is to produce confidence in health care decision-makers that the evidence generated by OHDSI—while undoubtedly imperfect in many ways—has been consistently measured for its weaknesses and strengths and that this information has been communicated in a rigorous and open manner.

Chapter 16

Data Quality

Chapter leads: Martijn Schuemie, Vojtech Huser & Andrew Williams

Most of the data used for observational healthcare research was not collected for research purposes. For example, electronic health records (EHRs) aim to capture the information needed to support the care of patients, and administrative claims are collected to provide a grounds for allocating costs to payers. Many have questioned whether it is appropriate to use such data for clinical research, with van der Lei (1991) even stating that “Data shall be used only for the purpose for which they were collected”. The concern is that because the data was not collected for the research that we would like to do, it is not guaranteed to have sufficient quality. If the quality of the data is poor (garbage in), then the quality of the result of research using that data must be poor as well (garbage out). An important aspect of observational healthcare research therefore deals with assessing data quality, aiming to answer the question:

Are the data of sufficient quality for our research purposes?

We can define data quality (DQ) as (Roebuck, 2012):

The state of completeness, validity, consistency, timeliness and accuracy that makes data appropriate for a specific use.

Note that it is unlikely that our data are perfect, but they may be good enough for our purposes.

DQ cannot be observed directly, but methodology has been developed to assess it. Two types of DQ assessments can be distinguished (Weiskopf and Weng, 2013b): assessments to evaluate DQ in general, and assessments to evaluate DQ in the context of a specific study.

In this chapter we will first review possible sources of DQ problems, after which we'll discuss the theory of general and study-specific DQ assessments, followed by a step-by-step description of how these assessments can be performed using the OHDSI tools.

16.1 Sources of data quality problems

There are many threats to the quality of the data, starting as noted in Chapter ??EvidenceQuality) when the doctor records her or his thoughts. Dasu and Johnson (2003) distinguish the following steps in the lifecycle of data, recommending DQ be integrated in each step. They refer to this as the DQ continuum:

1. **Data gathering and integration.** Possible problems include fallible manual entry, biases (e.g. upcoding in claims), erroneous joining of tables in an EHR, and replacing missing values with default ones.
2. **Data storage and knowledge sharing.** Potential problems are lack of documentation of the data model, and lack of meta-data.
3. **Data analysis.** Problems can include incorrect data transformations, incorrect data interpretation, and use of inappropriate methodology.
4. **Data publishing.** When publishing data for downstream use.

Often the data we use has already been collected and integrated, so there is little we can do to improve step 1. We do have ways to check the DQ produced by this step as will be discussed in subsequent sections in this chapter.

Similarly, we often receive the data in a specific form, so we have little influence over part of step 2. However, in OHDSI we convert all our observational data to the Common Data Model (CDM), and we do have ownership over this process. Some have expressed concerns that this specific step can degrade DQ. But because we control this process, we can build stringent safeguards to preserve DQ as discussed later in Section x. Several investigations (Defalco et al., 2013; Makadia and Ryan, 2014; Matcho et al., 2014; Voss et al., 2015a,b; Hripcsak et al., 2018) have shown that when properly executed, little to no error is introduced when converting to the CDM. In fact, having a well-documented data model that is shared by a large community facilitates data storage in unambiguous and clear manner.

Step 3 (data analysis) also falls under our control. In OHDSI, we tend to not use the term DQ for the quality issues during this step, but rather the terms *clinical validity*, *software validity* and *method validity*, which are discussed at length in Chapters 17, 18, and ??MethodValidity), respectively.

16.2 Data quality in general

We can ask the question whether our data is fit for the generic purpose of observational research. Kahn et al. (2016) define such generic DQ as consisting of three components:

1. **Conformance:** Do data values adhere to specified standard and formats? Three subtypes are identified:
 - **Value:** Are recorded data elements in agreement with the specified formats? For example, are all provider medical specialties valid specialties?
 - **Relational:** Is the recorded data in agreement with specified relational constraints? For example, is the provider_id in a DRUG_EXPOSURE data present in the PROVIDER table?

- **Computation:** Do computations on the data yield the intended results? For example, is BMI computed from height and weight equal to the verbatim BMI recorded in the data?
2. **Completeness:** Are data values present? For example, do all persons have a known gender?
 3. **Plausibility:** Are data values believable? Three subtypes are defined:
 - **Uniqueness:** For example, does each person_id occur only once in the PERSON table?
 - **Atemporal:** Do values, distributions, or densities agree with expected values? For example, is the prevalence of diabetes in line with the known prevalence?
 - **Temporal:** Are changes in values in line with expectations? For example, are immunization sequences in line with recommendations?

Each component can be evaluated in two ways:

- **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.

16.2.1 Data quality checks

Kahn introduces the term *data quality check* (sometimes referred to as data quality rule) that tests whether data conform to a given requirement (e.g., implausible age of 141 of a patient, potentially due to incorrect birth year or missing death event). We can implement such checks in software, creating automated DQ tools. One such tool is ACHILLES (Automated Characterization of Health Information at Large-scale Longitudinal Evidence Systems) (Huser et al., 2018). ACHILLES is a software tool that not only executes a wide array of DQ checks, it also provides characterization and visualization of a database conforming to the CDM. As such, it can be used to evaluate DQ in a network of databases (Huser et al., 2016). ACHILLES is available as a stand-alone tool, and is also integrated into ATLAS as the “Data Sources” function.

ACHILLES pre-computes over 170 data characterization analyses, with each analysis having 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”. The results of these analyses are stored in a database, and can be accessed by a web viewer or by ATLAS. Based on these analyses, a battery of DQ tests is performed known as “ACHILLES Heel”. These checks are categorized as “error”, “warning”, or “notification”. Errors are DQ issues that should not be present, constituting violations of some fundamental principles that must be resolved before the data can be used for research. Warnings indicate something is likely wrong although a closer investigation is needed to make a definite determination. Notifications hint add odd characteristics that should be explored, but fall within the range of what is expected. Table 16.1 shows some example rules.

Table 16.1: Example data quality rules in ACHILLES Heel.

Type	Description
Error	Age > 150 years
Error	A condition_concept_id refers to a concept that is not in the CONDITION domain
Warning	The rate of occurrence for a specific concept_id changes more than 100% from one month to the next

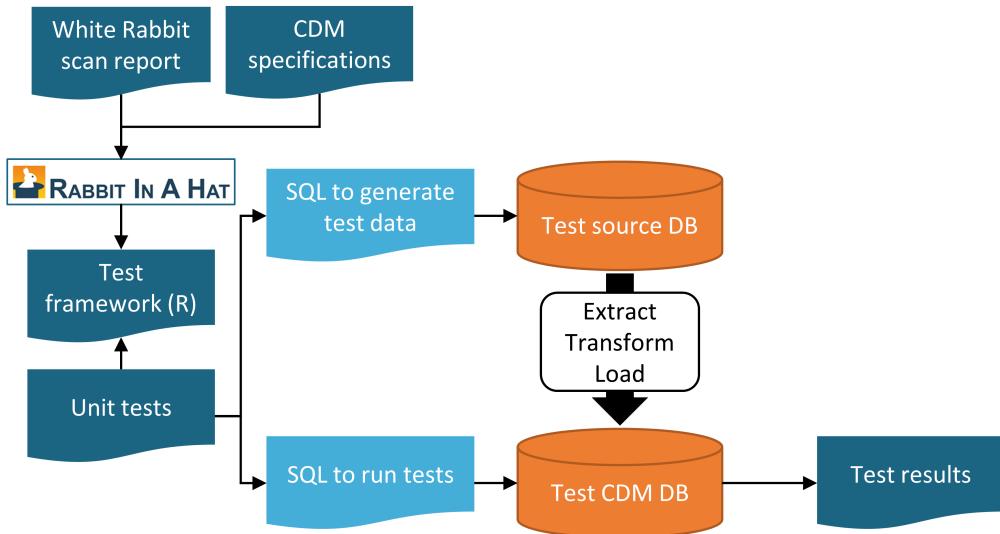


Figure 16.1: Unit testing an ETL (Extract-Transform-Load) process.

Type	Description
Warning	A prescription has a days_supply > 180
Notification	The number of patients without any visit exceeds a predefined threshold
Notification	There is no weight data in the MEASUREMENT table

! ACHILLES and ACHILLES Heel are executed against the data in the CDM. DQ issues identified this way may be due to the conversion to the CDM, but may also reflect DQ issues already present in the source data. If the conversion is at fault, it is usually within our control to remedy the problem, but if the underlying data is at fault the only course of action may be to delete the offending records.

16.2.2 ETL unit tests

The ETL (Extract-Transform-Load) process by which data is converted to the CDM is often quite complex, and with that complexity comes the danger of making mistakes that may go unnoticed.

Figure 16.1 shows

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 demonstrate study-specific checks.

16.3.1 Outcomes

For an international analysis, part of OHDSI study diagnostics (for a given 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) datasets.

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>)

16.4 ETL unit testing

Extract Transform Load (ETL) process that transforms data from source (in EHR system or claims sys) to target (OMOP CDM) can contain errors. Unit testing of ETL code allows for preventing coding errors in ETL to cause data errors.

16.4.1 Unit testing framework in Rabbit-in-a-Hat

OHDSI tool Rabbit-in-a-Hat includes an ETL unit testing framework. This framework defines a set of functions for each table in the source schema and a set of functions for each table in target OMOP CDM schema. Detailed description is available at https://www.ohdsi.org/web/wiki/doku.php?id=documentation:software:whiterabbit:test_framework.

Chapter 17

Clinical Validity

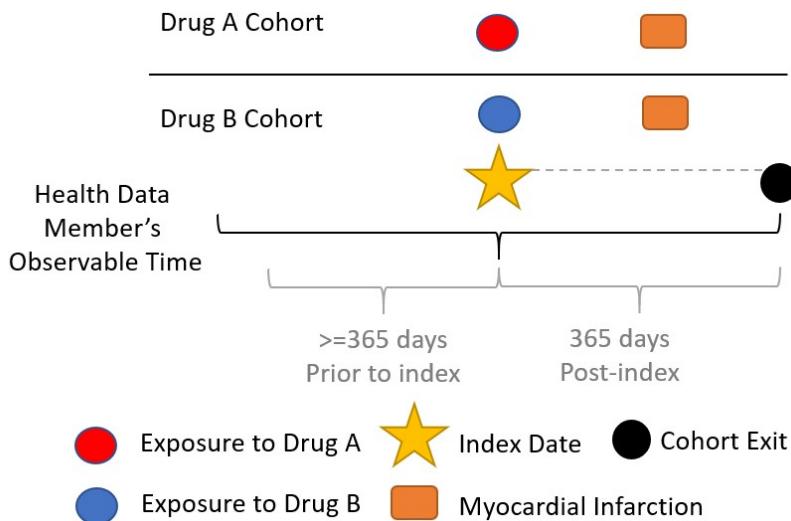
Chapter leads: Joel N. Swerdel, Seng Chan You

The likelihood of transforming matter into energy is something akin to shooting birds in the dark in a country where there are only a few birds. *Einstein, 1935*

The goal of the Research Network is to lower the barrier to performing large-scale collaborative research using observational data to generate high-quality evidence through peer review across study design, execution, and data analysis (Hripcsak et al., 2015). Patient care and policy decisions demand high-quality evidence. Some have hypothesized that the volume, velocity, and veracity of observational data from electronic health records, administrative claims, and investment in data networks can be positioned to meet this demand. Analyses in large data sets are not necessarily correct simply because they are larger. Deficient studies may lead to misuse of resources and result in poor health care outcomes for patients (Morton et al.). This chapter will focus on the question: ‘To what extent does the analysis conducted match the clinical intention?’

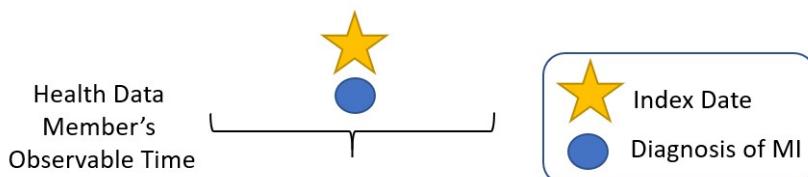
Studies using observational data usually begin by developing cohorts of subjects to compare for determining some effect estimate. During the development of these cohorts certain assumptions are made concerning the validity of the created cohorts, the most important of which is that the subjects in the cohorts have the characteristic that is the basis of the study. For example, if the study involves subjects with myocardial infarction (MI) each of the subjects in the cohort must have had an MI. Ideally, we would definitive evidence of the diagnosis of MI. However, with observational data, we use subject records derived from limited data collected for a specific purpose. In some cases, the data may be derived from data sets specifically collected from subjects with the health condition of interest such as disease registries. While this is high quality data, it is usually a subset of all the subject’s data. For example, the data for subjects with MI may include the interpretation of the electrocardiogram (ECG) and not the actual data from the ECG. Subjects are included in these registries based on a clinical review of each subject’s health record. In other cases, the data is derived from administrative datasets from insurance claims. These data are usually much more limited than data from health registries but have the advantage of usually including a larger number of subjects from a broader population which may be more generalizable to the overall population. In the case of administrative data, determination of the health claim for a subject is based on administrative codes for the health condition. In the US, for example, these codes are from the International Classification of Diseases (ICD). Regardless of the origin of the data, the validity of the health conditions based

on this data need to be validated. An example of a typical epidemiological study is shown in the diagram below:

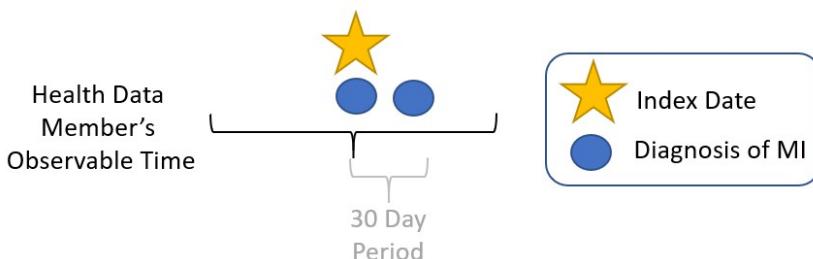


In this example, we are comparing the rates of the occurrence of MI in one year in cohorts of subjects who initiated either Drug A or Drug B. In this example, it is critical for the validity of the study to have valid measures of the rate of MI occurrence. For studies where administrative data is used, the determination of MI is typically from the use of a phenotype algorithm (PA). A PA is a heuristic-based set of rules used to determine the health condition with good precision. These algorithms are often derived from prior research some of which may have been validated. Examples of typical PAs for MI are illustrated below:

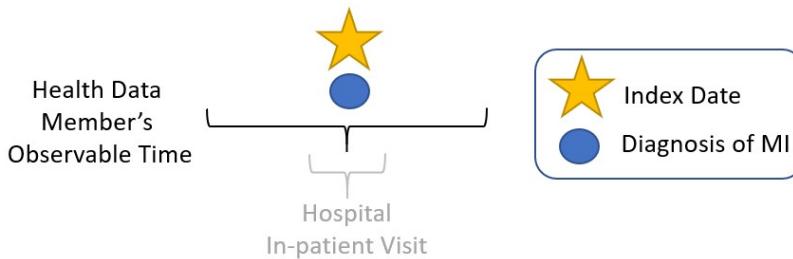
- 1) One or more occurrences of MI in the subject's record



- 2) One occurrence of MI in the subject's record followed by a second occurrence within 30 days



- 3) One or more occurrences of MI in the subject's record from a hospital in-patient setting



Once the PA for the study has been determined, the validity of the definition needs to be determined. To determine the validity of the different algorithms, we need to examine several performance characteristics of the PA including:

- 1) Sensitivity of the PA – what proportion of the subjects with the health condition in the whole cohort were determined to have the health outcome based on the PA?
- 2) Specificity of the PA - what proportion of the subjects without the health condition in the whole cohort were determined to not have the health outcome based on the PA?
- 3) Positive predictive value of the PA - what proportion of the subjects determined by the PA to have the health condition actually had the health condition?
- 4) Negative predictive value of the PA - what proportion of the subjects determined by the PA to not have the health condition actually did not have the health condition?

The methods used to determine these performance characteristics are described in the remainder of this section. Validation Methods for Phenotype Algorithms The traditional method that has been used to validate PAs has been through a thorough examination of subject records by one or more people with sufficient clinical knowledge to accurately determine the health condition of interest. The method generally follows these steps:

- 1) Select a random subset of subjects from the overall cohort.
- 2) Obtain permission from these subjects to receive health records.
- 3) Obtain the health records from those subjects who have granted permission to do so from their physicians.
- 4) Select one or more persons with sufficient clinical expertise to review subject records.
- 5) Determine the guidelines for adjudicating whether a subject is positive or negative for the health condition.
- 6) Use the results from the clinical adjudication to calculate the performance characteristics of the PA used in the study.

Each step in the above process has the potential to bias the results of the study. For example, obtaining permission from subjects may be difficult and may introduce selection bias if those subjects who provide permission differ from those who do not. In addition, obtaining the patient records and conducting a clinical review of those records is a time consuming and costly process. In order to complete this process, many studies only examine the records of those subjects the PA identified as cases for the health conditions. Under those conditions, the only performance characteristic that can be calculated is positive predictive value. In the OHDSI community, we were in the process

of developing a different approach. We are attempting to use diagnostic predictive models as an alternative method for cohort validation. The general idea is to simulate the ascertainment of the health outcome similar to the way clinicians would in a traditional phenotype algorithm validation but at scale. In this process we develop a diagnostic predictive model for a health outcome and then use that model to determine the probability of a health outcome in a large set of subjects, the “evaluation” cohort, within the data set. We then use that evaluation cohort to test our phenotype algorithms. Using this method, we are able to determine the full set of performance characteristics (i.e., sensitivity, specificity, and positive and negative predictive value) at scale. The tool is being developed as an open-source R package called **PheValuator**.

The process is as follows:

- 1) Develop a diagnostic predictive model for a phenotype: Diagnostic predictive models are used to estimate the probability that a specific outcome or disease is present in an individual.(Moons et al., 2015) The output of the model is a set of weighted predictors for diagnosing a phenotype.
- 2) Determine the probability of a phenotype for each individual in a large group of subjects: The set of predictors from the model can be used to estimate the probability of the presence of a phenotype in an individual. We use these predictions as a ‘probabilistic gold standard’.
- 3) Evaluate the performance characteristics of the PAs: We compare the predicted probability to the binary classification of a PA (the test conditions for the confusion matrix). Using the test conditions and the estimates for the true conditions, we can fully populate the confusion matrix and determine the full set of performance characteristics, i.e., sensitivity, specific, and predictive values. There are limitations using this approach. First, we can only use data that is in dataset; we are limited to diagnoses, procedures, observations, measurements, and drug exposures. Moreover, measurements are usually incomplete in administrative datasets as these do not include the actual values for the measures and, as such, we are limited to the existence or absence of the measurements as part of the model. Clinical notes are also not usually present in our data sets. Patient complaints or symptoms may not be recorded in administrative data sets. These may include things like lethargy and acute pain. In diagnostic predictive modeling we create a model that discriminates between those with the disease and those without the disease. For the PheValuator process, we use an extremely specific cohort definition, the “xSpec” cohort, to determine the cases for the models. The xSpec cohort uses a definition to find those with the disease with a very high probability of having the disease of interest. The xSpec cohort is may be defined as those subjects who have multiple condition code codes in their record for the health outcome of interest. For example, for atrial fibrillation, we may have subjects who have 10 or more codes for atrial fibrillation in their record. For MI, an acute outcome, we may use 5 occurrences of MI and include the requirement of having at least two occurrences from a hospital inpatient setting. For our non-cases, we exclude anybody from the data set who have any of the condition occurrences for the health outcome of interest. There are limitations to this method. It is possible that these xSpec cohort subjects may have may be more severe than other cases of the disease. It may also be that these subjects had longer observation time after initial diagnosis than the average patient. We use logistic regression to create these models, using the LASSO method.(Tibshirani, 1996) This method produces a parsimonious model. In so doing it removes many of the collinear covariates which may be present in many subjects. In the current version of our software we also do not include the temporality of events in the patient’s record.

Practice of Phenotype Algorithm Validation

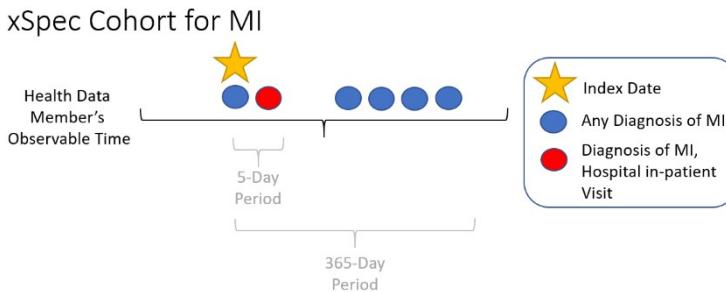
An example of the process to conduct a PA validation using chart review is provided by Cutrona and colleagues who validated their PA for MI for the US Food and Drug Administration's (FDA) Sentinel program.(Cutrona et al., 2013) The steps this group used to conduct the validation were as follows:

- 1) Develop a PA for MI: They used the PA “those with an ICD-9-CM code for AMI (410.x0, 410.x1) in the principal or primary position on facility claims for hospitalizations.”
- 2) Randomly select enough cases to be requested from the primary health care providers in order to achieve a sufficient successful return of records to achieve appropriate statistical precision for their performance measure, in this case PPV.
- 3) Request approximately an equal number of patient records from each of their four data providers.
- 4) Receive records from data providers redacted to ensure patient confidentiality.
- 5) Abstract the data from the records using the clinical expertise of two nurses. Abstracted information included EKG images, cardiac biomarkers, information on ischemic symptoms and results of cardiac diagnostic tests.
- 6) Test inter-rater reliability of the two data abstractors.
- 7) Develop an adjudication protocol based on standardized criteria from the joint European Society of Cardiology and American College of Cardiology Global Task Force
- 8) Review abstracted records using the clinical expertise of two cardiologists. The cardiologists were provided with all abstracted information listed above and an abstracted case summary. Detailed discharge information was not provided to the reviewers.
- 9) Classify each subject as: (1) definite MI; (2) probable MI; (3) no MI; or (4) unable to determine. Distinguishing between definite and probable was not defined for the clinicians but was to be based on their own clinical judgement. Subjects were considered cases if the clinicians determined the subject to be definite or probable for MI.
- 10) Disagreement between the two clinicians, i.e., one clinician determining the subject to be definite or probable and the other either not an MI or unable to determine, was settled through a joint discussion between the clinicians until agreement could be reached.

It appears evident that the above process is both very thorough as well as very time consuming and costly. In this example neither sensitivity nor specificity of the PA was determined likely owing to the cost of including records from a random selection of patients not determined to have an MI based on the PA. Overall the process examined the records of 143 of the 153 records requested. One advantage this group had was that patient permission was not required as the FDA Sentinel Initiative activities did not require institutional review board (IRB) approval. At the end of this process the researchers determined the PPV for this algorithm to be 86.0% (95% confidence interval; 79.2%, 91.2%). The above study was included in a review of validation efforts for MI PAs by Rubbo et al.(Rubbo et al., 2015b) In this review, the authors examined 33 studies involving validation of phenotype algorithms for acute myocardial infarction. They found that there was significant heterogeneity in the phenotype algorithms used in the studies as well as in the validation methods and the results reported. The

authors concluded that for acute myocardial infarction there is no gold standard phenotype algorithm available. They noted that the process was both costly and time consuming. Due to that limitation most studies had small sample sizes in their validation leading to wide variations in the estimates for the performance characteristics. They also noted that in the 33 studies, while all the studies reported positive predictive value, only 11 studies reported sensitivity and only five studies reported specificity. The question then needs to be asked is this really validation of the phenotype algorithm? As discussed previously an alternative approach currently being developed in the OHDSI community is through the use of diagnostic predictive modeling tool using a tool called PheValuator. The following are the steps for testing PAs for MI using PheValuator:

- 1) Develop an extremely specific, xSpec, cohort to determine those with MI with a high probability. For MI, we used an occurrence of MI with one or more occurrences of MI recorded from a hospital in-patient visit within 5 days, and 4 or more occurrences of MI in the patient record within 365 days. The following illustrates this PA for MI:



- 2) Develop the diagnostic predictive model for MI
 - Create a sample of subjects labeled as cases (from the xSpec cohort for MI) or non-cases in approximate proportion to the prevalence of MI in the population.
 - Use the OHDSI Patient Level Prediction package to develop a LASSO logistic regression model using all available data in the subject record.
- 3) Randomly select 2M subjects from the database, the evaluation cohort, and apply the model to this cohort to determine the probability of MI in each subject.
- 4) Test possible algorithms for MI, e.g., 1 occurrence of MI in the patient record, using the evaluation cohort.
- 5) Compare performance characteristics for the various algorithms to determine the PA for MI for use within a study.

Using this process, Table 1 displays the performance characteristics for four PAs for MI across five datasets. For a PA similar to the one evaluated by Cutrona and colleagues, “>=1 X HOI, In-Patient”, we found a mean PPV of 67% (range: 59%-74%).

Table 1: Performance Characteristics of Four Phenotype Algorithms using Diagnostic Condition Codes to Determine Myocardial Infarction on Multiple Datasets using PheValuator. The continuous 3-color heat map for the data in the table was defined as Red (value = 0), Yellow (value = 0.5), and Green (value = 1).

Phenotype Algorithm	Database	Acute Myocardial Infarction			
		Sens	PPV	Spec	NPV
>= 1 X HOI	CCAE	0.761	0.598	0.997	0.999
	Optum1862	0.723	0.530	0.995	0.998
	OptumGE66	0.643	0.534	0.973	0.982
	MDCD	0.676	0.468	0.990	0.996
	MDCR	0.665	0.553	0.977	0.985
>= 2 X HOI	CCAE	0.585	0.769	0.999	0.998
	Optum1862	0.495	0.693	0.998	0.996
	OptumGE66	0.382	0.644	0.990	0.971
	MDCD	0.454	0.628	0.996	0.993
	MDCR	0.418	0.674	0.991	0.975
>= 1 X HOI, In-Patient	CCAE	0.674	0.737	0.999	0.998
	Optum1862	0.623	0.693	0.998	0.997
	OptumGE66	0.521	0.655	0.987	0.977
	MDCD	0.573	0.593	0.995	0.994
	MDCR	0.544	0.649	0.987	0.980
1 X HOI, In-Patient, 1st Position	CCAE	0.633	0.788	0.999	0.998
	Optum1862	0.581	0.754	0.999	0.997
	OptumGE66	0.445	0.711	0.991	0.974
	MDCD	0.499	0.666	0.997	0.993
	MDCR	0.445	0.711	0.991	0.974

Sens – Sensitivity ; PPV – Positive Predictive Value ; Spec – Specificity; NPV – Negative Predictive Value; Dx Code – Diagnosis code for the phenotype; CCAE - IBM® MarketScan® Commercial Claims and Encounters Database, ages 18-62 years; MDCR - IBM® MarketScan® Medicare Supplemental and Coordination of Benefits Database, ages 66 years and greater; MDCD - IBM® MarketScan® Multi-State Medicaid, ages 18-62 years; Optum1862 - Optum© De-Identified Cliniformatics® Data Mart Database – Date of Death, ages 18-62 years; OptumGE66 - ages 66 years and greater

Chapter 18

Software Validity

Chapter lead: Martijn Schuemie

The central question of software validity is

Does the software do what it is expected to do?

Software validity is an essential component of evidence quality: only if our analysis software does what it is expected to do can we produce reliable evidence. As described in Section 18.1.1, it is essential to view every study as a software development exercise, creating an automated script that executes the entire analysis, from data in the Common Data Model (CDM) to the results such as estimates, figures as tables. It is this script, and any software used in this script, that must be validated. As described in Section 9.1, we can write the entire analysis as custom code, or we can use the functionality available in the OHDSI Methods Library. The advantage of using the Methods Library is that great care has already been taken to ensure its validity, so establishing the validity of the entire analysis becomes less burdensome.

In this chapter we first describe best practices for writing valid analysis code. After this we discuss how the Methods library is validated through its software development process and testing.

18.1 Study code validity

18.1.1 Automation as a requirement for reproducibility

Traditionally, observational studies are often viewed as a journey rather than a process: a database expert may extract a data set from the database and hand this over to the data analyst, who may open it in a spreadsheet editor or other interactive tool, and start working on the analysis. In the end, a result is produced, but little is preserved of how it came about. The destination of the journey was reached, but it is not possible to retrace the exact steps taken to get there. This practice is entirely unacceptable, both because it is not reproducible, but also because it lacks transparency; we do not know exactly what was done to produce the result, so we also cannot verify that no mistakes were made.

Every analysis generating evidence must therefore be fully automated. By automated we mean the analysis should be implemented as a single script, and we should be able to redo the entire analysis from database in CDM format to results, including tables and figures, with a single command. The analysis can be of arbitrary complexity, perhaps producing just a single count, or generating empirically calibrated estimates for millions of research questions, but the same principle applies. The script can invoke other scripts, which in turn can invoke even lower-level analysis processes.

The analysis script can be implemented in any computer language, although in OHDSI the preferred language is R. Thanks to the DatabaseConnector R package, we can connect directly to the data in CDM format, and many advanced analytics are available through the other R packages in the OHDSI Methods Library.

18.1.2 Programming best practices

Observational analyses can become very complex, with many steps needed to produce the final results. This complexity can make it harder to maintain the analysis code and increase the likelihood of making errors, as well as making it harder to notice errors. Luckily, computer programmers have over many years developed best practices for writing code that can deal with complexity, which are easy to read, reuse, adapt, and verify. (Martin, 2008) A full discussion of these best practices could fill many books. Here, we highlight these four important principles:

- **Abstraction:** Rather than write a single large script that does everything, leading to so-called “spaghetti code” where dependencies between lines of code can go from anywhere to anywhere (e.g. a value set on line 10 is used in line 1,000), we can organize our code in units called “functions.” A function should have a clear goal, for example “take random sample,” and once created we can then use this function in our larger script without having to think of the minutiae of what the function does; we can abstract the function to a simple-to-understand concept.
- **Encapsulation:** For abstraction to work, we should make sure that dependencies of a function are minimized and clearly defined. Our example sampling function should have a few arguments (e.g. a dataset and a sample size), and one output (e.g. the sample). Nothing else should influence what the function does. So-called “global variables”, variables that are set outside a function, are not arguments of a function, but are nevertheless used in the function, should be avoided.
- **Clear naming:** Variables and functions should have clear names, making code read almost like natural language. For example, instead of `x <- sp1(y, 100)`, we can write code that reads `sampledPatients <- takeSample(patients, sampleSize = 100)`. Try to resist the urge to abbreviate. Modern languages have no limits on the length of variable and function names.
- **Reuse:** One advantage of writing clear, well encapsulated functions is that they can often be reused. This not only saves time, it also means there will be less code, so less complexity and fewer opportunities for errors.

18.1.3 Code validation

Several approaches exist to verify the validity of software code, but two are especially relevant for code implementing an observational study:

- **Code review:** One person writes the code, and another person reviews the code.
- **Double coding:** Two persons both independently write the analysis code, and afterwards the results of the two scripts are compared.

Code review has the advantage that it is usually less work, but the disadvantage is that the reviewer might miss some errors. Double coding on the other hand is usually very labor intensive, but it is less likely, although not impossible, that errors are missed. Another disadvantage of double coding is that two separate implementations *almost always* produce different results, due to the many minor arbitrary choices that need to be made (e.g. should “until exposure end” be interpreted as including the exposure end date, or not?). As a consequence, the two supposedly independent programmers often need to work together to align their analyses, thus breaking their independence.

Other software validation practices such as unit testing are less relevant here because a study is typically a one-time activity with highly complex relationships between input (the data in CDM) and outputs (the study results), making these practices less usable. Note that these practices are applied in the Methods Library.

18.1.4 Using the Methods Library

The OHDSI Methods Library provides a large set of functions, allowing most observational studies to be implemented using only a few lines of code. Using the Methods Library therefore shifts most of the burden of establishing the validity of one’s study code to the Library. Validity of the Methods Library is ensured by its software development process and by extensive testing.

18.2 Methods Library 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 (for example the CohortMethod issue tracker¹) and the OHDSI Forums². 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 leadership (Drs. Marc Suchard and Martijn Schuemie) and OHDSI Patient-Level Prediction Workgroup leadership (Drs. Peter Rijnbeek and Jenna Reps) 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.

¹<https://github.com/OHDSI/CohortMethod/issues>

²<http://forums.ohdsi.org/>

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 the Methods Library is subject to continuous critique and improvement relative to its accuracy, reliability and consistency.

18.2.1 Source Code Management

All of the Methods Library’s source code is managed in the source code version control system “git” publicly accessible 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 requests, 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 made in terms of compatibility

18.2.2 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 documentation can be viewed though the Methods Library website³.

³<https://ohdsi.github.io/MethodsLibrary/>

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.

18.2.3 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.

18.2.4 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.

18.2.5 Qualified Personnel

Members of the 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.

18.2.6 Physical and Logical Security

The OHDSI Methods Library is hosted on the GitHub⁴ system. GitHub’s security measures are described at <https://github.com/security>. Usernames and passwords are required by all members of the OHDSI community to contribute modifications to the Methods Library, and only the Population-Level Estimation Workgroup and Patient-Level Prediction Workgroup leadership can make changes to the master branches. User accounts are limited in access based upon standard security policies and functional requirements.

18.2.7 Disaster Recovery

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

⁴<https://github.com/>

18.3 Methods Library 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 for more complex functionality using simulations.

18.3.1 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 among 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.

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 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.

18.3.2 Simulation

For more complex functionality it is not always obvious what the expected output should be given the input. In these cases simulations are sometimes used, generating input given a specific statistical model, and establishing whether the functionality produces results in line with this known model. For example, in the SelfControlledCaseSeries package simulations are used to verify that the method is able to detect and appropriately model temporal trends in simulated data.

18.4 Summary

-  – An observational study should be implemented as an automated script that executes the entire analysis, from data in the CDM to the results, to ensure reproducibility and transparency.
- Custom study code should adhere to best programming practices, including abstraction, encapsulation, clear naming, and code reuse.

- Custom study code can be validated using code review or double coding.
- The Methods Library provides validated functionality that can be used in observational studies.
- The Methods Library is validated by using a software development process aimed at creating valid software, and by testing.

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?

“Method” includes not only the study design, but also 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 verify 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 many standardized diagnostics that should be generated and evaluated whenever an analysis is performed.

In this chapter we will focus on the validity of methods used in population-level estimation. We will first briefly highlight some study design-specific diagnostics, and will then discuss diagnostics that are applicable to most if not all population-level estimation studies. Following this is a step-by-step description of how to execute these diagnostics using the OHDSI tools. We close this chapter with an advanced topic, reviewing the OHDSI Methods Benchmark and its application to the OHDSI Methods Library.

19.1 Design-specific diagnostics

For each study design there are diagnostics specific to such a design. Many of these diagnostics are implemented and readily available in the R packages of the OHDSI Methods Library. For example, Section 13.9 lists a wide range of diagnostics generated by the CohortMethod package, including:

- **Propensity score distribution** to assess initial comparability of cohorts.

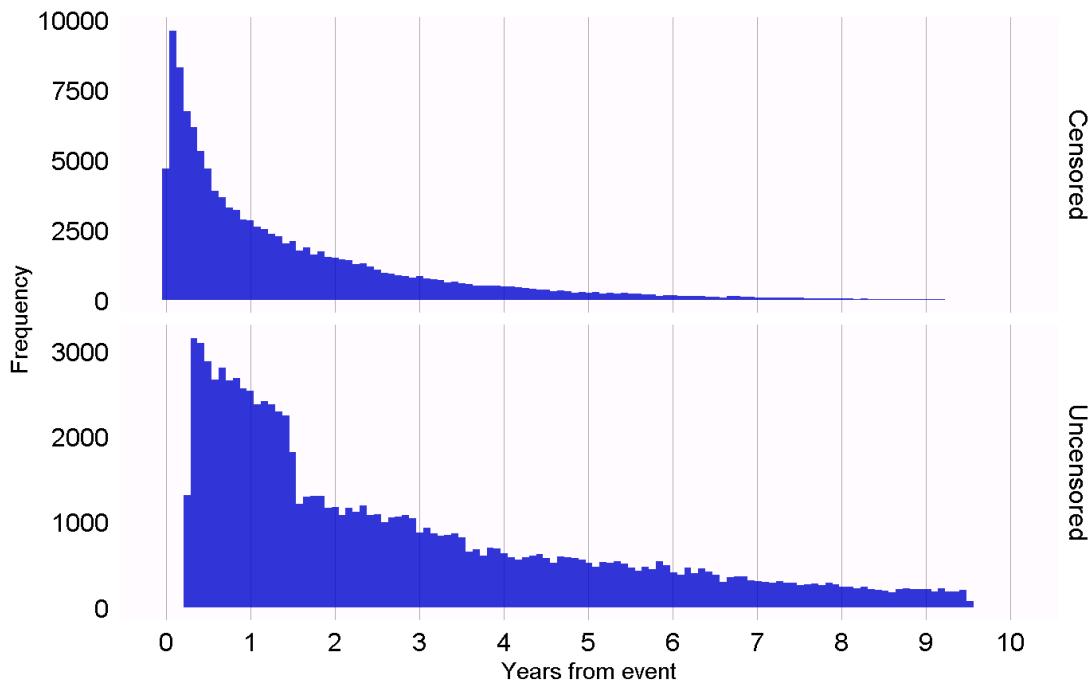


Figure 19.1: Time to observation end for those that are censored, and those that are uncensored.

- **Propensity model** to identify potential variables that should be excluded from the model.
- **Covariate balance** to evaluate whether propensity score adjustment has made the cohorts comparable (as measured through baseline covariates).
- **Attrition** to observe how many subjects were excluded in the various analysis steps, which may inform on the generalizability of the results to the initial cohorts of interest.
- **Power** to assess whether enough data is available to answer the question.
- **Kaplan Meier curve** to asses typical time to onset, and whether the proportionality assumption underlying Cox models is met.

Other study designs require different diagnostics to test the different assumptions in those designs. For example, for the self-controlled case series (SCCS) design we may check the necessary assumption 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 19.1, which shows histograms of the time to observation period end for those that are censored, and those that are 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 19.1 we see only minor differences between the two distributions, suggesting our assumptions holds.

19.2 Diagnostics for all estimation

Next to the design-specific diagnostics, there are also several diagnostics that are applicable across all causal effect estimation methods. Many of these rely on the use of control hypotheses, research questions where the answer is already known. Using control hypotheses 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 controls

Negative controls are exposure-outcome pairs where one believes no causal effect exists, and it includes negative controls or “falsification endpoints” (Prasad and Jena, 2013) that have 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”). Our negative controls should further meet these criteria:

- The exposure **should not cause** the outcome. One way to think of causation is to think of the counterfactual: could the outcome be caused (or prevented) if a patient was not exposed, compared to if the patient had been exposed? Sometimes this is clear, for example ACEi are known to cause angioedema. Other times this is far less obvious. For example, a drug that may cause hypertension can therefore indirectly cause cardiovascular diseases that are a consequence of the hypertension.
- The exposure should also **not prevent or treat** the outcome. This is just another causal relationship that should be absent if we are to believe the true effect size (e.g. the hazard ratio) is 1.
- The negative control should **exist in the data**, ideally with sufficient numbers. We try to achieve this by prioritizing candidate negative controls based on prevalence.
- Negative controls should ideally be **independent**. For example, we should avoid having negative controls that are either ancestors of each other (e.g. “ingrown nail” and “ingrown nail of foot”) or siblings (e.g. “fracture of left femur” and “fracture of right femur”).
- Negative controls should ideally have **some potential for bias**. For example, the last digit of someone’s social security number is basically a random number, and is unlikely to show confounding. It should therefore not be used as a negative control.

Some argue that negative controls should also have the same confounding structure as the exposure-outcome pair of interest. (Lipsitch et al., 2010) However, we believe this confounding structure is unknowable; the relationships between variables found in reality is often far more complex than people imagine. Also, even if the confounder structure was known, it is unlikely that a negative

control exists having that exact same confounding structure, but lacking the direct causal effect. For this reason in OHDSI we rely on a large number of negative controls, assuming that such a set represents many different types of bias, including the ones present in the hypothesis of interest.

The absence of a causal relationship between an exposure and an outcome is rarely documented. Instead, we often make the assumption that a lack of evidence of a relationship implies the lack of a relationship. This assumption is more likely to hold if the exposure and outcome have both been studied extensively, so a relationship could have been detected. For example, the lack of evidence for a completely novel drug likely implies a lack of knowledge, not the lack of a relationship. With this principle in mind 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 negative controls. This list must then undergo manual review, not only to verify that the automated extraction was accurate, but also to impose additional criteria such as biological plausibility.

19.2.2 Positive controls

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., 2018a) created by modifying a negative control through injection of additional, simulated occurrences of the outcome during the time at risk of the exposure. For example, assume that, during exposure to ACEi, n occurrences of our negative control outcome “ingrowing nail” were observed. If we now add an additional n simulated occurrences during exposure, we have doubled the risk. Since this was a negative control, the relative risk compared to the counterfactual was one, but after injection, it becomes two.

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, for each outcome we train a model to predict the survival rate with respect to the outcome during exposure using covariates captured prior to exposure. These covariates include demographics, as well as all recorded diagnoses, drug exposures, measurements, and medical procedures. An L1-regularized Poisson regression (Suchard et al., 2013) using 10-fold cross-validation to select the regularization hyperparameter fits the prediction model. We then use the predicted rates to sample simulated outcomes during exposure to increase the true effect size to the desired magnitude. The resulting positive control thus contains both real and simulated outcomes.

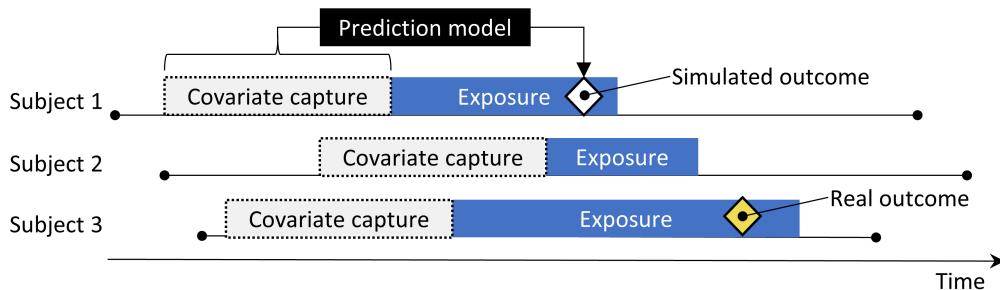


Figure 19.2: Synthesizing positive controls from negative controls.

Figure 19.2 depicts this process. Note that although this procedure simulates several important sources of bias, it does not capture all. For example, some effects of measurement error are not present. The synthetic positive controls imply constant positive predictive value and sensitivity, which may not be true in reality.

Although we refer to a single true “effect size” for each control, different methods estimate different statistics of the treatment effect. For negative controls, where we believe no causal effect exists, all such statistics, including the relative risk, hazard ratio, odds ratio, incidence rate ratio, both conditional and marginal, as well as the average treatment effect in the treated (ATT) and the overall average treatment effect (ATE) will be identical to 1. Our process for creating positive controls synthesizes outcomes with a constant incidence rate ratio over time and between patients, using a model conditioned on the patient where this ratio is held constant, up to the point where the marginal effect is achieved. The true effect size is thus guaranteed to hold as the marginal incidence rate ratio in the treated. Under the assumption that our outcome model used during synthesis is correct, this also holds for the conditional effect size and the ATE. Since all outcomes are rare, odds ratios are all but identical to the relative risk.

19.2.3 Empirical evaluation

Based on the estimates of a particular method for the negative and positive controls, we can then understand the operating characteristics 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 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 1 and type 2 error, or if we are willing to modify our α threshold, we may inspect the AUC instead.

19.2.4 P-value calibration

Often the type 1 error (at $\alpha = 0.05$) is larger than 5%. In other words, we are often more likely than 5% to reject the null hypothesis when in fact the null hypothesis is true. The reason is that the p-value only reflects random error, the error due to having a limited sample size. It does not reflect systematic error, for example the error due to confounding. OHDSI has developed a process for calibrating p-values to restore the type 1 error to nominal. (Schuemie et al., 2014) We derive an empirical null distribution from the actual effect estimates for the negative controls. These negative control estimates give us an indication of what can be expected when the null hypothesis is true, and we use them to estimate an empirical null distribution.

Formally, we fit a Gaussian probability distribution to the estimates, taking into account the sampling error of each estimate. Let $\hat{\theta}_i$ denote the estimated log effect estimate (relative risk, odds or incidence rate ratio) from the i th negative control drug–outcome pair, and let $\hat{\tau}_i$ denote the corresponding estimated standard error, $i = 1, \dots, n$. Let θ_i denote the true log effect size (assumed 0 for negative controls), and let β_i denote the true (but unknown) bias associated with pair i , that is, the difference between the log of the true effect size and the log of the estimate that the study would have returned for control i had it been infinitely large. As in the standard p-value computation, we assume that $\hat{\theta}_i$ is normally distributed with mean $\theta_i + \beta_i$ and standard deviation $\hat{\tau}_i^2$. Note that in traditional p-value calculation, β_i is always assumed to be equal to zero, but that we assume the β_i 's arise from a normal distribution with mean μ and variance σ^2 . This represents the null (bias) distribution. We estimate μ and σ^2 via maximum likelihood. In summary, we assume the following:

$$\beta_i \sim N(\mu, \sigma^2) \text{ and } \hat{\theta}_i \sim N(\theta_i + \beta_i, \hat{\tau}_i^2)$$

where $N(a, b)$ denotes a Gaussian distribution with mean a and variance b , and estimate μ and σ^2 by maximizing the following likelihood:

$$L(\mu, \sigma | \theta, \tau) \propto \prod_{i=1}^n \int p(\hat{\theta}_i | \beta_i, \theta_i, \hat{\tau}_i) p(\beta_i | \mu, \sigma) d\beta_i$$

yielding maximum likelihood estimates $\hat{\mu}$ and $\hat{\sigma}$. We compute a calibrated p-value that uses the empirical null distribution. Let $\hat{\theta}_{n+1}$ denote the log of the effect estimate from a new drug–outcome pair, and let $\hat{\tau}_{n+1}$ denote the corresponding estimated standard error. From the aforementioned assumptions and assuming β_{n+1} arises from the same null distribution, we have the following:

$$\hat{\theta}_{n+1} \sim N(\hat{\mu}, \hat{\sigma} + \hat{\tau}_{n+1})$$

When $\hat{\theta}_{n+1}$ is smaller than $\hat{\mu}$, the one-sided calibrated p-value for the new pair is then

$$\phi\left(\frac{\theta_{n+1} - \hat{\mu}}{\sqrt{\hat{\sigma}^2 + \hat{\tau}_{n+1}^2}}\right)$$

where $\phi(\cdot)$ denotes the cumulative distribution function of the standard normal distribution. When $\hat{\theta}_{n+1}$ is bigger than $\hat{\mu}$, the one-sided calibrated p-value is then

$$1 - \phi\left(\frac{\theta_{n+1} - \hat{\mu}}{\sqrt{\hat{\sigma}^2 + \hat{\tau}_{n+1}^2}}\right)$$

19.2.5 Confidence interval calibration

Similarly, we typically observe that the coverage of the 95% confidence interval is less than 95%: the true effect size is inside the 95% confidence interval less than 95% of the time. For confidence interval calibration (Schuemie et al., 2018a) we extend the framework for p-value calibration by also making use of our positive controls. 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.

Formally, we assume that β_i , the bias associated with pair i , again comes from a Gaussian distribution, but this time using a mean and standard deviation that are linearly related to θ_i , the true effect size:

$$\beta_i \sim N(\mu(\theta_i), \sigma^2(\theta_i))$$

where

$$\mu(\theta_i) = a + b \times \theta_i \text{ and } \sigma(\theta_i)^2 = c + d \times |\theta_i|$$

We estimate a , b , c and d by maximizing the marginalized likelihood in which we integrate out the unobserved β_i :

$$l(a, b, c, d | \theta, \hat{\theta}, \hat{\tau}) \propto \prod_{i=1}^n \int p(\hat{\theta}_i | \beta_i, \theta_i, \hat{\tau}_i) p(\beta_i | a, b, c, d, \theta_i) d\beta_i,$$

yielding maximum likelihood estimates $(\hat{a}, \hat{b}, \hat{c}, \hat{d})$.

We compute a calibrated CI that uses the systematic error model. Let $\hat{\theta}_{n+1}$ again denote the log of the effect estimate for a new outcome of interest, and let $\hat{\tau}_{n+1}$ denote the corresponding estimated standard error. From the assumptions above, and assuming β_{n+1} arises from the same systematic error model, we have:

$$\hat{\theta}_{n+1} \sim N(\theta_{n+1} + \hat{a} + \hat{b} \times \theta_{n+1}, \hat{c} + \hat{d} \times |\theta_{n+1}|) + \hat{\tau}_{n+1}^2).$$

We find the lower bound of the calibrated 95% CI by solving this equation for θ_{n+1} :

$$\Phi\left(\frac{\theta_{n+1} + \hat{a} + \hat{b} \times \theta_{n+1} - \hat{\theta}_{n+1}}{\sqrt{(\hat{c} + \hat{d} \times |\theta_{n+1}|) + \hat{\tau}_{n+1}^2}}\right) = 0.025,$$

where $\Phi(\cdot)$ denotes the cumulative distribution function of the standard normal distribution. We find the upper bound similarly for probability 0.975. We define the calibrated point estimate by using probability 0.5.

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

19.2.6 Replication across sites

Another form of method validation comes from executing the study across several different databases that represent different populations, different health care systems, and/or 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 that either the effect differs greatly for different populations, or that the design does not adequately address the different biases found in the different databases. In fact, we observe that accounting for residual bias in a database through empirical calibration of confidence intervals can greatly reduce between-study heterogeneity. (Schuemie et al., 2018a)

One way to express between-database heterogeneity is the I^2 score, describing the percentage of total variation across studies that is due to heterogeneity rather than chance. (Higgins et al., 2003) A naive categorization of values for I^2 would not be appropriate for all circumstances, although one could tentatively assign adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%. In a study estimating the effects for many depression treatments using a new-user cohort design with large-scale propensity score adjustment, (Schuemie et al., 2018b) observed only 58% of the estimates to have an I^2 below 25%. After empirical calibration this increased to 83%.



Observing between-database heterogeneity casts doubt on the validity of the estimates. Unfortunately, the inverse is not true. Not observing heterogeneity 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.

19.2.7 Sensitivity analyses

When designing a study there are often design choices that are uncertain. For example, should propensity score matching or 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 defines sensitivity analysis to “appraise how the conclusions of a study might be altered by hidden biases of various magnitudes.”

19.3 Method validation in practice

Here we build on the example in Chapter 13, where we investigate the effect of ACE inhibitors (ACEi) on the risk of angioedema and acute myocardial infarction (AMI), compared to thiazides and thiazide-like diuretics (THZ). In that chapter we already explore many of the diagnostics specific to the design we used, the cohort method. Here, we apply additional diagnostics that could also have been applied had other designs been used. If the study is implemented using ATLAS as described in Section 13.7 these diagnostics are available in the Shiny app that is included in the study R package generated by ATLAS. If the study is implemented using R instead, as described in Section 13.8, then R functions available in the various packages should be used, as described in the next sections.

19.3.1 Selecting negative controls

We must select negative controls, exposure-outcome pairs where no causal effect is believed to exist. For comparative effect estimation such as our example study, we select negative control outcomes that are believed to be neither caused by the target nor the comparator exposure. We want enough negative controls to make sure we have a diverse mix of biases represented in the controls, and also to allow empirical calibration. As a rule-of-thumb we typically aim to have 50-100 such negative controls. We could come up with these controls completely manually, but fortunately ATLAS provides features to aid the selection of negative controls using data from literature, product labels, and spontaneous reports.

To generate a candidate list of negative controls, we first must create a concept set containing all exposures of interest. In this case we select all ingredients in the ACEi and THZ classes, as shown in Figure 19.3.

Next, we go to the “Explore Evidence” tab, and click on the  **Generate** button. Generating the evidence overview will take a few minutes, after which you can click on the  **View Evidence** button. This will open the list of outcomes as shown in Figure 19.4.

This list shows condition concepts, along with an overview of the evidence linking the condition to any of the exposures we defined. For example, we see the number of publications that link the exposures to the outcomes found in PubMed using various strategies, the number of product labels

ACEi and THZ combined									Optimize							
Concept Set Expression		Included Concepts 14		Included Source Codes		Explore Evidence		Export	Compare							
Show 25 ▾ entries Search: <input type="text"/>																
Showing 1 to 14 of 14 entries Previous 1 Next																
▼	Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	<input type="checkbox"/> Exclude	<input checked="" type="checkbox"/> Descendants	<input checked="" type="checkbox"/> Mapped								
	1342439	38454	trandolapril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>								
	1334456	35296	Ramipril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>								
	1331235	35208	quinapril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>								
	1373225	54552	Perindopril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>								
	1310756	30131	moexipril	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>								

Figure 19.3: A concept set containing the concepts defining the target and comparator exposures.

Evidence for all conditions for ACEi and THZ combined										
Save New Concept Set From Selection Below			View database record counts (RC) and descendant record counts (DRC) for: SYNPUF 5% ▾							
						Show 15 ▾ entries	Filter: <input type="text"/>			
Showing 1 to 15 of 13,787 entries Previous 1 2 3 4 5 ... 920 Next										
▼ Suggested Negative Control	Name	Suggested Negative Control	Sort Order	Publication Count (Descendant Concept Match)	Publication Count (Exact Concept Match)	Publication Count (Parent Concept Match)	Product Label Count (Descendant Concept Match)	Product Label (Exact Concept Match)	Product Label (Parent Concept Match)	
No (12777) Yes (1010)	Rift valley fever	Y	13,781	0	0	0	0	0	0	
▼ Found in Publications	Obstruction due to foreign body accidentally left in operative wound AND/OR body cavity during a procedure	Y	13,780	0	0	0	0	0	0	
▼ Found on Product Label	Infection by Shigella	Y	13,766	0	0	0	0	0	0	
▼ Found in Product Label Or Publications										
No (10951) Yes (Parent) (1949)										
▼ Signal in FAERS										

Figure 19.4: Candidate control outcomes with an overview of the evidence found in literature, product labels, and spontaneous reports.

of our exposures of interest that list the condition as a possible adverse effect, and the number of spontaneous reports. By default the list is sorted to show candidate negative controls first. It is then sorted by the “Sort Order,” which represents the prevalence of the condition in a collection of observational databases. The higher the Sort Order, the higher the prevalence. Although the prevalence in these databases might not correspond with the prevalence in the database we wish to run the study, it is likely a good approximation.

The next step is to manually review the candidate list, typically starting at the top, so with the most prevalent condition, and working our way down until we are satisfied we have enough. One typical way to do this is to export the list to a CSV (comma separated values) file, and have clinicians review these, considering the criteria mentioned in Section 19.2.1.

For our example study we select the 76 negative controls listed in Appendix C.1.

19.3.2 Including controls

Once we have defined our set of negative controls we must include them in our study. First we must define some logic for turning our negative control condition concepts into outcome cohorts. Section 13.7.3 discusses how ATLAS allows creating such cohorts based on a few choices the user must make. Often we simply choose to create a cohort based on any occurrence of a negative control concept or any of its descendants. If the study is implemented in R, then SQL (Structured Query Language) can be used to construct the negative control cohorts. Chapter 10 describes how cohorts can be created using SQL and R. We leave it as an exercise for the reader to write the appropriate SQL and R.

The OHDSI tools also provide functionality for automatically generating and including positive controls derived from the negative controls. This functionality can be found in the Evaluation Settings section in ATLAS described in Section 13.7.3, and it is implemented in the `injectSignals` function in the `MethodEvaluation` package. Here we generate three positive controls for each negative control, with true effect sizes of 1.5, 2, and 4, using a survival model:

```
library(MethodEvaluation)
# Create a data frame with all negative control exposure-
# outcome pairs, using only the target exposure (ACEi = 1).
eoPairs <- data.frame(exposureId = 1,
                      outcomeId = ncs)

pcs <- injectSignals(connectionDetails = connectionDetails,
                      cdmDatabaseSchema = cdmDbSchema,
                      exposureDatabaseSchema = cohortDbSchema,
                      exposureTable = cohortTable,
                      outcomeDatabaseSchema = cohortDbSchema,
                      outcomeTable = cohortTable,
                      outputDatabaseSchema = cohortDbSchema,
                      outputTable = cohortTable,
                      createOutputTable = FALSE,
                      modelType = "survival",
                      firstExposureOnly = TRUE,
```

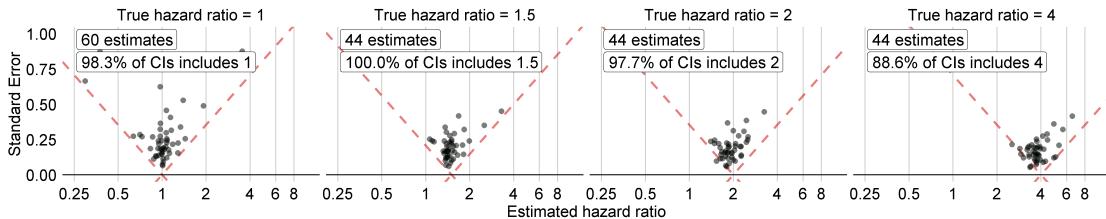


Figure 19.5: Estimates for the negative (true hazard ratio = 1) and positive controls (true hazard ratio > 1). Each dot represents a control. Estimates below the dashed line have a confidence interval that doesn't include the true effect size.

```
firstOutcomeOnly = TRUE,
removePeopleWithPriorOutcomes = TRUE,
washoutPeriod = 365,
riskWindowStart = 1,
riskWindowEnd = 0,
addExposureDaysToEnd = TRUE,
exposureOutcomePairs = eoPairs,
effectSizes = c(1.5, 2, 4),
cdmVersion = cdmVersion,
workFolder = file.path(outputFolder,
                        "pcSynthesis"))
```

Note that we must mimic the time-at-risk settings used in our estimation study design. The `injectSignals` function will extract information about the exposures and negative control outcomes, fit outcome models per exposure-outcome pair, and synthesize outcomes. The positive control outcome cohorts will be added to the cohort table specified by `cohortDbSchema` and `cohortTable`. The resulting `pcs` data frame contains the information on the synthesized positive controls.

Next we must execute the same study used to estimate the effect of interest to also estimate effects for the negative and positive controls. Setting the set of negative controls in the comparisons dialog in ATLAS instructs ATLAS to compute estimates for these controls. Similarly, specifying that positive controls be generated in the Evaluation Settings includes these in our analysis. In R, the negative and positive controls should be treated as any other outcome. All estimation packages in the OHDSI Methods Library readily allow estimation of many effects in an efficient manner.

19.3.3 Empirical performance

Figure 19.5 shows the estimated effect sizes for the negative and positive controls included in our example study, stratified by true effect size. This plot is included in the Shiny app that comes with the study R package generated by ATLAS, and can be generated using the `plotControls` function in the `MethodEvaluation` package. Note that the number of controls is often lower than what was defined because there was not enough data to either produce an estimate or to synthesize a positive control.

Based on these estimates we can compute the metrics shown in Table 19.1 using the `computeMetrics` function in the `MethodEvaluation` package.

Table 19.1: Method performance metrics derived from the negative and positive control estimates.

Metric	Value
AUC	0.96
Coverage	0.97
Mean Precision	19.33
MSE	2.08
Type 1 error	0.00
Type 2 error	0.18
Non-estimable	0.08

We see that coverage and type 1 error are very close to their nominal values of 95% and 5%, respectively, and that the AUC is very high. This is certainly not always the case.

Note that although in Figure 19.5 not all confidence intervals include one when the true hazard ratio is one, the type 1 error in Table 19.1 is 0%. This is an exceptional situation, caused by the fact that confidence intervals in the `Cyclops` package are estimated using likelihood profiling, which is more accurate than traditional methods but can result in asymmetric confidence intervals. The p-value instead is computed assuming symmetrical confidence intervals, and this is what was used to compute the type 1 error.

19.3.4 P-value calibration

We can use the estimates for our negative controls to calibrate our p-values. This is done automatically in the Shiny app, and can be done manually in R. Assuming we have created the summary object `summ` as described in Section 13.8.6, we can plot the empirical calibration effect plot:

```
# Estimates for negative controls (ncs) and outcomes of interest (ois):
ncEstimates <- summ[summ$outcomeId %in% ncs, ]
oiEstimates <- summ[summ$outcomeId %in% ois, ]

library(EmpiricalCalibration)
plotCalibrationEffect(logRrNegatives = ncEstimates$logRr,
                      seLogRrNegatives = ncEstimates$seLogRr,
                      logRrPositives = oiEstimates$logRr,
                      seLogRrPositives = oiEstimates$seLogRr,
                      showCis = TRUE)
```

In Figure 19.6 we see that the orange area almost exactly overlaps with the area denoted by the dashed lines, indicating hardly any bias was observed for the negative controls. One of the outcomes of interest (AMI) is above the dashed line and the orange area, indicating we cannot reject the null

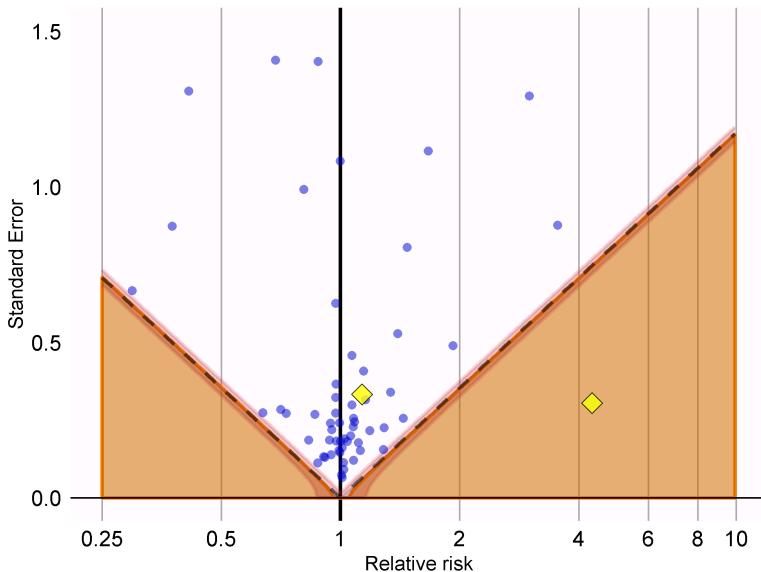


Figure 19.6: P-value calibration: estimates below the dashed line have a conventional $p < 0.05$. Estimates in the orange area have calibrated $p < 0.05$. The pink area denotes the 95% credible interval around the edge of the orange area. Blue dots indicate negative controls. Yellow diamonds indicate outcomes of interest.

according to both the uncalibrated and calibrated p-value. The other outcome (angioedema) clearly stands out from the negative control, and falls well within the area where both uncalibrated and calibrated p-values are smaller than 0.05.

We can compute the calibrated p-values:

```
null <- fitNull(logRr = ncEstimates$logRr,
                 seLogRr = ncEstimates$seLogRr)
calibrateP(null,
            logRr= oiEstimates$logRr,
            seLogRr = oiEstimates$seLogRr)
```

```
## [1] 1.604351e-06 7.159506e-01
```

And contrast these with the uncalibrated p-values:

```
oiEstimates$p
```

```
## [1] [1] 1.483652e-06 7.052822e-01
```

As expected, because little to no bias was observed, the uncalibrated and calibrated p-values are very similar.

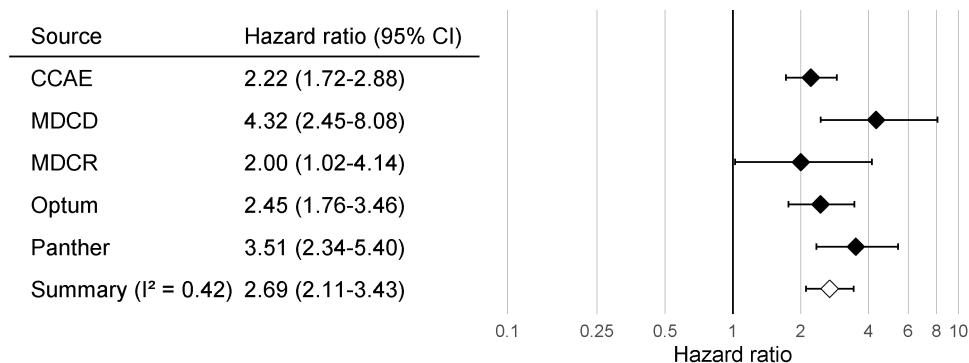


Figure 19.7: Effect size estimates and 95% confidence intervals (CI) from five different databases and a meta-analytic estimate when comparing ACE inhibitors to thiazides and thiazide-like diuretics for the risk of angioedema.

19.3.5 Confidence interval calibration

Similarly, we can use the estimates for our negative and positive controls to calibrate the confidence intervals. The Shiny app automatically reports the calibrated confidence intervals. In R we can calibrate intervals using the `fitSystematicModelError` and `calibrateConfidenceInterval` functions in the `EmpiricalCalibration` package, as described in detail in the “Empirical calibration of confidence intervals” vignette.

Before calibration, the estimated hazard ratios (95% confidence interval) are 4.32 (2.45 - 8.08) and 1.13 (0.59 - 2.18), for angioedema and AMI respectively. The calibrated hazard ratios are 4.75 (2.52 - 9.04) and 1.15 (0.58 - 2.30).

19.3.6 Between-database heterogeneity

Just as we executed our analysis on one database, in this case the IBM MarketScan Medicaid (MDCD) database, we can also run the same analysis code on other databases that adhere to the Common Data Model (CDM). Figure 19.7 shows the forest plot and meta-analytic estimates (assuming random effects) (DerSimonian and Laird, 1986) across a total of five databases for the outcome of angioedema. This figure was generated using the `plotMetaAnalysisForest` function in the `EvidenceSynthesis` package.

Although all confidence intervals are above one, suggesting agreement on the fact that there is an effect, the I^2 suggests between-database heterogeneity. However, if we compute the I^2 using the calibrated confidence intervals as shown in Figure 19.8, we see that this heterogeneity can be explained by the bias measured in each database through the negative and positive controls. The empirical calibration appears to properly take this bias into account.

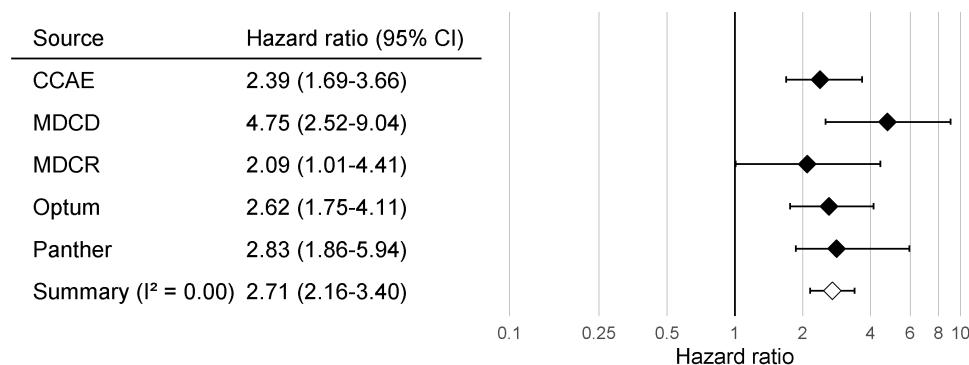


Figure 19.8: Calibrated Effect size estimates and 95% confidence intervals (CI) from five different databases and a meta-analytic estimate for the hazard ratio of angioedema when comparing ACE inhibitors to thiazides and thiazide-like diuretics.

19.3.7 Sensitivity analyses

One of the design choices in our analysis was to use variable-ratio matching on the propensity score. However, we could have also used stratification on the propensity score. Because we are uncertain about this choice, we may decide to use both. Table 19.2 shows the effect size estimates for AMI and angioedema, both calibrated and uncalibrated, when using variable-ratio matching and stratification (with 10 equally-sized strata).

Table 19.2: Uncalibrated and calibrated hazard ratios (95% confidence interval) for the two analysis variants.

Outcome	Adjustment	Uncalibrated	Calibrated
Angioedema	Matching	4.32 (2.45 - 8.08)	4.75 (2.52 - 9.04)
Angioedema	Stratification	4.57 (3.00 - 7.19)	4.52 (2.85 - 7.19)
Acute myocardial infarction	Matching	1.13 (0.59 - 2.18)	1.15 (0.58 - 2.30)
Acute myocardial infarction	Stratification	1.43 (1.02 - 2.06)	1.45 (1.03 - 2.06)

We see that the estimates from the matched and stratified analysis are in strong agreement, with the confidence intervals for stratification falling completely inside of the confidence intervals for matching. This suggests that our uncertainty around this design choice does not impact the validity of our estimates. Stratification does appear to give us more power (narrower confidence intervals), which is not surprising since matching results in loss of data, whereas stratification does not. The price for this could be an increase in bias, due to within-strata residual confounding, although we see no evidence of increased bias reflected in the calibrated confidence intervals.



Study diagnostics allow us to evaluate design choices even before fully executing a study. It is recommended not to finalize the protocol before generating and reviewing all study diagnostics. To avoid p-hacking (adjusting the design to achieve a desired result), this should be done while blinded to the effect size estimate of interest.

19.4 OHDSI Methods Benchmark

Although the recommended practice is to empirically evaluate a method’s performance within the context that it is applied, using negative and positive controls that are in ways similar to the exposures-outcomes pairs of interest (for example using the same exposure or the same outcome) and on the database used in the study, there is also value in evaluating a method’s performance in general. This is why the OHDSI Methods Evaluation Benchmark was developed. The benchmark evaluates performance using a wide range of control questions, including those with chronic or acute outcomes, and long-term or short-term exposures. The results on this benchmark can help demonstrate the overall usefulness of a method, and can be used to form a prior belief about the performance of a method when a context-specific empirical evaluation is not (yet) available. The benchmark consists of 200 carefully selected negative controls that can be stratified into eight categories, with the controls in each category either sharing the same exposure or the same outcome. From these 200 negative controls, 600 synthetic positive controls are derived as described in Section 19.2.2. To evaluate a method, it must be used to produce effect size estimates for all controls, after which the metrics described in Section 19.2.3 can be computed. The benchmark is publicly available, and can be deployed as described in the Running the OHDSI Methods Benchmark vignette in the MethodEvaluation package.

We have run all the methods in the OHDSI Methods Library through this benchmark, with various analysis choices per method. For example, the cohort method was evaluated using propensity score matching, stratification, and weighting. This experiment was executed on four large observational healthcare databases. The results, viewable in an online Shiny app¹, show that although several methods show high AUC (the ability to distinguish positive controls from negative controls), most methods in most settings demonstrate high type 1 error and low coverage of the 95% confidence interval, as shown in Figure 19.9.

This emphasizes the need for empirical evaluation and calibration: if no empirical evaluation is performed, which is true for almost all published observational studies, we must assume a prior informed by the results in Figure 19.9, and conclude that it is likely that the true effect size is not contained in the 95% confidence interval!

Our evaluation of the designs in the Methods Library also shows that empirical calibration restores type 1 error and coverage to their nominal values, although often at the cost of increasing type 2 error and decreasing precision.

19.5 Summary



- A method’s validity depends on whether the assumptions underlying the method are met.
- Where possible, these assumptions should be empirically tested using study diagnostics.
- Control hypotheses, questions where the answer is known, should be used to evaluate whether a specific study design produces answers in line with the truth.

¹<http://data.ohdsi.org/MethodEvalViewer/>



Figure 19.9: Coverage of the 95% confidence interval for the methods in the Methods Library. Each dot represents the performance of a specific set of analysis choices. The dashed line indicates nominal performance (95% coverage). SCCS = Self-Controlled Case Series, GI = Gastrointestinal, IBD = inflammatory bowel disease.

- Often, p-values and confidence intervals do not demonstrate nominal characteristics as measured using control hypotheses.
- These characteristics can often be restored to nominal using empirical calibration.
- Study diagnostics can be used to guide analytic design choices and adapt the protocol, as long as the researcher remains blinded to the effect of interest to avoid p-hacking.

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

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The mission of OHDSI is to generate high-quality evidence through observational research. A primary way this is accomplished is through collaborative research studies. In prior chapters we discussed how the OHDSI community has authored standards and tools to facilitate high-quality, reproducible research, including Standardized Vocabularies , the Common Data Model (CDM) , analytical methods packages, ATLAS and the study steps (Chapter20) to run a retrospective database study. OHDSI Network Studies represent the culmination of a transparent, consistent and reproducible way to conduct research across a large number of geographically dispersed data. In this chapter we will discuss what constitutes an OHDSI network study, how to run a network study and discuss enabling technologies such as the ARACHNE Research Network.

21.1 What is the OHDSI Research Network?

The OHDSI Research Network is an international collaboration of researchers seeking to advance observational data research in healthcare. Today, the network consists of over 1.2 billion patient records (~650 million de-duplicated patient records) in the OMOP CDM. This includes more than 200 researchers and 82 observational health databases across 17 countries with regional central co-ordinating centers housed at Columbia University (USA), Erasmus Medical Center (Europe) and Ajou University (South Korea). The OHDSI community continues to grow rapidly across Europe (in collaboration with the IMI EHDEN project), Central America (e.g. Argentina, Brazil, Colombia), and Asia (e.g. China, Japan, Singapore).

OHDSI is open network, inviting healthcare institutions across the globe with active patient data to join the network and convert data to the OMOP CDM. As OMOP data conversions are complete, collaborators are invited to report site information in the Data Network census maintained by the OHDSI Program Manager (beaton@ohdsi.org). Each OHDSI network site participates voluntarily. There are no hard obligations. Each site opts-in to each respective network study. In each study, data remains at the site behind a firewall. No data pooling across network sites. Only aggregate results are shared.



Benefits of Joining the OHDSI Network Unlock the power of institutional data: Transforming institutional EHR data in the OMOP Common Data Model enables clinical research on populations of your patients, something EHR systems don't support. Access to free tools: OHDSI publishes free, open source tools for data characterization and analytics (e.g. browsing the clinical concepts, defining and characterizing cohorts, running Population-Level Estimation and Patient-Level Prediction studies). Participate in a premier research community: Author and publish network research, gain access to eminent leaders in global real-world evidence community. Buildout Quality Benchmarks: Network can validate quality improvement benchmarks against other institutions (e.g. On average how long does it take to get an appendectomy discharged?)

21.2 What is an OHDSI Network Study?

In the study steps chapter (Chapter 20), we discussed the steps to execute a retrospective database study using the OMOP CDM. A study may be conducted on a single OMOP CDM or on multiple OMOP CDMs. It can be conducted within a single institution's OMOP CDM data or across many institutions. There is no requirement that an OHDSI research study package be shared across the entire OMOP network. In fact, there may be legitimate instances when a study protocol is written for specific clinical practice that cannot be generalized to the entirety of the network. The principal investigator of each OHDSI research study will determine which, if any, sites they would like to include in an analysis.



When is a study considered a network study? An OHDSI research project becomes a network study when it is published and shared for execution across the OHDSI community.

Elements of a Network Study:

- Must have a protocol (a description of the analysis to be performed)
- Must have a study code package designed for the OMOP CDM
- Must be executed across two or more network sites (not just 2 or more databases at a single site)
- Encouraged to publish all documentation on GitHub
- At the end of the analysis, the results are made available in Github or other public repository (e.g. a Shiny Application)

21.3 Executing an OHDSI Network Study

Conducting an OHDSI Network Study requires a substantial amount of preparation to ensure success.

"You'll never walk alone in your OHDSI journey." - Peter Rijnbeek



New to Network Studies? The OHDSI Study Nurture Committee is a resource for you as you navigate your journey. This committee helps train and guide researchers to complete OHDSI Studies including how to effectively use OHDSI tools, providing guidance to the OHDSI study

design for increase reproducibility and reliability and assisting with helping study investigators recruit data partners to run study packages.

Running an OHDSI Network Study has three distinct stages:

- Study Feasibility and Design
- Study Execution
- Results Dissemination and Publication

21.3.1 Study Feasibility and Design

The study feasibility stage (*pre-study stage*) is focused on supporting a definition of a study and a creation of the study protocol, *e.g. undertaking activities to make sure the study is feasible to be executed as described in the formal protocol.*

The feasibility stage does not have a well-defined process but rather is driven by various supporting activities, including identification and enrollment of relevant databases that contain the targeted patient population with required drug exposure, procedure information, condition or demographics information through data characterization, validating and agreeing on target analytical methods and algorithms. These activities may involve sharing JSON files of cohort definitions from ATLAS and provisional test of study R packages. A study lead may have enough data to do this inside their own organization or may opt for support from other OHDSI network sites.

The outcome of the feasibility stage is generation of a final protocol as well as a list of target collaborators. The formal protocol will detail the study team, including the designated study lead (often the corresponding author for publication purposes), and information on the timeline for the study. The protocol is a critical component for additional network sites to review, approve and execute the study package on their OMOP CDM data. A protocol must include information on study population, the methods being used, how the results will be stored and analyzed as well as how the study results will be disseminated after completion (*e.g. a publication, a poster, etc.*)

21.3.2 Study Execution

After completing feasibility, a study advances to the execution phase. The key activities in executing a network study include the following:

- The study lead formally initiates a new OHDSI network study with the OHDSI Coordinating Center. *In tandem, this may include undertaking other organization-specific processes to approve an OHDSI study.*
- The study lead publishes the study protocol to the OHDSI GitHub.
- The study lead announces the study on the OHDSI Community Call and OHDSI Forum, inviting participating centers and collaborators.
- Study participating organizations assemble teams within each site, assign study roles (*e.g. data analyst(s)* executing the study package, site leadership reviewing the study design and manuscript).

- The data scientist/statisticians for the study lead will use a study protocol to design study analyses and generate study code.
- The data scientist/statisticians will conduct a feasibility test of study code within their own environment. The package will be shared to 1-2 network sites for additional validation.
- The data scientist/statistician will publish the validated study code in the OHDSI GitHub for execution at participating sites.
- Site data scientists/statisticians access the OHDSI study package and generate results in the standardized format following OHDSI guidelines. Each participating site will follow internal institutional processes regarding data sharing rules. **Sites should not share results unless approval is obtained from IRB or other institutional approval processes.**
- Data scientist/statisticians and Study Lead collect and review the analysis execution results.
- Iterate steps 5-7, if reasonable adjustments required.
- Collaboratively finalize study results. Study lead disseminates study results (e.g. a Shiny Application).
- Study lead formally closes the study out with OHDSI Coordinating Center.

While OHDSI processes can be executed rapidly, it is advised to allow for a few weeks to months for all participating sites to execute the study and receive appropriate approvals to publish results. A study leads should set study milestones and anticipated closure date in advance to assist with managing the overall study timeline.

21.3.3 Results Dissemination and Publication

During this stage, the study lead will collaborate with other sites on various administrative tasks, such as manuscript development and optimizing data visualizations.



Not sure where to publish your OHDSI network study? Consult JANE (Journal/Author Name Estimator), a tool which takes your abstract and scans publications for relevance and fit (<http://jane.biosemantics.org/>).

Researchers are also invited to present OHDSI Network Studies on weekly OHDSI community calls and at OHDSI Symposia across the globe.

21.4 Types of Network Studies

The network studies can be of different types - ranging from simple characterization questions to more advanced predictive studies. A large number of studies conducted today are focused on epidemiology and drug efficacy and safety and thus carry different type of characterization analyses such as patient population characterization, incidence rates of certain outcomes/conditions, comparative drug effectiveness comparison, prevalence of disease and similar. However, more and more studies carry predictive nature including the probability of an outcome for a certain type of a patient (personalized medicine).

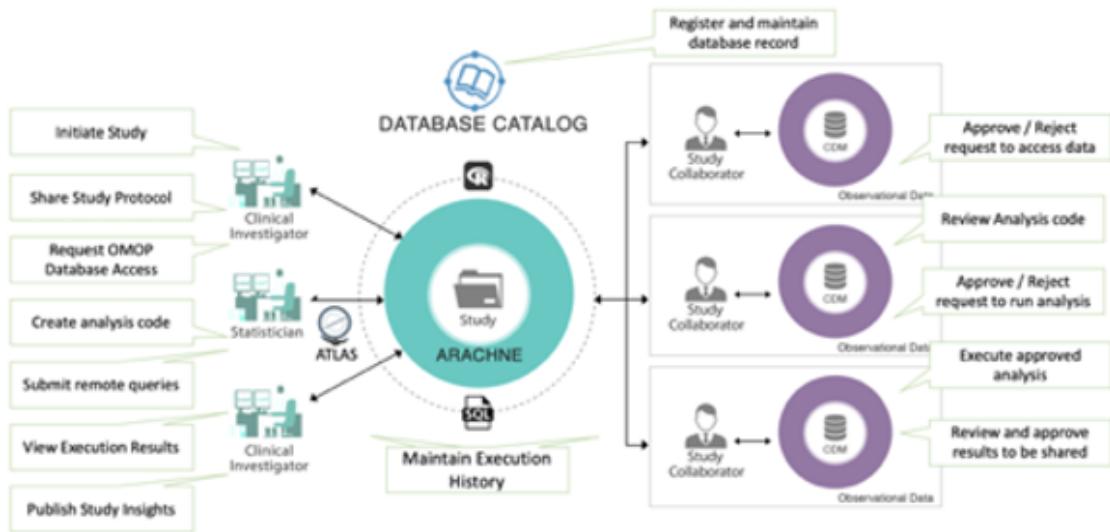


Figure 21.1: The ARACHNE Network Study Process.

21.5 Forward Looking: Using Network Study Automation

The current network study process is manual and rudimentary - with study team members using various mechanisms (including Wiki, GitHub and email) to collaborate on study design, share code and results. This process is not consistent and scalable and to solve that issue, the OHDSI community is actively working to systemize study processes. The ARACHNE Research Network platform is a community-driven solution to streamline and automate the process of network studies.

The ARACHNE Platform includes multiple core components:

- The **ARACHNE Data Catalog** where different network participants register and maintain information about data sets available for network research
- The **Study Workflow Manager** that allows study teams to orchestrate and end to end network study process. The ARACHNE Research Network platform It is taking full advantage of OHDSI standards and establishes a consistent, transparent, secure and compliant observational research process, across multiple organizations. ARACHNE standardizes the communication protocol to access the data and exchange analysis results, while enabling authentication and authorization for restricted content. It brings participating organizations - data providers, investigators, sponsors and data scientists - into a single collaborative study team and facilitates an end-to-end observational study. The tool enables the creation of a complete, standards-based R, Python and SQL execution environment including approval workflows controlled by the data custodian.

ARACHNE is built to provide a seamless integration with other OHDSI tools, including ACHILLES reports and an ability to import ATLAS design artefacts, create self-contained packages and automatically execute those across multiple sites. The future vision is to eventually enable multiple networks to be linked together for the purpose of conducting research not only between organizations within a single network, but also between organizations across multiple networks.



Figure 21.2: The ARACHNE Network of Networks.

21.6 Best Practices for Network Research

There are multiple best practices that study teams should be following while executing the network study:

- Make sure that study questions can be supported by data available. Perform study feasibility to identify the best databases.
- Write code in generic way and parametrize all functions and variables e.g. do not hard database connection, local hard drive path, assume a certain operating system.
- Ensure the target databases have required OMOP CDM version and OMOP Standardized Vocabularies.
- Ensure the target database ETL has followed THEMIS business rules and conventions and correct data was placed into correct CDM tables and fields.
- Do not tweak the study code to get desired results

21.7 Example: LEGEND - Hypertension

To be added.

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.

Parametrized 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

Concept Id	Concept Name	Excluded	Descendants	Mapped
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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 monotherapy

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

Concept Id	Concept Name	Excluded	Descendants	Mapped
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
1353766	Propranolol	NO	YES	NO
1353776	Felodipine	NO	YES	NO
1363053	Doxazosin	NO	YES	NO

Concept Id	Concept Name	Excluded	Descendants	Mapped
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

Concept Id	Concept Name	Excluded	Descendants	Mapped
9203	Emergency Room Visit	NO	YES	NO

B.5 New users of Thiazide-like diuretics monotherapy

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
932745	Bumetanide	NO	YES	NO
942350	torsemide	NO	YES	NO
956874	Furosemide	NO	YES	NO
970250	Spiironolactone	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	ezetimibe	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

Concept Id	Concept Name	Excluded	Descendants	Mapped
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
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.6 Patients initiating first-line therapy for hypertension

Initial Event Cohort

People having any of the following:

- a drug exposure of *First-line hypertension drugs* (Table B.12) for the first time in the person's history

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

Inclusion Rules

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of *Hypertension drugs* (Table B.13) where event starts between all days Before and 1 days Before index start date
- and at least 1 occurrences of a condition occurrence of *Hypertensive disorder* (Table B.14) where event starts between 365 days Before and 0 days After index start date

Limit cohort of initial events to: earliest event per person. Limit qualifying cohort to: earliest event per person.

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy

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

Concept Set Definitions

Table B.12: First-line hypertension drugs

Concept Id	Concept Name	Excluded	Descendants	Mapped
907013	Metolazone	NO	YES	NO
974166	Hydrochlorothiazide	NO	YES	NO
978555	Indapamide	NO	YES	NO
1307863	Verapamil	NO	YES	NO
1308216	Lisinopril	NO	YES	NO
1308842	valsartan	NO	YES	NO
1310756	moexipril	NO	YES	NO
1317640	telmisartan	NO	YES	NO
1318137	Nicardipine	NO	YES	NO
1318853	Nifedipine	NO	YES	NO
1319880	Nisoldipine	NO	YES	NO
1326012	Isradipine	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
1340128	Captopril	NO	YES	NO

Concept Id	Concept Name	Excluded	Descendants	Mapped
1341927	Enalapril	NO	YES	NO
1342439	trandolapril	NO	YES	NO
1346686	eprosartan	NO	YES	NO
1347384	irbesartan	NO	YES	NO
1351557	candesartan	NO	YES	NO
1353776	Felodipine	NO	YES	NO
1363749	Fosinopril	NO	YES	NO
1367500	Losartan	NO	YES	NO
1373225	Perindopril	NO	YES	NO
1395058	Chlorthalidone	NO	YES	NO
40226742	olmesartan	NO	YES	NO
40235485	azilsartan	NO	YES	NO

Table B.13: 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

Concept Id	Concept Name	Excluded	Descendants	Mapped
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
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

Table B.14: Hypertensive disorder

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

B.7 Patients initiating first-line therapy for hypertension with >3 yr follow-up

Same as *cohort definition B.6* but with continuous observation of at least 365 days prior and **1095 days** after event index date

B.8 ACE inhibitor use

Initial Event Cohort

People having any of the following:

- a drug exposure of *ACE inhibitors* (Table B.15)

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.

Limit qualifying cohort to: all events per person.

End Date Strategy

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.15)

- 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.15: 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.9 Angiotensin receptor blocker (ARB) use

Same as *cohort definition B.8* with *Angiotensin Receptor Blockers (ARBs)* (Table B.16) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.16: Angiotensin Receptor Blockers (ARBs)

Concept Id	Concept Name	Excluded	Descendants	Mapped
1308842	valsartan	NO	YES	NO
1317640	telmisartan	NO	YES	NO
1346686	eprosartan	NO	YES	NO
1347384	irbesartan	NO	YES	NO
1351557	candesartan	NO	YES	NO
1367500	Losartan	NO	YES	NO
40226742	olmesartan	NO	YES	NO
40235485	azilsartan	NO	YES	NO

B.10 Thiazide or thiazide-like diuretic use

Same as *cohort definition B.8* with *Thiazide or thiazide-like diuretic* (Table B.17) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.17: 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

B.11 dihydropyridine Calcium Channel Blocker (dCCB) use

Same as *cohort definition B.8* with *dihydropyridine Calcium Channel Blocker (dCCB)* (Table B.18) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.18: Dihydropyridine Calcium channel blockers (dCCB)

Concept Id	Concept Name	Excluded	Descendants	Mapped
1318137	Nicardipine	NO	YES	NO
1318853	Nifedipine	NO	YES	NO
1319880	Nisoldipine	NO	YES	NO
1326012	Isradipine	NO	YES	NO
1332418	Amlodipine	NO	YES	NO
1353776	Felodipine	NO	YES	NO

B.12 non-dihydropyridine Calcium Channel Blocker (ndCCB) use

Same as *cohort definition B.8* with *non-dihydropyridine Calcium channel blockers (ndCCB)* (Table B.19) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.19: non-dihydropyridine Calcium channel blockers (ndCCB)

Concept Id	Concept Name	Excluded	Descendants	Mapped
1307863	Verapamil	NO	YES	NO
1328165	Diltiazem	NO	YES	NO

B.13 beta blocker use

Same as *cohort definition B.8* with *Beta blockers* (Table B.20) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.20: Beta blockers

Concept Id	Concept Name	Excluded	Descendants	Mapped
1307046	Metoprolol	NO	YES	NO
1313200	Nadolol	NO	YES	NO
1314002	Atenolol	NO	YES	NO
1314577	nebivolol	NO	YES	NO
1319998	Acebutolol	NO	YES	NO
1322081	Betaxolol	NO	YES	NO
1327978	Penbutolol	NO	YES	NO
1338005	Bisoprolol	NO	YES	NO
1345858	Pindolol	NO	YES	NO

Concept Id	Concept Name	Excluded	Descendants	Mapped
1346823	carvedilol	NO	YES	NO
1353766	Propranolol	NO	YES	NO
1386957	Labetalol	NO	YES	NO

B.14 Diuretic-loop use

Same as *cohort definition B.8* with *Diuretics - Loop* (Table B.21) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.21: Diuretics - Loop

Concept Id	Concept Name	Excluded	Descendants	Mapped
932745	Bumetanide	NO	YES	NO
942350	torsemide	NO	YES	NO
956874	Furosemide	NO	YES	NO

B.15 Diuretic-potassium sparing use

Same as *cohort definition B.8* with *Diuretics - potassium sparing* (Table B.22) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.22: Diuretics - potassium sparing

Concept Id	Concept Name	Excluded	Descendants	Mapped
904542	Triamterene	NO	YES	NO
991382	Amiloride	NO	YES	NO

B.16 alpha-1 blocker use

Same as *cohort definition B.8* with *Alpha-1 blocker* (Table B.23) in place of *ACE inhibitors* (Table B.15).

Concept Set Definitions

Table B.23: Alpha-1 blocker

Concept Id	Concept Name	Excluded	Descendants	Mapped
1341238	Terazosin	NO	YES	NO
1350489	Prazosin	NO	YES	NO
1363053	Doxazosin	NO	YES	NO

Appendix C

Negative controls

This Appendix contains negative controls used in various chapters of the book.

C.1 ACEi and THZ

Table C.1: Negative control outcomes when comparing ACE inhibitors (ACEi) to thiazides and thiazide-like diuretics (THZ).

Concept ID	Concept Name
434165	Abnormal cervical smear
436409	Abnormal pupil
199192	Abrasions and/or friction burn of trunk without infection
4088290	Absence of breast
4092879	Absent kidney
44783954	Acid reflux
75911	Acquired hallux valgus
137951	Acquired keratoderma
77965	Acquired trigger finger
376707	Acute conjunctivitis
4103640	Amputated foot
73241	Anal and rectal polyp
133655	Burn of forearm
73560	Calcaneal spur
434327	Cannabis abuse
4213540	Cervical somatic dysfunction
140842	Changes in skin texture
81378	Chondromalacia of patella
432303	Cocaine abuse
4201390	Colostomy present
46269889	Complication due to Crohn's disease

Concept ID	Concept Name
134438	Contact dermatitis
78619	Contusion of knee
201606	Crohn's disease
76786	Derangement of knee
4115402	Difficulty sleeping
45757370	Disproportion of reconstructed breast
433111	Effects of hunger
433527	Endometriosis
4170770	Epidermoid cyst
4092896	Feces contents abnormal
259995	Foreign body in orifice
40481632	Ganglion cyst
4166231	Genetic predisposition
433577	Hammer toe
4231770	Hereditary thrombophilia
440329	Herpes zoster without complication
4012570	High risk sexual behavior
4012934	Homocystinuria
441788	Human papilloma virus infection
4201717	Ileostomy present
374375	Impacted cerumen
4344500	Impingement syndrome of shoulder region
139099	Ingrowing nail
444132	Injury of knee
196168	Irregular periods
432593	Kwashiorkor
434203	Late effect of contusion
438329	Late effect of motor vehicle accident
195873	Leukorrhea
4083487	Macular drusen
4103703	Melena
4209423	Nicotine dependence
377572	Noise effects on inner ear
40480893	Nonspecific tuberculin test reaction
136368	Non-toxic multinodular goiter
140648	Onychomycosis due to dermatophyte
438130	Opioid abuse
4091513	Passing flatus
4202045	Postviral fatigue syndrome
373478	Presbyopia
46286594	Problem related to lifestyle
439790	Psychalgia
81634	Ptotic breast
380706	Regular astigmatism

Concept ID	Concept Name
141932	Senile hyperkeratosis
36713918	Somatic dysfunction of lumbar region
443172	Splinter of face, without major open wound
81151	Sprain of ankle
72748	Strain of rotator cuff capsule
378427	Tear film insufficiency
437264	Tobacco dependence syndrome
194083	Vaginitis and vulvovaginitis
140641	Verruca vulgaris
440193	Wristdrop
4115367	Wrist joint pain

Appendix D

Suggested Answers

This Appendix contains suggested answers for the exercises in the book.

D.1 SQL and R

Exercise 10.1

To compute the number of people we can simply query the PERSON table:

```
library(DatabaseConnector)
connection <- connect(connectionDetails)
sql <- "SELECT COUNT(*) AS person_count
FROM @cdm.person;"

renderTranslateQuerySql(connection, sql, cdm = "main")
```



```
##    PERSON_COUNT
## 1      2694
```

Exercise 10.2

To compute the number of people with at least one prescription of celecoxib, we can query the DRUG_EXPOSURE table. To find all drugs containing the ingredient celecoxib, we join to the CONCEPT_ANCESTOR and CONCEPT tables:

```
library(DatabaseConnector)
connection <- connect(connectionDetails)
sql <- "SELECT COUNT(DISTINCT(person_id)) AS person_count
FROM @cdm.drug_exposure
INNER JOIN @cdm.concept_ancestor
  ON drug_concept_id = descendant_concept_id
INNER JOIN @cdm.concept ingredient
  ON ancestor_concept_id = ingredient.concept_id"
```

```

WHERE LOWER(ingredient.concept_name) = 'celecoxib'
  AND ingredient.concept_class_id = 'Ingredient'
  AND ingredient.standard_concept = 'S';"

renderTranslateQuerySql(connection, sql, cdm = "main")

```

```

## PERSON_COUNT
## 1 1844

```

Note that we use COUNT(DISTINCT(person_id)) to find the number of distinct persons, considering that a person might have more than one prescription. Also note that we use the LOWER function to make our search for “celecoxib” case-insensitive.

Alternatively, we can use the DRUG_ERA table, which is already rolled up to the ingredient level:

```

library(DatabaseConnector)
connection <- connect(connectionDetails)

sql <- "SELECT COUNT(DISTINCT(person_id)) AS person_count
FROM @cdm.drug_era
INNER JOIN @cdm.concept ingredient
  ON drug_concept_id = ingredient.concept_id
WHERE LOWER(ingredient.concept_name) = 'celecoxib'
  AND ingredient.concept_class_id = 'Ingredient'
  AND ingredient.standard_concept = 'S';"

renderTranslateQuerySql(connection, sql, cdm = "main")

```

```

## PERSON_COUNT
## 1 1844

```

Exercise 10.3

To compute the number of diagnoses during exposure we extend our previous query by joining to the CONDITION_OCCURRENCE table. We join to the CONCEPT_ANCESTOR table to find all condition concepts that imply a gastrointestinal haemorrhage:

```

library(DatabaseConnector)
connection <- connect(connectionDetails)
sql <- "SELECT COUNT(*) AS diagnose_count
FROM @cdm.drug_era
INNER JOIN @cdm.concept ingredient
  ON drug_concept_id = ingredient.concept_id
INNER JOIN @cdm.condition_occurrence
  ON condition_start_date >= drug_era_start_date
    AND condition_start_date <= drug_era_end_date
INNER JOIN @cdm.concept_ancestor
  ON condition_concept_id = descendant_concept_id
WHERE LOWER(ingredient.concept_name) = 'celecoxib'"

```

```
AND ingredient.concept_class_id = 'Ingredient'  
AND ingredient.standard_concept = 'S'  
AND ancestor_concept_id = 192671;"  
  
renderTranslateQuerySql(connection, sql, cdm = "main")
```

```
##   DIAGNOSE_COUNT  
## 1           41
```

Note that in this case it is essential to use the DRUG_ERA table instead of the DRUG_EXPOSURE table, because drug exposures with the same ingredient can overlap, but drug eras can. This could lead to double counting. For example, imagine a person received two drug drugs containing celecoxib at the same time. This would be recorded as two drug exposures, so any diagnoses occurring during the exposure would be counted twice. The two exposures will be merged into a single non-overlapping drug era.

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