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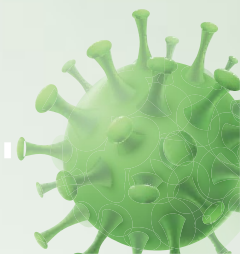
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International Society
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COVID-19

Real-World Evidence Primer





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Disclosure and Disclaimer:

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COVID-19 Real-World Evidence Primer

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A Note from the Editorial Committee

In the early phase of the SARS-CoV-2 (COVID-19) pandemic, the Reagan-Udall Foundation for the Food and Drug Administration (FDA Foundation), in collaboration with Friends of Cancer Research, and at the request of the FDA, launched the COVID-19 Evidence Accelerator to rapidly share information on the epidemiology, prevention, and treatment of COVID-19. Much of the information shared and generated through the parallel approach to analyses leveraged real-world data (RWD). Through the Evidence Accelerator, the FDA Foundation in collaboration with the International Society for Pharmacoepidemiology (ISPE) has developed this COVID-19 Real-World Evidence Primer to provide an overview of available RWD sources and appropriate methods for study conduct. An Editorial Committee comprising representatives from the FDA Foundation and ISPE guided the development of this primer, and committees of authors were responsible for writing each chapter. As the pandemic has exemplified the need for rapid evidence generation using existing data sources, it has also emphasized the importance of careful design and methodological approaches to support causal inferences in RWD studies that can guide clinical and regulatory decision. The Editorial Committee hopes that this primer can provide introductory level insight in core pharmacoepidemiologic methods for RWE study conduct. The committee would like to express its gratitude to all chapter authors and Karen Staman and Amy Bokser for editorial support.

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Executive Summary: COVID-19 Real-World Evidence Primer

In response to the COVID-19 pandemic, the use of real-world data (RWD) for research accelerated, supporting the global response to the COVID-19 pandemic via conduct of rigorous studies on the safety and effectiveness of diagnostics, drug repurposing, and novel therapies and vaccines in near real time. The use of RWD has many advantages, most notably that data typically are collected as a part of routine health care and are available expeditiously and often for large populations. However, there are special considerations for the use of these data for the secondary purpose of research. To learn from the evolving lessons of addressing the COVID-19 pandemic and to bolster the future use of real-world evidence (RWE), we created this primer to describe the RWD ecosystem. We included key principles of study design and potential sources of bias, examples of COVID-19 studies that use RWD, and mechanisms for disseminating RWE gleaned from the conduct of RWD research. We also introduce the COVID-19 Evidence Accelerator initiative that was established during the pandemic to support RWD study conduct.¹

Chapter 1: Overview of Real-World Data

RWD include information recorded in electronic health records (EHRs); administrative claims; patient-reported outcomes (generally responses surveyed directly from patients on feeling and function); patient-generated health data (from apps, smartwatches, pedometers, etc.); product- and disease-specific registries; and information about environmental factors and social determinants of health. These RWD sources can both describe the patient experience and depict an overview of population health. Although much work had been done to lay the groundwork for the use of RWD, including the FDA RWE framework² as part of the 21st Century Cures Act,³ many challenges for the use of RWD to support causal inferences of treatment effects exist — challenges that were further compounded by the need for accelerated research and evidence during the pandemic. To generate reliable RWE from RWD, the data should meet acceptable thresholds for validity and provenance in addition to being fit for the intended purpose. Data governance, privacy, and security are also important factors for RWD studies.

Chapter 2: Methods in Real-World Evidence Generation – Study Design

There are various observational study designs that are typically used to generate RWE, including between-person designs (cohort and case-control studies) and within-person designs, which compare different time windows (i.e., lengths of time) within the same

person. The concept of a target trial, an observational study that aims to emulate the key features of a randomized control trial, provides a useful framework to think about potential biases in RWE studies. Descriptive designs examine disease or exposure patterns in the population, focusing on characteristics related to person, place, and time. This chapter describes the key features of each design, the types of questions that can be answered, and advantages and disadvantages of each type of design.

Chapter 3: Methods in Real-World Evidence Generation – Sources of Error

Because RWD are not collected for research purposes, there are potential sources of error that are typically tied to the context in which the data were originally collected. These potential sources of error, as well as the failure to consider these issues in study design and / or analysis, can cause a variety of biases, such as confounding or misclassification bias. In addition, investigators can compound such problems, resulting in problems such as selection bias or immortal time bias. This chapter describes common mechanisms for these biases in observational research and how to mitigate them.

Chapter 4: Examples of COVID-19 Real-World Evidence Studies

In response to the unprecedented impact and evolution of COVID-19, collaboration was critical for the launch of rigorous studies to address the evolving needs across the globe. This chapter describes selected example studies:

- **Cohort study presented in the context of target trial emulation:** BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting
- **Cohort study:** Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform
- **Case-control study:** Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings
- **Self-control case series:** Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study
- **Drug utilization study:** Use of repurposed and adjuvant drugs in hospital patients with COVID-19: multinational network cohort study
- **Diagnostic test evaluation study:** Optimizing SARS-CoV-2 Surveillance in the United States: Insights From the National Football League Occupational Health Program

Chapter 5: Major Multi-stakeholder Initiatives - Defining the Future of COVID-19 Observational Research

The pandemic of COVID-19 laid bare the limited interoperability capacity of the existing health care data infrastructure for assembling data to quickly address critical questions about a novel disease. Several initiatives have emerged to address this shortfall using RWD for COVID-19 observational research. This chapter features a selection of multi-stakeholder COVID-19 RWD initiatives that have contributed to our understanding of the COVID-19 pandemic and/or are structured to continue to provide opportunities for observational research about emerging issues related to the disease.

Six COVID-19 RWD multi-stakeholder initiatives are also covered in depth in this chapter:

- **Observational Health Data Science and Informatics (OHDSI):** Initiative leveraging existing international distributed health care data in an interdisciplinary collaborative that facilitates open-source analyses to conduct observational studies on COVID-19 disease characterization, treatment, and care
- **FDA Sentinel:** Food and Drug Administration (FDA) system leveraging a distributed data network with a common data model as well as other standalone data sources to conduct COVID-19-related studies
- **OpenSAFELY:** Initiative that enables the access of multiple United Kingdom (UK) government data sources in a reliable and protected platform to address COVID-19 research needs
- **Vaccine Monitoring Collaboration for Europe (VAC4EU):** International non-profit association set up with the aim of conducting collaborative real-world analysis on vaccines. The entity was founded as a result of the Innovative Medicines Initiative-funded ADVANCE project that was initiated after the H1N1 pandemic
- **COVID-19 Research Database:** Cross-industry, cross-sector initiative composed of institutions that donate technology services, health care expertise, and de-identified data in the United States (US) for COVID-19 observational research. The data repository contains integrated, linked data sets from multiple sources, from the more traditional RWD (claims, EHR) to life insurance claims, consumer data, and mortality records
- **COVIDRIVE:** Public-private partnership leveraging the existing vaccine effectiveness platform in Europe to comprehensively examine COVID-19 vaccine effectiveness across a range of products and assist vaccine companies in fulfilling their regulatory obligations

Chapter 6: The COVID-19 Evidence Accelerator

The COVID-19 Evidence Accelerator initiative ¹ was launched by the [Reagan-Udall Foundation for the FDA](#) (FDA Foundation), ⁴ in collaboration with [Friends of Cancer Research](#) (Friends) ⁵ and on behalf of the FDA, to provide a unique open venue for major data organizations, government and academic researchers, and health systems to share information about COVID-19 efforts, and to convene a community to urgently address questions about COVID-19.

Chapter 7: Communicating about Real-World Evidence

The pandemic illustrated the need for rapid, reliable dissemination of information — not only among researchers, but to other stakeholders including regulators, clinicians, and other health care workers, as well as to the general population. This demand for evidence that can guide regulatory and clinical decision-making must be weighed against the need for adequate vetting of RWE. The growing skepticism regarding scientific evidence is a critical problem that highlights the need for timely and trustworthy communication. This chapter provides practical guidance about dissemination, including the publication processes for developing a communications plan, creating messaging and communication channels, and transmitting internal communications.

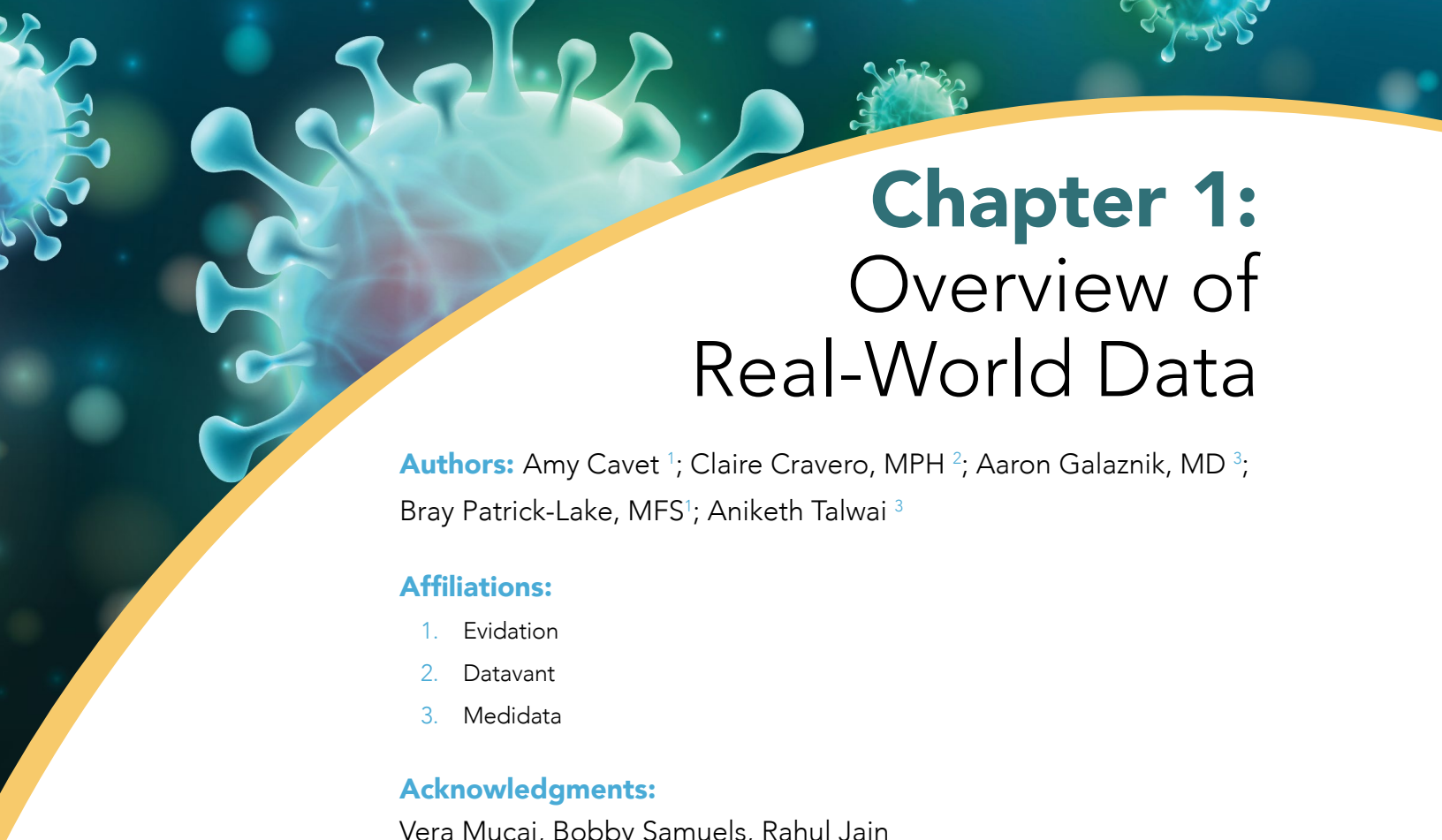
Conclusion

Although RWD was being used for research prior to COVID-19, the pandemic pushed researchers to be more collaborative, be more efficient, react faster, and disseminate information more frequently, all while ensuring adequate study quality and high scientific standards. By learning from our experiences, we can build on the momentum of these collaborations to continue to address COVID-19 as well as other diseases and important public health issues.

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Chapter 1: Overview of Real-World Data

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Background on Real-World Data

In response to the COVID-19 pandemic, use of real-world data (RWD) for research accelerated, supporting the global response to the pandemic via conduct of rigorous studies in the safety and effectiveness of diagnostics and of existing and newly approved therapies and vaccines in near real time. RWD include information recorded in the electronic health record (EHR), administrative claims, patient-reported outcomes (including surveys about how a patient feels and functions), patient-generated health data (from apps, smartwatches, pedometers, etc.), product- and disease-specific registries, mortality data, and information about environmental factors and social determinants of health. Taken together, these RWD sources can enable a broad and specific picture of a patient's journey and population health as a whole. The use of RWD has many advantages, most notably that data, typically collected as a part of routine health care, are available expeditiously and commonly for large populations. However, there are special considerations for the use of these data for the secondary purpose of research because they are created in individual health care systems for the primary purposes of patient care and billing.

As part of the 21st Century Cures Act (Cures Act) of 2016, the Food and Drug Administration (FDA) created [Framework for FDA's Real-World Evidence Program](#) to satisfy these provisions and bolster the use of RWD for approval of new indications for medical products and use in post-approval study requirements.¹ More recently, the FDA published a series of [draft guidance documents](#), including a guidance on [“Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products.”](#)² In the past two decades, large networks in the US, such as Sentinel³⁻⁵ and the Patient-Centered Outcomes Research Network (PCORnet),⁶⁻⁸ were launched to use administrative claims and electronic health record data for evaluation and research purposes. Globally, other countries have built similar data repositories, particularly countries with universal health care systems.

Definitions from the Framework for FDA's Real-World Evidence Program¹

Real-World Data (RWD): data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE): clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

When the COVID-19 pandemic started, a foundation had been laid such that researchers could effectively launch studies to investigate COVID-19-related questions using RWD, including the burden of COVID-19 infection, the effectiveness of therapies (pharmacologic and non-pharmacologic treatments and vaccines), and the impact of programs and policies on disease outcomes.⁹ RWD are poised to address key themes, such as those listed in Table 1.1.

Table 1.1. Example Themes to Explore with RWD

Characterization of COVID-19 Disease
COVID-19 Specific Treatment Utilization and Outcomes
Influence of Concomitant Diseases and Comorbidities on COVID-19 Outcomes
Health Disparities and Health Equity Research
Drug Repurposing to Treat COVID-19
Longitudinal Impact of COVID-19 on Health Conditions
Post-Acute Sequelae of SARS CoV-2 infection (PASC)
COVID-19 Testing Patterns
COVID-19 Vaccine Uptake and Immunity Studies

Use of RWD may allow researchers to quickly generate clinical evidence while reducing the burden and cost of research conduct in some cases as compared to randomized controlled trials. Importantly, the RWD must be fit-for-purpose – that is, reliable, valid, and relevant. While not every research question can be addressed with RWD, the ability to generate real-world evidence (RWE) if adequate RWD are available depends further on the application of appropriate methodology based on epidemiologic principles to answer the research question.¹

Types of Real-World Data

Data in the United States and many other countries are distributed across a complex ecosystem of thousands of institutions. Each type of RWD generation within various layers of health care delivery has a different set of strengths and potential weaknesses. Data in Europe are distributed across many nations, which have their own health care systems and vocabularies. Whether a real-world data set (or combination of data sets) is fit-for-purpose depends on the on the research question.¹⁰

As part of its 2018 framework for using real-world data to support regulatory decision making, the FDA has identified a number of potential sources of real-world data:¹



Electronic health records (EHRs)

EHRs contain information collected in the ordinary course of hospital and ambulatory care visits and can include structured data on diagnoses, procedures, laboratory results, vital signs, medication orders, and medication administrations, as well as information that is unstructured, such as clinical notes.¹¹ Structured data can include preliminary administrative claims, such as billing diagnoses and procedure codes (e.g., ICD, CPT).



Administrative claims

Administrative claims include information attached to charges submitted by health care providers for reimbursement by private insurers and federal insurance programs (e.g., Medicare and Medicaid). These administrative data typically include basic demographic characteristics and enrollment information in addition to detail on diagnoses and procedures associated with medical encounters and outpatient pharmacy prescription fills, or other specialized data such as charges from skilled nursing facilities or home health care providers. In comparison to the billing and diagnosis codes from EHRs, administrative claims from payors have been adjudicated for payment and thus have been somewhat verified, although are often delayed compared to EHR data.



Patient-generated health data (PGHD)

PGHD are “wellness and/or health-related data created, recorded, or gathered by individuals for themselves (or by family members or others who care for an individual).”¹² These data can be generated from devices such as smart watches, internet-connected scales, phone apps, pedometers, and home blood pressure monitors. PGHD can include patient reported outcomes (PROs), which report the status of a patient’s health directly from the patient.¹³



Registries

Most patient registries can be categorized as either product or disease/condition registries. Product registries are typically created to prospectively capture data to support post-marketing surveillance of medical products. Disease or condition registries are defined by condition (e.g., pregnancy, HIV) to manage patient care and/or address questions related to the natural history of the disease or condition as well as comparative effectiveness and/or safety of treatments.



Environmental factors and social determinants of health

Environmental factors and social determinants of health (SDoH) such as socioeconomic status, food insecurity, and access to transportation may or may not be captured in EHRs, although collection of this information is increasing.¹⁴ Administrative claims may have supplemental information related to patients' eligibility (e.g., employment status, income level). Researchers can also use geographic information, such as zip code, to obtain information about neighborhood level characteristics that may provide insight into SDoH.

MORTALITY DATA

Despite being one of the more common endpoints in clinical studies of treatment safety and effectiveness, information on deaths, including date and cause, is often not captured in health care data. In these cases, health care data must be linked to external sources of mortality data (e.g., death certificates, vital statistics systems, civil registries) to capture death outcomes. In the US, sources of data on death include but are not limited to the National Death Index, State Vital Statistics, the Social Security Administration Death Master File, Medicare Master Beneficiary Summary File, and the [National Association of Statistics and Information Systems](#) Fact of Death Service.¹⁵

Linking Real-World Data Sets to Answer Key Questions

RWD can be linked to allow investigators to enhance their depth and breadth in an effort to capture integrated, longitudinal care and health outcomes.^{16,17} Linkages across RWD sets can be done via clear text matching or privacy preserving methodologies, depending on the necessary privacy framework. The use of large linked data sets can improve the statistical precision of estimates made with smaller data sets, but biases that appear due to missing information do not dissipate with a large sample size. Data linkages can help address missing information, thereby reducing measurement biases in large RWD analyses. Moreover, triangulating data points across multiple data sources not only mitigates potential missingness inherent to RWD, but it can also facilitate data validation and enhance accuracy. While linkages can be advantageous, paradigms regarding the evaluation of the aggregated RWD as fit-for-purpose remain. Care must be taken to assess the reliability and validity of the data linkage. For example, linkages may further create issues with selection bias; reduced geographic, demographic, or clinical representation; missingness; and harmonization problems that could affect analysis.⁹

Assessing Fitness for Purpose

The research team should assess whether the target data set (including the data source, any linkages that may be performed, and the subsequent data operations on the combined data set) is fit for purpose.^{1,2,18} The Structured Process to Identify Fit-For-Purpose Data (SPIFD) is one example of a systematic process for conducting feasibility assessments that can be used to evaluate whether a data source is fit for decision making, and for documenting the rationale for selected data sources.¹⁹

Real-World Data Governance

Data governance comprises several core concepts that are critical to the secure and appropriate use of RWD to generate RWE. These core concepts include: data privacy and de-identification; data security; and IRB review.

Data Privacy and De-Identification: As more RWD are collected digitally and available for analysis, there is a risk that a patient's privacy could be compromised. Much of the data available in RWD sources are subject to [US Health Insurance Portability and Accountability Act](#) (HIPAA) and EU [General Data Protection Regulation](#) (GDPR) provisions, and there are well understood methods for removing identifiable information and then using those data for research purposes without the explicit consent of the patient. In recent years, there has been renewed focus on privacy-preserving methods for linking or analyzing records across different data sets. These novel methods include privacy-preserving record linkage, differential privacy, secure multi-party computing, federated learning, and hashing and pseudonymization. These approaches vary in complexity, maturity, and adoption, but each represents a way to de-identify patient information while maintaining the ability to link patient data across different data sets.

HIPAA provides for two methods to assure that the re-identification risk is low for a given data set: One is safe harbor, in which data elements that contain personally identifiable information (PII) are removed. A second method is expert determination, which assures that there is a very small risk of re-identification in the combined or linked data set. A research team must pair the appropriate method of linkage with the necessary HIPAA-compliant data evaluation, preparation, and (if necessary) certification by an expert determination service.

Data Security:

Data security is fundamental to any infrastructure design for a given RWD project. In the US, the Federal Information Security Management Act (FISMA) defines three components of secure data:

1. **Confidentiality:** the data are protected from unauthorized disclosure
2. **Integrity:** the data are protected from unauthorized modification or destruction
3. **Availability:** the data are protected from disruption of access ²⁰

A data breach can threaten any of the three components and can be the result of ransomware and cyberattacks (such as the WannaCry ransomware attack), ²¹ data theft by employees, loss of devices, and human error. Data security for a RWD project begins with a governance and management framework that typically includes a data use agreement (DUA) and a formal plan for how the data will be used and secured. Considerations include technical components (such as cloud versus premise-based security), access policies, physical security and training, data protection, endpoint security, network security, defect and vulnerability management, identity management, monitoring, and independent testing and review.

IRB review:

Once the data source definition, fit-for-purpose assessment, and data privacy considerations have been incorporated into a study protocol, the research team should ensure that they have identified the appropriate IRB process to engage with for review.

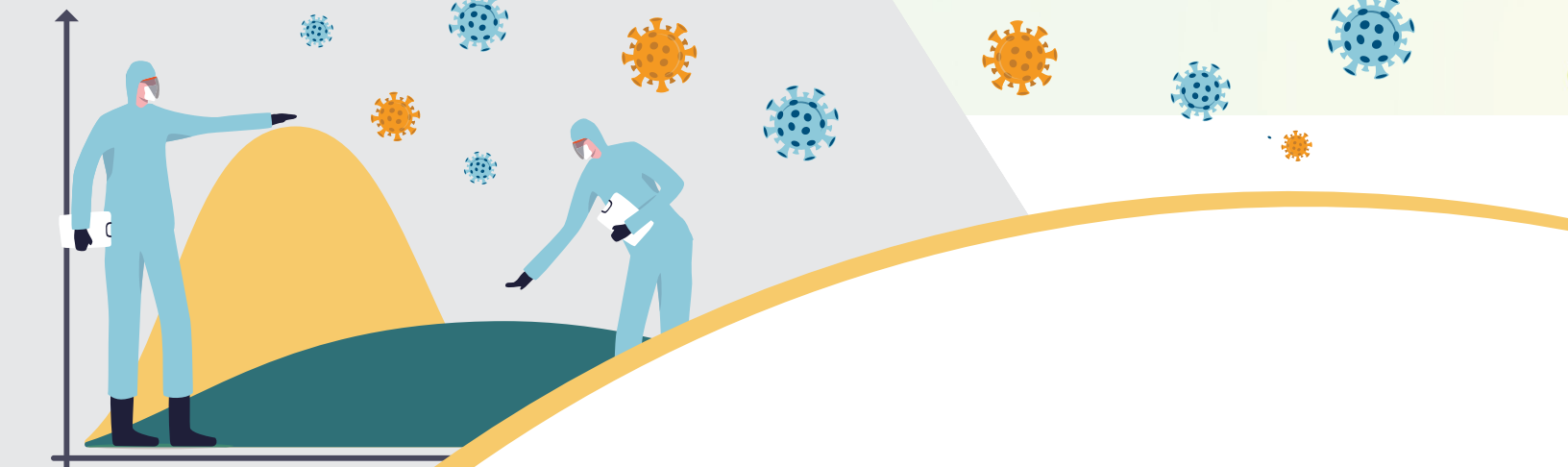
Conclusion

Well conducted research begins by articulating a clear, discrete question of interest. One of the first steps in generating RWE to address the research question is to identify a fit-for-purpose RWD source. In assessing potential data sources, consideration should be given to the PICO of interest – i.e., the Population [or Problem or Patient], Intervention [or Exposure], Comparator [or Control or Comparison], and Outcome. Specifying the PICO helps elucidate the care settings in which the patients, exposure, comparator, and outcomes are likely to be identified, informing decisions about the type and source of data likely to be relevant and valid for the research question. After selection of a fit-for-purpose data set, a well-defined study question in the PICO can help guide the selection of appropriate study design, approaches for assessing key study variables, and methods for addressing bias in RWE studies, which are the subject of Chapters 2 and 3.

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Chapter 2: Methods in Real-World Evidence Generation — Study Design

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In this chapter, we discuss 4 different observational study design families commonly used with real-world data (RWD):

1. Target trial paradigm, which typically uses cohort study designs to emulate randomized controlled clinical trials (RCTs)
2. Between-person designs, including cohort and case-control studies
3. Within-person designs, which compare different time windows (i.e., lengths of time) within the same person
4. Descriptive designs, which examine disease or exposure patterns in the population, focusing on characteristics related to person, place, and time

The chapter begins with the target trial paradigm and the concept of a randomized controlled trial, therefore providing an intuitive introduction into core methodological considerations when generating real-world evidence (RWE). Studies that utilize the target trial paradigm most commonly employ cohort study designs with a between-person approach, which is further addressed in section two of this chapter. The third section of the chapter introduces within-person designs, in which different time periods within the same person are compared. Finally, the fourth section covers descriptive study designs.

1. Target Trial Paradigm

Author: Bradley MC

What is it used for?

Causal questions on the comparative effectiveness and safety of COVID-19 treatments and vaccines are ideally addressed in well-designed and well-conducted RCTs using protocol-based outcome ascertainment and adjudication. However, if an RCT is not feasible, ethical, or timely, or is cost prohibitive, data from observational studies using best pharmacoepidemiologic practices^{1,2} might offer a valuable alternative. To illustrate these study design practices, analogies to RCTs have been made: the target trial paradigm applies design principles from RCTs to the analysis of observational data to explicitly emulate the hypothetical RCT that would have been conducted. This hypothetical RCT is referred to as the target trial.³

The target trial is specified using a structured process to refine the causal goal of the research, formulate meaningful questions, and evaluate appropriate observational data sources and causal inference analysis strategies. If the target trial is specified as precisely as possible for the question of interest, it informs the design of the observational study. The inferences drawn from the observational study are then based on the principles applied in the target trial to assess a causal effect.⁴

A protocol specifying the target trial and detailing the emulation in observational data should include seven key domains:⁵

1. Eligibility criteria
2. Treatment strategies
3. Treatment assignment
4. Start and end of follow-up
5. Outcomes
6. Causal contrasts (intention-to-treat effect, per-protocol effect)
7. Statistical analysis

Eligibility criteria for the observational study should be informed by the target trial, in most cases a hypothetical pragmatic trial.⁶ Pragmatic trials are designed to compare effectiveness of interventions in real-life practice. In contrast, typical RCTs are explanatory trials aimed to test whether the intervention works under optimal conditions.

Key considerations in emulating the target trial, which can help identify and minimize potential bias and confounding in the observational study, include:

1. Emulation of random assignment of treatment at baseline; all relevant confounding factors should be balanced to ensure comparability (exchangeability) of the treatment cohorts.
2. Proper specification of time zero; time zero is the point at which follow-up for outcomes begins, and it should be synchronized with determination of eligibility and assignment of treatment strategies. In the observational study, emulation of the time zero of the target trial is usually achieved by defining it as the time when an eligible patient initiates an intervention.⁷

Observational studies designed according to a framework that allows causal inference such as the target trial paradigm can estimate causal effects, rather than associations.⁸ Specifying the target trial can help with methodologic evaluation of observational

studies. It can highlight deviations from ideal study conditions and allow identification of potential biases in the observational study — for example, when certain information required for emulation is not available⁵ — as well as any changes in eligibility criteria or other parameters as a result.⁹

What kinds of questions can be addressed?

The target trial paradigm can be used to evaluate important causal questions on COVID-19 treatment effectiveness and safety, and on COVID-19 vaccine effectiveness in real world settings. Target trial emulations using RWD are designed to overcome limitations seen in the COVID-19 vaccine RCTs, such as inability to perform adequate subgroup analysis due to sample size limitations, restrictive inclusion criteria, and a highly controlled setting that is difficult to replicate in real world mass vaccination programs.¹⁰ Using RWD may allow inclusion of groups often excluded from traditional RCTs, such as older adults and patients with comorbidities. Also, RWD can address questions that might be outside of traditional RCT conduct, such as duration of vaccine protection against infection, transmission, severe disease, death, and comparative effectiveness of different vaccines.¹¹ The following illustrates the use of the target trial paradigm to inform pharmacoepidemiologic studies of COVID-19 treatments.

Dagan et al.^{11,12} used RWD from a large health care organization in Israel to emulate a target trial evaluating the effectiveness of the BNT162b2 mRNA vaccine. Evaluated outcomes included: infection with SARS-CoV-2, symptomatic COVID-19, and COVID-19–related hospitalization, severe illness, and death among 596,618 vaccinated persons and 596,618 controls. The findings suggested high effectiveness of the BNT162b2 vaccine for preventing symptomatic COVID-19 in the real world, and high effectiveness for preventing outcomes such as hospitalization, severe illness, and death; similar to the vaccine efficacy reported in the RCT.¹³ The large observational study (1,192,236 participants compared to 21,720 in the RCT) allowed examination of outcomes in specific subpopulations that the RCT was not sufficiently powered to evaluate, such as those with multiple coexisting conditions. The finding that vaccine effectiveness might be slightly lower in those with more coexisting conditions is notable. However, a limitation to the use of RWD was the speed of vaccination, which contributed to frequent censoring of matched unvaccinated controls, especially among older individuals, and a reduction in the average follow-up time.

In the absence of data from RCTs, Gupta et al.¹⁴ used RWD from a large multi-site cohort, the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP- COVID),¹⁵ to emulate a target trial. The study estimated the effect of early treatment with tocilizumab on mortality in COVID-19 patients in the intensive care unit (ICU). Again, the large size of the emulated study allowed subgroup analyses not always possible in the RCTs that were subsequently conducted. The results showed that patients treated with tocilizumab in the first 2 days of ICU admission had an almost 30% lower risk of death compared with those not treated with tocilizumab. The United Kingdom RECOVERY RCT later reported similar results.¹⁶ However, other RCTs did not show the same mortality benefit.^{17–19}

Similarly, in the absence of evidence from RCTs, Al-Samkari et al.²⁰ emulated an RCT as a target trial using RWD on COVID-19 patients admitted to ICUs in the US. In this study, survival was compared in patients who received therapeutic anticoagulation in the 2 days after ICU admission to those who did not receive therapeutic anticoagulation. Those who received anticoagulation in the first 2 days of ICU admission had similar in-hospital survival compared with those who did not. These results supported the recommendations of several professional societies against broad empirical therapeutic anticoagulation in patients with COVID-19.^{21,22}

Gatto et al. used HealthVerity data to emulate a hypothetical target trial to examine the effectiveness of dexamethasone in preventing 28-day mortality among hospitalized patients with moderate to severe COVID-19.²³ While the RECOVERY RCT already examined this question in the UK, the authors sought to emulate RECOVERY as a hypothetical target trial with varied design elements, and tailored for US practice and US patients.²³

Using data from routine care in France, the target trial paradigm was also used to inform an observational study on the effectiveness of hydroxychloroquine for patients hospitalized with a COVID-19 infection and requiring supplemental oxygen. The findings suggested that hydroxychloroquine treatment at 600 mg/day added to standard of care was not associated with a reduction of admissions to ICUs or death 7 days after hospital admission compared to standard of care alone.^{24,25} These findings were consistent with data from RCTs that found hydroxychloroquine to be ineffective for treatment of COVID-19.²⁶

What are the benefits and limitations of this design?

Emulating a hypothetical target trial can improve the conduct of observational studies, decreasing some common biases and confounding by emulation of random assignment and correct specification of time zero. For a robust observational study, other issues such as attrition, changes in treatment, and misclassification of outcomes should be accounted for, but these are discussed elsewhere. Misspecifying time zero can lead to selection and time-related biases such as immortal time bias.²⁷ For example, an observational study on postmenopausal hormone therapy and heart disease reported >30% lower risk of the outcome in current users vs. never users,²⁸ while an RCT reported >20% higher risk.²⁹ Prevalent hormone therapy users were included in the observational design, whereas the RCT only followed incident users. As prevalent users were depleted of patients who were susceptible to thromboembolic risk imposed by postmenopausal hormone therapy, which would manifest early during exposure, they were less likely to experience the outcome.³⁰ When the observational data were re-analysed using a new-user design (resembling a trial), the findings aligned with those of the RCT.³¹ Incorrectly specifying time zero and including prevalent users^{33,34} can also cause postbaseline information (collected during treatment) to be used in defining baseline characteristics.⁷ Constructing causal diagrams when specifying the target trial helps identify baseline confounders (non-colliders [See Chapter 3]) that should be balanced and colliders that should be left uncontrolled to prevent collider bias.³⁵ The process of specifying a target trial helps to explicitly define the causal question, better understand the data that are required, and generally improve the quality of observational studies.⁵

Target trials are pragmatic, and therefore cannot always emulate key elements of an ideal RCT. For example, RWD cannot be used to emulate a placebo-controlled trial (an active comparator is generally needed), a trial with blinding (patients are typically aware of their treatment), treatment strategies that do not exist in the real world (enforcing adherence to a treatment), or any other type of monitoring that is not reflective of real-world practice.³ However, the pragmatic nature of the emulated target trial is not necessarily considered a limitation when the aim is to compare treatments to reflect use in the real world. RWD needed for the target trial emulation might not be available in the chosen data source (e.g., availability of clinical laboratory results for a specific disease biomarker). Data availability might also limit the ability to adequately balance comparison groups with regard to critical outcome risk factors that are associated with treatment assignment, thus acting as confounders.⁵

2. Between-Person Designs

Authors: Gatto N, Rassen J

What is it used for?

Between-person observational study designs include cohort studies and case-control studies.^{36,37}

Cohort studies (specifically parallel-group cohort studies) compare exposed and unexposed groups of patients over time for the occurrence of the outcome of interest. Cohort study designs have been used to examine the effectiveness and safety of COVID-19 treatments, and can be designed to emulate a hypothetical parallel-group randomized clinical trial.

Case-control studies differ from cohort studies with respect to patient selection, first identifying patients with the disease or outcome of interest (cases) and then a sample of those without the disease or outcome (controls). Case-control studies compare these cases and controls and examine differences in their preceding exposure status. Case-control studies may be sampled from a corresponding cohort study (i.e., a nested case-control study) or sampled from an underlying source population representing a hypothetical cohort if a full cohort study was performed (i.e., all available controls would have been included, rather than just a sample). Cases and controls are selected that recreate the exposure distribution in the underlying source population.

For the examination of COVID-19 vaccine effectiveness, there is growing interest in using a type of case-control study—the test-negative study design—in which patients with a positive COVID-19 test are considered cases and those with a negative test, controls, and vaccine status is the preceding exposure of interest.^{38–40} The rationale for this study design is to ensure cases and controls have equal access to health care and health seeking behavior by including only persons with an encounter (here, a COVID-19 test) for surveillance of the outcome. Of note, while this design may help overcome differential outcome misclassification where COVID testing is dependent on certain patient characteristics including vaccination status or symptoms, outcome misclassification may still occur because of low test sensitivity, specificity, and timing of the diagnostic assay.^{41,42} Thompson et al. conducted a simulation study, reporting that the presence of both exposure and outcome misclassification led to an underestimation of the effectiveness of COVID-19 vaccines.³⁹

Data from health care settings such as primary and specialty care, hospitals, emergency rooms, and urgent care allow access to cases and controls who can then be queried for previous exposures. If longitudinal RWD are available and no primary data ascertainment is required, both nested case-control and cohort studies are feasible. Because nested case-control studies typically provide little advantage or efficiency over conducting cohort studies using existing RWD, and should yield a substantially similar result,⁴³ we focus on study design considerations for cohort studies throughout this section. With that said, case-control designs can be useful if key variables are difficult or expensive to measure, or if nuances of timing between exposure and outcome are of particular interest.

Study Population

For COVID-19, the population of interest often includes patients diagnosed with COVID-19 in the ambulatory outpatient setting (with mild disease) or inpatient setting (with moderate to severe disease). Identifying these analytic cohorts requires careful consideration of several study design parameters (see Table 2.1).

Table 2.1. Key Study Design Parameters

Term and Definition	Key Considerations
Index date: Date of cohort entry or the date the patient enters the analytical study population	<ul style="list-style-type: none">• Index date is considered “time zero” and anchors temporal parameters such as covariate assessment, exposure, follow-up period, and outcomes on the longitudinal patient timeline.⁴⁴• It is critical to specify “time zero” and ensure proper alignment of meeting the eligibility criteria, treatment exposure, and start of follow-up. Hernan et al. provide an in-depth discussion of the “target trial failures” of misaligning time zero with eligibility and treatment assignment.⁷• While randomized controlled trials use the date of randomization as the study entry date and beginning of follow-up, selecting the index date for cohort studies is not always straightforward and is dependent on the research question and care setting. For example, studies in the ambulatory outpatient setting may assign treatment initiation as the index date. Depending on the specific research question, studies in the inpatient setting may define the index date as the exact hospital admission date (see Figure 2.1a) or treatment initiation, which may be at or after hospital admission (see Figure 2.1b).
Eligibility criteria: Inclusion and exclusion criteria applied in identifying the patients to be included in the study	<ul style="list-style-type: none">• Existence of sufficient observable patient-time is also often included as an eligibility criterion to allow an assessment of baseline characteristics and outcomes during follow-up. In administrative claims data—where information on patients’ characteristics and the occurrence of outcomes is obtained from insurance claims—enrollment dates for insurance coverage are used to determine observability.⁴⁵ For example, eligibility criteria often include COVID-19 diagnosis based on diagnosis codes or positive laboratory test results.

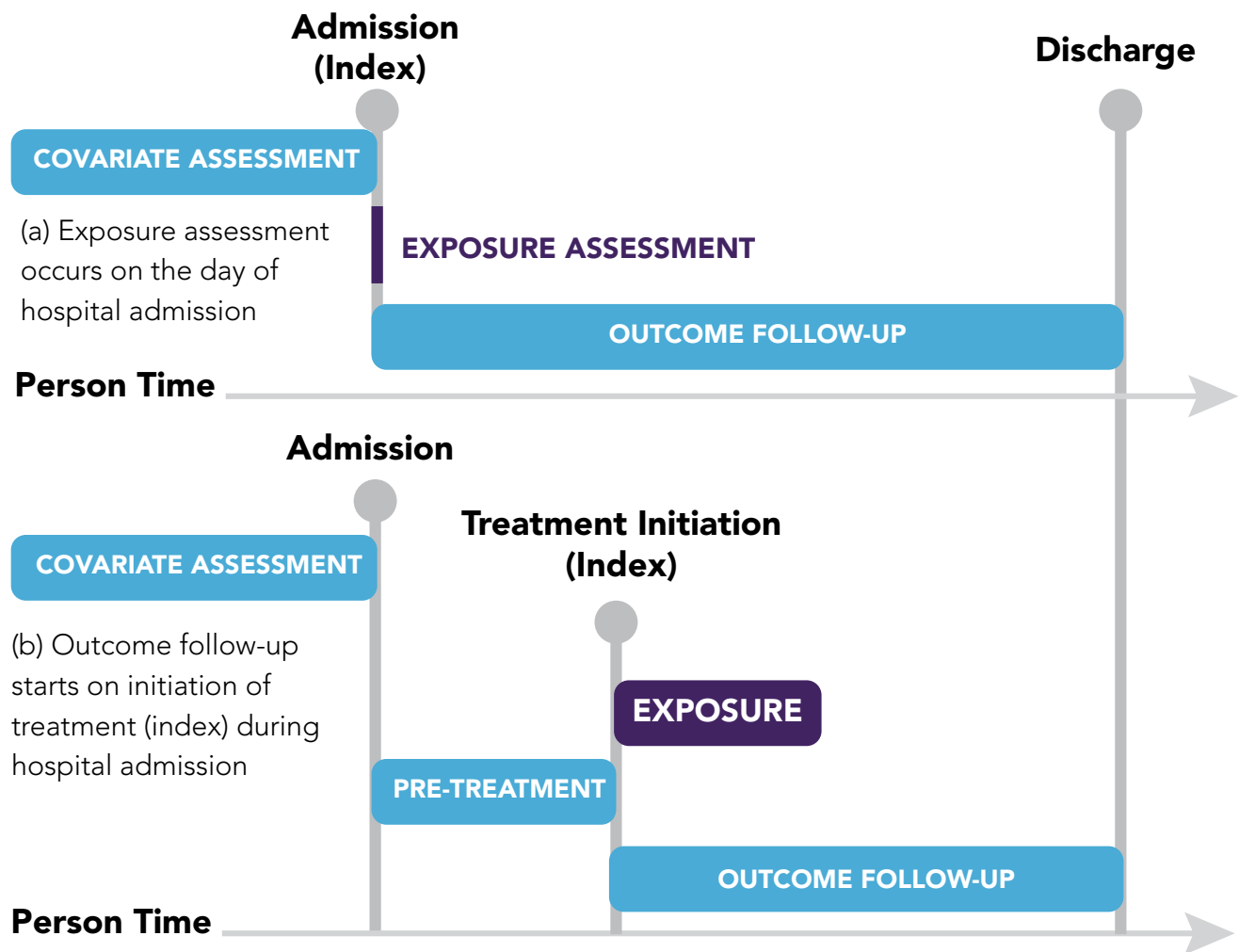


Figure 2.1. Defining the index date for cohort studies in the inpatient setting. Adapted from Franklin et al. *Clinical Pharmacology & Therapeutics* 2021.⁴⁸

Treatment Exposure

The new-user design (also known as incident-user design) and prevalent-user design are common approaches for identifying drug exposure (see Figure 2.2). The new-user study design has been previously well-described.^{34,46,47} Under this design, patients who are new users of a drug of interest—with new use defined as using the drug with no prior use over a prespecified washout period—are compared to patients who are new users of another drug (active comparator) or patients who did not initiate the drug of interest (non-user comparator). The index date for new-user design with an active comparator is typically the day of medication initiation for both groups (see Figure 2.2b). For example, in a study to evaluate whether corticosteroid A reduces the risk of inpatient mortality compared to corticosteroid B, the index date would typically be the date of inpatient treatment initiation of the first corticosteroid.

In contrast, the prevalent-user study design examines both current and new initiators of treatment during the study period.⁴⁸ The index date for patients in the prevalent-user design would vary. As seen in Figure 2.2c, the index date for patients 4 – 7 only would be treatment initiation, while the index date for patients 1 – 3 would occur at different periods of high-, medium-, and low-risk of the outcome event after treatment initiation depending on the patient. For example, in a study evaluating the effect of medications on COVID-19 severity that are commonly used but not specifically indicated for COVID-19, such as angiotensin converting enzyme (ACE) inhibitors/angiotensin-receptor blocker (ARB), patients may have had prior exposure to the medication for indications other than COVID-19. If so, the new-user design may be deemed inappropriate (or infeasible) in this particular setting and a prevalent-user design may be considered in which all medications used at the time of or shortly following a positive COVID-19 test may be evaluated as the treatment exposure. Patients would then be followed from the time of treatment to ascertain COVID-19-related outcomes.

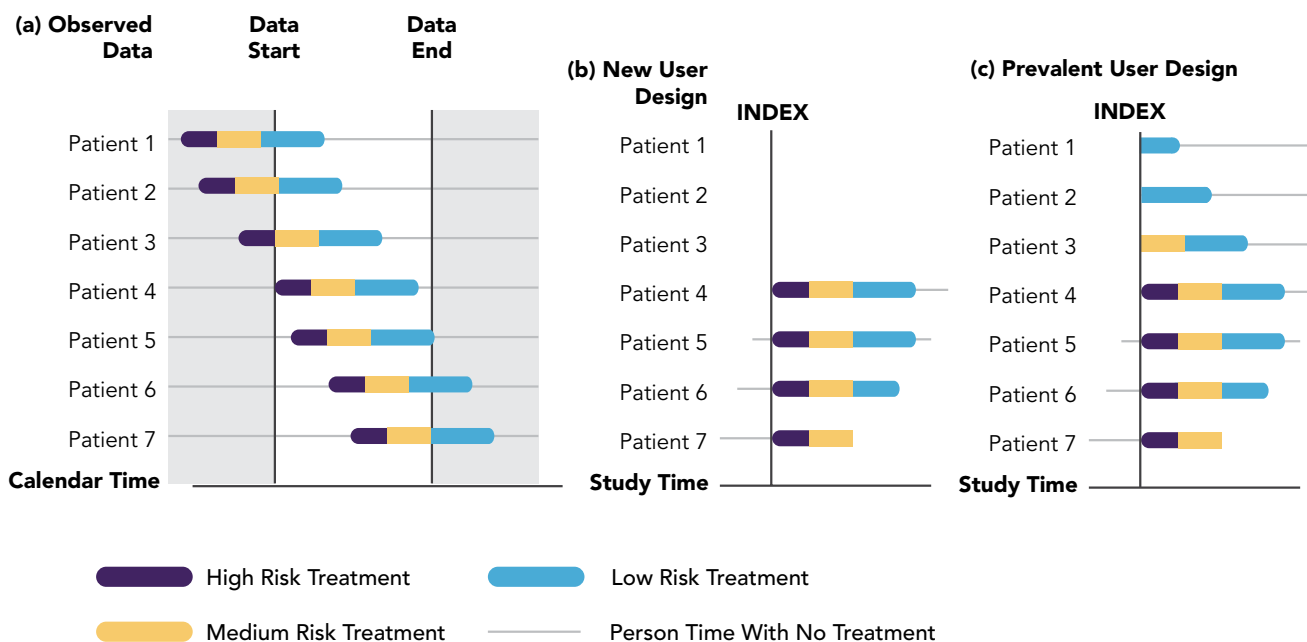


Figure 2.2. New-user and prevalent-user design. Adapted from Yoshida et al. *Nat Rev. Rheumatol.* 2015.61 (a) Illustrates a hypothetical study cohort during the study period, as represented by the white, unshaded area. The color bars represent treatment and high-, medium-, and low-risk for the outcome event during treatment exposure. The gray line indicates untreated person time. (b) The new user design shows the index date as the date of treatment initiation. The cohort includes only newly treated patients 4–7. (c) The prevalent user design shows a defined index date including all the treated patients 1–7.

More recently, the prevalent new-user design has emerged as another approach to identify exposure to the treatment of interest. A prevalent new-user design creates comparison groups by matching patients on time-based propensity scores, allowing patients who have switched treatments to enter the study.⁴⁹⁻⁵¹ The prevalent new-user design can result in greater statistical power than conventional new-user designs by allowing all or a majority of exposed patients to enter the study, versus designs that substantially limit the eligible population. Another advantage of this study design is its ability to mimic a randomized controlled trial since both exposed and unexposed patients are matched based on time.⁵²

Choice of Comparator or Control

One of the most critical considerations in designing a cohort study is ensuring balance between the exposure and comparator groups with regard to factors that may influence the outcome, such as calendar time (given the rapidly evolving nature of COVID-19 spread, treatment, and management), disease severity, comorbidities (e.g., diabetes and cardiovascular disease), and race and social determinants of health.⁴⁸ An active comparator is another medication with a similar indication and is ideal to balance measured characteristics between the two treatment groups and minimize confounding by indication. Paired with the new user design, assuming the two treatment options are clinically interchangeable, an active comparator also minimizes confounding by severity and starts patients at a similar time zero (start of a new treatment), thus allowing emulation of a target trial, with the index date defining the date of treatment initiation for each group.

With rapidly changing treatment regimens for COVID-19, an active comparator may not be possible if there is no standard of care available, or if standard of care is rapidly evolving. Another option is selecting non-users of the treatment of interest, sometimes called “best available care,” i.e., patients with a COVID-19 diagnosis who did not receive the treatment of interest. A major concern about this design is confounding, including confounding by indication if patients receiving and not receiving the treatment are inherently different in unmeasurable ways, as well as prescribing patterns and drug access which may introduce additional unmeasurable bias. Identifying an appropriate index date for the non-user group is also challenging since there is no treatment initiation date to anchor on, and one must avoid using a treatment index date that inadvertently incorporates immortal time into the study design (see Chapter

3 for more on immortal time bias).^{7,52,53} Employing a risk-set sampling design to identify comparators who have not (yet) initiated the treatment of interest and assigning the same study entry date to that comparator allows exposed patients to be matched with unexposed patients on important factors such as calendar time (e.g., month of hospitalization), disease severity (e.g., need for oxygen support), other relevant medications, etc., at the time each exposed patient initiates their treatment.^{48,54} For example, Figure 2.3 illustrates a simplified cohort of patients hospitalized for COVID-19 during the study period. Patients 1, 4, and 7 received inpatient treatment for COVID-19 and were risk-set sampled with 1:2 matching to non-users. Non-user patients will be included in the referent comparator group.

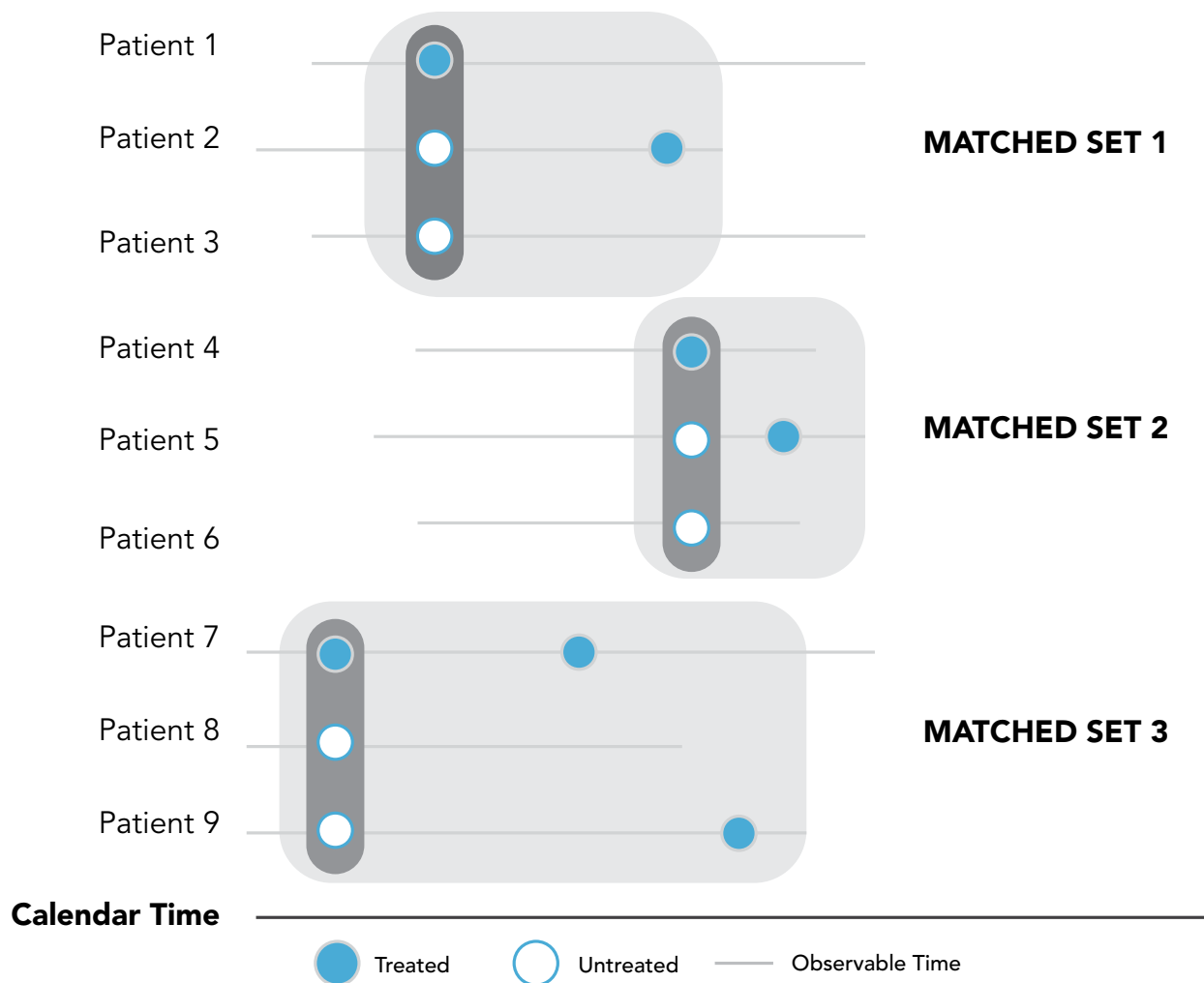


Figure 2.3. Illustrative example of risk-set sampling with users and non-users.

Outcomes and Covariates

For studies using RWD, outcomes are generally defined by applying algorithms to recorded codes, the sensitivity and specificity of which is highly dependent on the type of the data source and data availability. Clinical covariates, such as use of inpatient oxygen support, may also be derived from the data. The importance of clinical expertise to define the case or covariates definitions and develop algorithms cannot be overstated, especially given the rapidly-changing nature of COVID-19 care.

The care setting and point-of-service for COVID-19 is also an important consideration (e.g., outpatient setting or inpatient setting). For example, common inpatient setting-based outcomes when looking at the effectiveness of COVID-19 treatment regimens may include death, use of mechanical ventilation, or hospital discharge; these variables—and in the United States, death in particular—may not always be readily available in commonly-used existing data sources. Best practices also require reporting the performance or validity of case definition algorithms; referencing the positive predictive values, sensitivity, or specificity if available; and providing sensitivity analysis to evaluate the impact of outcome misclassification.^{55,56} Refer to Section 3.4 for more details of misclassification.

During the outcome assessment (follow-up) period, censoring due to treatment crossover needs to be considered as well.^{32,57,58} For example, in evaluating the effectiveness of dexamethasone among hospitalized COVID-19 patients for mortality over a 28-day period, follow-up can begin one day after the treatment index and continue until the earliest occurrence of mortality, end of follow-up, or discharge from the hospital. This “initial-treatment” approach approximates the intention-to-treat approach often used in trials and assumes patients continue their initial treatment.²⁵
²⁶ An “as-treated”-style analysis can also be conducted that censors patients upon treatment changes, and the implications of either approach should be carefully weighted based on the postulated pharmacological pathway (e.g., Should follow-up time without the treatment be counted towards the treatment effect if it is expected that the drug effect ceases shortly after the drug is discontinued?).⁵⁷

Lastly, the overall study design should be visually communicated to show the temporal relationship between the index date and eligibility criteria, covariate assessments, and follow-up period to assess outcome events.⁴⁴ Such standardized displays for allowing readers to quickly understand how investigators approached the research problem is particularly important in COVID-19 studies given the volume and variety of research being published.

What kinds of questions can be addressed?

Between-person studies can address effectiveness and safety research questions. For example:

- What is the effectiveness of hydroxychloroquine with or without azithromycin among hospitalized COVID-19 patients on mechanical ventilation, hospital discharge, or in-hospital mortality?⁵⁹
- Are angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) safe among patients diagnosed with COVID-19?⁶⁰

What are the benefits and limitations of this design?

The advantage of a carefully-controlled cohort study design is the ability to emulate a target trial by specifying time zero to approximate randomization in a trial (i.e., eligibility criteria are met, treatment is assigned, and follow-up period begins) and adjust for potential confounders,^{3,7} which—in the absence of measurement and selection biases—allows for the determination of causality between the exposure and outcome of interest. As such, the cohort study design is well-suited to examine medication effectiveness and safety in outpatient and inpatient hospitalization settings. Cohort studies also allow multiple outcomes to be examined for a single treatment of interest (for example, primary outcome of mortality and secondary outcomes of hospital discharge).

Cohort study designs may not be well-suited due to insurmountable challenges in identifying appropriate comparison groups or the inability to minimize potential confounding or biases. For example, if the vast majority of the population is vaccinated or potential unmeasured differences between patients choosing and not choosing vaccination exist, a self-controlled study design may be superior.

Key considerations in relation to sources of error related to study designs are covered in Chapter 3.

3. Within-Person Design

Author: Iwagami M

What is it used for?

Within-person study designs, also known as self-controlled study designs, case-only designs, or Self-controlled Crossover Observational PharmacoEpidemiologic (SCOPE)

studies, mainly include self-controlled case series (SCCS) and case-crossover (CCO).⁶² These designs compare different time windows (i.e., lengths of time) within the same person, instead of comparing different people in between-person study designs such as cohort and case-control studies. An SCCS compares the occurrence of an outcome (event) during periods with and without exposure in the same person, whereas a CCO compares periods with and without the outcome for exposure (see Figure 2.4). Table 2.2 contrasts the between-person and within-person study designs.

The within-person study designs are used for electronic health record (EHR) research, sometimes together with the between-person study designs for the same research question. In addition, when primary data collection is newly planned, the within-person study design can be efficient, because only data for people with the outcome of interest are needed. In addition, the within-person study designs are feasible if most people in the study population were already exposed (to a vaccine for children,⁶³ for example), whereas a small number (proportion) of non-exposed people make the between-person study designs infeasible.

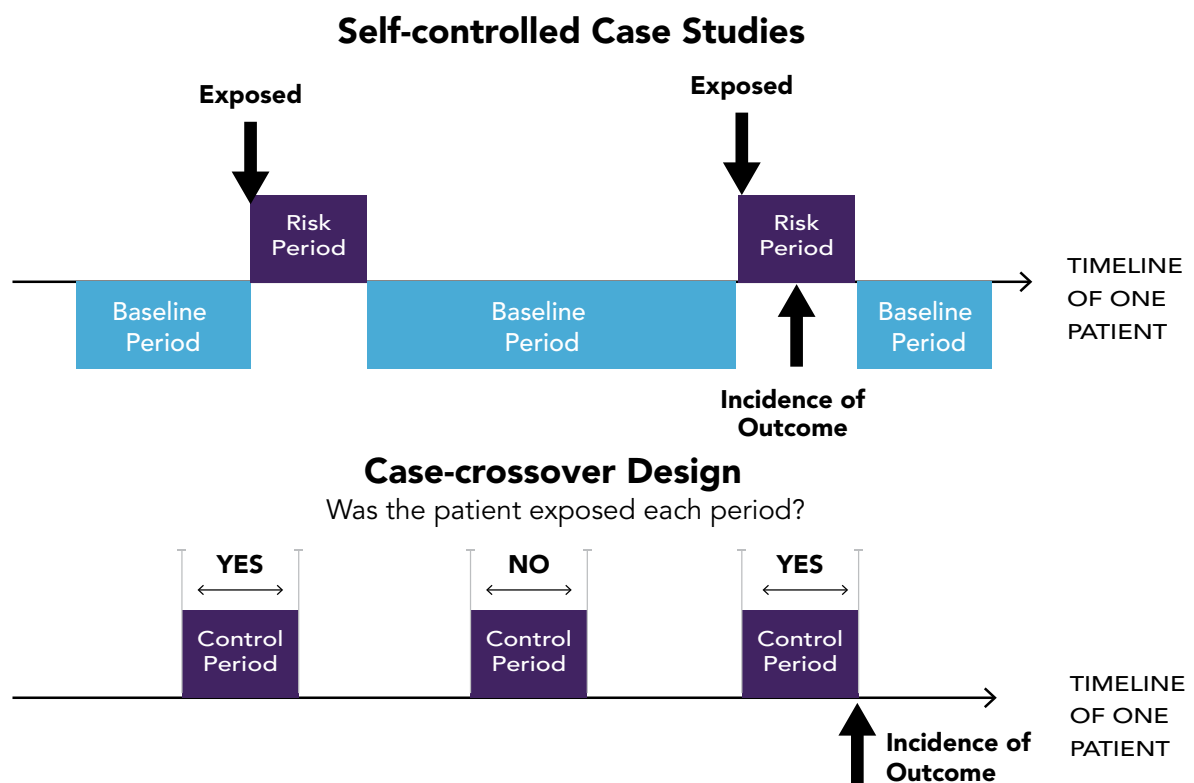


Figure 2.4. Graphical representation of self-controlled case series (SCCS) and case-crossover (CCO)

Table 2.2. Between-person and within-person study designs

	Exposure-anchored	Outcome-anchored
Between-person study designs	Cohort study (comparing people with and without exposure)	Case-control study (comparing people with and without an outcome)
Within-person study designs	Self-controlled case series (comparing periods with and without exposure)	Case-crossover design (comparing periods with and without an outcome)

What kinds of questions can be addressed?

Between-person study designs and within-person study designs can be used for the same research question, applied somewhat differently.⁶⁴ Table 2.3 shows the difference of population, intervention/exposure, comparison, and outcome [PI(E)CO] between a cohort study and SCCS for the research question on the association between COVID-19 infection and myocardial infarction (MI). The more specific research question that has been tailored to each study design is somewhat different. However, if there was a true causal association between COVID-19 and MI, both study designs should find a statistically significant association between them and reach the same conclusion (provided that they were well powered and appropriately conducted, minimizing biases inherent in each study design).

Table 2.3. Difference of PI(E)CO between a cohort study and self-controlled case series for an example of the association between COVID-19 and myocardial infarction (MI)⁶⁴

	Cohort study design (a between-person study design)	Self-controlled case series (a within-person study design)
General research question	Is there a (causal) association between COVID-19 infection and MI?	
More specific research question	Is the risk of MI increased among people with COVID-19 infection, compared to people without COVID-19 infection?	Is the risk of MI increased during periods with COVID-19 infection, compared to periods without COVID-19 infection?
Population	General population	People with MI
Exposure	People with COVID-19 infection	Periods with COVID-19 infection
Comparison	People without COVID-19 infection	Periods without COVID-19 infection
Outcome	Incidence of MI	Incidence of MI

What are the benefits and limitations of this design?

The main strength of within-person study designs is that they can minimize confounding factors that do not change over time (e.g., sex, genetics, habitual healthy or unhealthy behaviors). This is because the effects of these factors are cancelled out by design, even if they are unknown or unmeasured. Therefore, the within-person study designs can be used when there is concern about unmeasured or unknown confounding factors in between-person study designs. There are some examples in which an apparent association between an exposure and an outcome in a between-person study design was not confirmed by the within-person study design, possibly suggesting unmeasured confounding inherent in the between-person study design (or violation of the key assumptions that would allow use of the within-person study design, as shown below).⁶⁵

However, within-person study designs cannot be used for all research questions. The SCCS and CCO designs require several assumptions specific to each study design. In the SCCS, (i) occurrence of an event should not (appreciably) affect subsequent exposures or opportunity for subsequent observation, which can happen when, for example, the outcome is fatal, (ii) the background risk for the event must be constant within intervals, and (iii) events must be independently recurrent or rare.⁶⁶ In the CCO there should be no substantial change in exposure trends during the study period. Assumptions for both designs are best met when the exposure is transient (intermittent) and the outcome onset is abrupt (sudden), and there is no within-person confounding within the periods of observation.⁶⁷ If these assumptions are violated, within-person study designs can result in biased estimates.

Judging whether (or not) these assumptions are met is case-by-case, usually based on biological and clinical knowledge, whereas some statistical tests have been proposed to test (part of) the assumptions.⁶⁷ An article from Petersen et al. shows an example of how to assess SCCS assumptions, with some solutions for if the assumption is violated, for the association between COVID-19 vaccination and thrombocytopenia and thromboembolism events, which was indeed examined within SCCS design using UK electronic health records.^{66,68,69}

4. Descriptive Designs

Author: Lerro C

Descriptive epidemiology involves analysis of disease or exposure patterns in the population, focusing on characteristics related to person, place, and time (see Table

2.4).⁷⁰ Descriptive studies are broadly used for both scientific and administrative public health purposes.

For scientific purposes, descriptive studies can inform our understanding of disease etiology. We can make inferences about the underlying causes of disease by monitoring how disease incidence and prevalence change over time; differ with respect to age, sex, and race; and vary geographically. These studies cannot answer causal questions. However, information gleaned from descriptive studies might be used to generate hypotheses for high-quality rigorously controlled observational studies or trials.

Descriptive studies are used for administrative purposes to establish public health priorities, allocate funding, and evaluate the effectiveness of public health interventions. A health department monitoring uptake of COVID-19 vaccination might observe a sharp increase following implementation of a vaccine lottery, most pronounced in persons age 20-29. These descriptive results might indicate that this strategy is effective in motivating younger adults to get vaccinated.

In the context of the COVID-19 pandemic, descriptive data have become ubiquitous as a means of informing the public about patterns of testing, treatment, and disease (see Table 2.4 for examples of person, place, and time in descriptive studies of COVID-19). These descriptive data allow individuals and governments to take steps to protect personal and public health, respectively. Worldwide, many localities and federal agencies regularly publish information on case counts, vaccination rates, testing, hospitalizations, and deaths and use descriptive data to monitor the medical product supply chain to anticipate potential drug shortages.

Table 2.4. *Person, Place, and Time in Descriptive Studies*

Characteristic	Example	COVID-19 Application
Person	Age, sex, race, socioeconomic status	Identification of vulnerable populations to provide targeted interventions. Increasing numbers of pediatric COVID-19 cases might provide evidence to support mask mandates in schools.
Place	Country, city, neighborhood, hospital catchment area	Geographic differences in COVID-19 transmission metrics might be used to understand the role of local public health guidance or vaccine implementation strategies in reducing case counts and hospitalizations.
Time	Month, season, year	Evaluation of trends over time can inform planning for increased hospitalizations if case counts are increasing, or relaxing of public health measures if case counts are decreasing.

What kinds of questions can be assessed?

Descriptive studies are best suited to assessing patterns (person, time, place) of disease and exposure incidence and prevalence. In the context of pharmacoepidemiology, the exposure of interest is often a therapeutic or vaccine. Descriptive studies of drug utilization can demonstrate inappropriate use of therapeutics and underutilization of necessary therapeutics, including the impact of drug shortages on patterns of utilization and vice versa. A study conducted across Denmark, Finland, Iceland, Norway, and Sweden described public health measures as well as patterns of clinical management and outcomes of patients with severe COVID-19 in the ICU during the first wave of the COVID-19 pandemic.⁷¹ Authors found substantial variability in the critical care response across these countries, including in the use of invasive mechanical ventilation and use of certain treatments (e.g., IL-6 antagonists, hydroxychloroquine, and corticosteroids). A strength of this study is that it uses high-quality data to evaluate demographic factors, clinical characteristics, and patterns of ICU care across several countries, allowing authors to hypothesize potential reasons for variation in ICU mortality rates that could be addressed further using an inferential study design. This study also highlighted limitations of the RWD that were used; for example, some variables were missing for certain countries including use of specific types of therapeutics and certain comorbidities such as obesity.

A descriptive analysis in the National COVID Cohort Collaborative evaluated inpatient use of hydroxychloroquine, remdesivir, and dexamethasone among 137,870 US adults hospitalized with COVID-19.⁷² The authors were interested in evaluating both prevalence of use and trends in use over time. Hydroxychloroquine and remdesivir received emergency use authorization (EUA) from the Food and Drug Administration (FDA) for treatment of COVID-19 during 2020 (hydroxychloroquine EUA was later rescinded) and remdesivir and dexamethasone were included in the National Institutes of Health treatment guidelines for some adults hospitalized for COVID-19. The authors found that 6.3%, 21.2%, and 39.1% of the 137,870 patients were treated with hydroxychloroquine, remdesivir, and dexamethasone, respectively. Trends in use over time indicated that hydroxychloroquine use increased following the EUA and started declining after the EUA was revoked. The authors hypothesized that lower use of remdesivir compared to dexamethasone might be due to reported remdesivir shortages during the study time period. Following release of results of the RECOVERY trial, which demonstrated clinical benefit of dexamethasone among patients with mechanical ventilation or oxygen, 78-84% of patients who had invasive mechanical ventilation

were treated with dexamethasone or other corticosteroids. The findings suggest that dexamethasone might be underutilized among patients who are mechanically ventilated, and that wide variation in patterns of dexamethasone and remdesivir use across health centers indicates differences in patient case mix, drug access, treatment protocols, and quality of care. The lower-than-expected use of dexamethasone and variation across health centers might have been a consequence of drug shortages, indicating that hospitals restricted use to patients who were critically ill.

In a multinational study conducted across 11 data sources in 4 countries (the US, Spain, China, and South Korea), authors described the use of repurposed and adjuvant drugs in patients admitted to the hospital with COVID-19.⁷³ Commonly used repurposed drugs included hydroxychloroquine, azithromycin, combined lopinavir and ritonavir, and umifenovir, and the prevalence of use across data sources and countries varied widely. Though trends in use of repurposed drugs varied widely over time and often increased or decreased following regulatory guidance or highly publicized trial results, trends across data sources and even countries were generally similar. Authors reported large variation in use of adjunctive drugs across data sources, with the 5 most used treatments being enoxaparin, fluoroquinolones, ceftriaxone, vitamin D, and corticosteroids. This study fills an important knowledge gap by describing the drugs most used in this patient population and comparing use across different institutions worldwide. Inferential studies might be used to quantify the risk and benefit of these treatments in the management of patients with COVID-19.

Descriptive studies can also inform our understanding of disease etiology and might be used to identify vulnerable individuals who are at greater risk of disease compared to the general population. For example, early descriptive studies in the COVID-19 pandemic noted that rates of COVID-19 infection and COVID-19 mortality were higher among individuals with pre-existing hypertension.⁷⁴ Based on this descriptive evidence and biologic plausibility, several observational studies evaluated this association with rigorous control for potential confounders, yet found no clear relationship between hypertension and severe COVID-19 independent of age, sex, and other risk factors.

What are the benefits and limitations of this design?

An important strength of descriptive studies that has not previously been highlighted is that they can often be done at low cost with existing data. Many descriptive studies can repurpose existing surveillance data to answer their research questions. For example, studies have used vital records and census data to estimate excess deaths attributed to

the COVID-19 pandemic in many countries, including the US, Italy, Norway and Sweden, England and Wales, Guatemala, and Korea. Other descriptive studies, particularly those seeking to evaluate patterns of drug utilization, might instead use large existing administrative databases.⁷⁵

Descriptive studies are not suited to answering causal research questions. This study design does not involve comparative analysis or rigorous consideration of concerns known to impact interpretation of observational studies that aim to make causal inferences including confounding, measurement bias, and selection bias. A descriptive analysis of monoclonal antibody use in a large claims data source highlights both the capabilities of descriptive designs as well as the limitations.⁷⁶ Of the 211 million patients in the data source, 69,377 received monoclonal antibody treatments from January 2020 through April 2021. Bamlanivimab accounted for 85% of administered treatments, though trends indicated that combination bamlanivimab and etesevimab use was increasing. The study used outpatient data only, and without data from the inpatient setting, results underestimate overall monoclonal antibody use. The authors found that patients who received monoclonal antibodies were less likely to have Medicaid insurance compared to patients in the database overall, indicating possible barriers to care for these patients. Among patients receiving monoclonal antibodies, missing data was systematically lower for certain variables (e.g., race/ethnicity and household income) compared to patients in the database overall, which might impact the inferences made regarding these patient characteristics.

Descriptive studies are unique in that the purpose is often to generate research questions for inferential analyses as opposed to providing definitive answers. In addition, they might be able to provide important data to inform public health and clinical decision-making even in settings where there would be significant challenges to conducting a well-designed inferential study. When used correctly, descriptive studies can be a powerful tool to inform our understanding of disease etiology, inform public health, and monitor drug uptake and utilization.

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Chapter 3: Methods in Real-World Evidence Generation - Sources of Error

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When using real-world data, key potential sources of systematic error or bias include confounding, selection bias, immortal time bias, and measurement bias resulting from misclassification and missing data. In this chapter we describe the sources of error and provide solutions for detecting and handling these errors.

1. Confounding

Author: Li H

Description

Confounding is the distortion of the treatment-outcome association when the groups being compared differ with respect to variables that influence the outcome. Real-world evidence (RWE) studies can be challenging in observational settings where treatments are not randomly prescribed. Structurally, confounding occurs when a variable is a common cause of the exposure and outcome, as illustrated in Figure 3.1. In other words, confounders must be distributed unequally among the groups being compared, be associated with the outcome of interest, and cannot be intermediate factors between the exposure and outcome.¹ As a note of caution, authors sometimes use the term “selection bias” to refer to structural confounding in that treatments might be “selected” for patients based on certain characteristics that might be risk factors for outcomes. While selection bias is the result of differential selection into one or more of study groups, it may induce confounding if the characteristic on which differential selection is centered is associated with both the exposure and outcome of interest. These are distinct biases, as illustrated in Figure 3.1 and as described below in Section 2 of this chapter on selection bias.

In comparing drug treatments, confounding by indication is a common issue that occurs because patients are treated for a specific condition with a particular drug² or because patients have conditions that are contraindications to treatment with the medication, and these conditions or contraindications affect the outcome of interest. For example, patients with a history of gastric problems may preferentially receive cyclooxygenase-2-inhibitors (e.g., celecoxib) rather than traditional non-steroidal anti-inflammatory agents such as ibuprofen, which will result in a higher risk for gastric ulcer or bleeding in the celecoxib group.³ To the extent that confounders (variables that are associated with both exposure and outcome) are measured in real-world data, observational studies can address potential bias due to confounding. However, many real-world data sources lack information on important prognostic variables, including confounders.

Restriction, such as to patients with evidence of a particular condition, is a common strategy to reduce confounding in real-world evidence studies. However, even a study including patients with the same condition but differing levels of disease severity might

be susceptible to strong confounding. For example, patients with COVID-19 infection can experience a wide range of clinical manifestations, from no symptoms to critical illness; furthermore, patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19 or mortality. The prognosis of COVID-19 infection differs by underlying disease severity.⁴ When comparing treatments for COVID-19, it is therefore critical to account for disease severity and prognosis at the time of treatment initiation. In addition, it is important to recognize how treatment is evaluated when comparing different lines of therapy or dose levels in in RWE studies (e.g., second or third line therapy or higher doses are likely given to patients with more severe disease), as it might result in confounding by severity when the association reflects the underlying disease severity rather than the study drug effect.⁵

1: Confounding by indication/contraindication

Paranjpe et al. published a retrospective cohort study examining the association between therapeutic anticoagulation and in-hospital mortality among patients with COVID-19.⁶ Several commentators have raised concerns about potential confounding by indication, alongside other concerns including unmeasured confounding and immortal time bias.⁷ One of the concerns was that clinicians prescribe anticoagulation for some patients hospitalized with COVID-19 based on evidence of clotting and clinical judgment of their medical needs, while patients who do not receive anticoagulation typically do not have a clinical indication or may have contraindications such as advanced age, prior hemorrhage, or other bleeding risk factors. Without a full accounting of the treatment indications and contraindications that might influence treatment decisions and affect mortality, uncontrolled confounding is likely to affect the results.

2: Confounding by disease severity

Schultze et al. examined the association between use of inhaled corticosteroids and COVID-19-related death in patients with chronic obstructive pulmonary disease (COPD) or asthma using the OpenSAFELY platform. To the extent that asthma and COPD severity affect corticosteroid use and COVID-19-related death, confounding by severity is possible.⁸ The investigators sought to measure and adjust for underlying health conditions that may differ between individuals prescribed inhaled corticosteroids

and those using other medications for asthma and COPD. The evaluation for confounding by severity was further addressed using negative control outcomes. A persistent harmful association between inhaled corticosteroid use and non-COVID-19 related death was also observed, which could be related to the severity of disease requiring treatment exposure, suggesting that the real-world data source did not capture all markers of disease severity, resulting in a distorted exposure-outcome association. Negative control outcomes can be used to detect⁹ and correct for otherwise unaddressed sources of confounding.¹⁰

Why it is a problem?

Confounding is one of the major threats to observational studies and is frequently cited as an important difference regarding the internal validity of observational studies and randomized trials. Confounding by indication and severity can be particularly problematic in real-world evidence studies conducted in the context of a rapidly evolving pandemic as treatment decisions might vary across clinical, functional, and behavioral patient characteristics. Treatment decisions might also vary over time as trends in determinants of treatments are frequently changing as evidence of outcome risk factors and which treatments are effective evolve quickly. Physicians prescribe drugs based on the most current diagnostic and prognostic information available at the time of treatment decision-making, and in the context of current, but potentially rapidly changing, practice patterns. Regional and temporal patterns of infection transmission and the waxing and waning of different SARS-CoV-2 variants associated with different degrees of outcome severity can also be a source of confounding in the pandemic. Investigators must carefully consider and account for how these factors might vary over the course of a study period.¹¹

How to handle it

Schneeweiss et al. outline a framework for addressing measured and unmeasured confounding.¹²

Measured confounders can be addressed either in the design, by restriction or matching, or in the analysis through standardization (or weighting), stratification, or multivariable regression modeling. Propensity scores are a commonly used tool to implement many of these strategies. Variables that are not measured in the available

data but could be available in a subset could be addressed via 2-stage sampling or external adjustment approaches. Unmeasured variables can sometimes be addressed by certain design and analysis strategies. For example, a self-controlled design is not subject to between-person confounding, although it is susceptible to time-varying confounding. Instrumental variable analysis, which relies on leveraging a variable that is associated with the exposure, but not the outcome, except through its association with the exposure, can yield valid results even in the presence of unmeasured confounding of the treatment-outcome association.

In observational studies, confounding by indication and severity may be strongest and most difficult to adjust for when comparing treated with untreated persons, since individuals who require and use a medication may be clinically different from those that do not.¹³ Comparing patients exposed to a particular treatment to patients exposed to an active comparator addresses confounding by both measured and unmeasured factors to the extent that the treatments are used interchangeably. Using appropriate active comparators has been shown to reduce the impact of confounding by indication by balancing some unmeasured patient characteristics.^{14,15}

In certain clinical contexts, important confounders may be unmeasured and should be addressed by available methods.¹⁶ Quantitative bias analysis, including the E-value,¹⁷ allows researchers to correct or bound their estimates by making certain assumptions about the direction and magnitude of potential unmeasured confounding. The E-value represents the smallest magnitude of the association between the unmeasured confounder and the exposure and the unmeasured confounder and the outcome that would explain away an observed association between an exposure and an outcome. Quantitative bias analysis methods, including empirical calibration using negative control outcomes, can also be used to correct for unmeasured confounding.

2. Selection Bias

Author: Li H

Description

Selection bias occurs “when the estimate of occurrence or of etiologic effect obtained from a study population differs systematically from the estimate that would have

been obtained had the source population been available.”¹⁸ Selection bias can be present when the criteria used to select patients into study cohorts (e.g., exposed and unexposed cohorts) are inherently different. Much of the scientific evidence informing health policy and clinical decision making during the COVID-19 pandemic has been provided from non-interventional, observational studies. Although the evaluation of data obtained from non-interventional studies offers insights into medication effectiveness, caution is required when interpreting results. Selection bias can occur when studies use data sets with selection mechanisms that govern how patients enter the data set or cohort, such as when eligibility is based on patients admitted to the hospital, tested for active infection, or who volunteer to participate in a study, as recently articulated by Griffiths et al.¹⁹

Directed acyclic graphs are useful for depicting causal structures and can be used to illustrate common biases, including selection bias. Structurally, selection bias occurs when an investigator conditions on a common effect of 2 or more variables, such as when conditioning on effects of both an exposure (or a descendent of exposure) and an outcome (or a descendent of the outcome). This is sometimes referred to as collider stratification bias, and it induces a statistical relation between the exposure and outcome that is not causal. A structural classification of bias and confounding, illustrated in Figure 3.1, distinguishes between biases resulting from conditioning on common effects (“selection bias”) and those resulting from the existence of common causes of exposure and outcome (“confounding”), which is described above.²⁰ Immediately below are some example studies that have highlighted concerns in selection bias in the setting of COVID-19 real world evidence studies.

Selection bias: Conditioning on the covariate, which is caused by both exposure and outcome, induces a non-causal association between exposure and outcome.

Confounding: The covariate is a common cause of the exposure and the outcome, inducing a non-causal association between exposure and outcome.



Figure 3.1. Selection bias in the association between outpatient medication collected at hospital admission and outcomes occurring during hospitalization

Several studies have been published to evaluate the association between outpatient medications in relation to SARS-CoV-2 infection, recovery, or mortality using records of outpatient medications collected at hospital admission for COVID-19. These include studies of oral medications including diphenhydramine,²¹ angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers,^{22–24} HMG-CoA reductase inhibitors (statins).²⁵ Griffith and colleagues describe several scenarios in which restricting study cohorts to individuals who are hospitalized with COVID-19 or who are tested for SARS-CoV-2 can induce selection bias.¹⁹ For example, conditioning on having a SARS-CoV-2 test could induce selection bias in a study that seeks to determine whether cigarette smoking is associated with COVID-19 severity if health care workers are less likely to smoke but more likely to be tested for SARS-CoV-2 as compared to non-health care workers. In this situation, SARS-CoV-2 is a potential collider because both being a health care worker and COVID-19 severity are likely to be causes of testing. Therefore, conditioning on SARS-CoV-2 testing would induce a potential statistical, but non-causal, relation between smoking and COVID-19 severity.

Selection bias in the association between inpatient medication use and clinical outcomes during hospitalization

In any observational cohort study aiming to compare 2 or more treatment strategies, selection bias can occur when the criteria for selecting patients into—and particularly excluding patients from—the cohort is different between groups. For example, in one study, exposure was based on receiving hydroxychloroquine²⁶ within 48 hours of hospitalization. Hydroxychloroquine-exposed patients were compared to unexposed patients. Unexposed patients were defined as those who did not initiate hydroxychloroquine at any time during hospitalization; those patients who initiated treatment more than 48 hours after hospital admission were therefore excluded in the primary analysis. Because hydroxychloroquine was used as a treatment for severe COVID, excluding from the unexposed group those patients who went on to initiate treatment after the 48-hour exposure assessment window effectively selected out from the unexposed group many patients who deteriorated and went on to have poor outcomes. A similar design was used to compare remdesivir exposure to non-exposure.²⁷ Looking beyond the start of follow-up to exclude patients from the study can introduce selection bias in addition to immortal time bias (see Section 3.3).

Self-selection into studies, missing data, and loss to follow-up are threats to the validity of exposure-outcome association estimates

Prospective studies in which COVID-19 status can be determined through voluntary participation, such as survey data that are linked to administrative records²⁸ or mobile phone-based applications,¹⁹ can be subject to selection forces that govern who is included in the study, which can affect the generalizability of study findings. As population testing for COVID-19 is not generally performed in random samples, studies have found that participants who volunteer for scientific studies conditional on having had a test are more likely to be highly educated, health conscious, and non-smokers as compared to the general population.¹⁹

Both missing data when selection is based on availability of such data (see Section 3.4) and differential losses to follow-up (i.e., informative censoring) can introduce selection bias. Differential losses to follow-up occur when participants drop out of a study or can no longer be followed for reasons related to the outcome(s) of interest and when this dropout occurs more frequently in more treatment groups.²⁹

Why it is a problem?

Selection bias can compromise the internal validity of a study by distorting the association between exposure and outcomes. Furthermore, collider stratification bias can also be introduced when making statistical adjustments for variables that lie on the causal pathway between an exposure and outcome, when confounders (i.e., common causes) exist between these intermediate variables and the outcome of interest. Independent of this potential form of collider stratification bias, conditioning variables that are intermediates on the causal pathway between exposure and outcome can also obscure the ability to identify a causal effect.

How to handle it

While loss to follow-up, self-selection, and missing data are generally not fully avoidable in real-world data studies, careful study design can reduce these issues and mitigate resulting bias. Researchers can also mitigate selection bias by clearly defining the target population of interest and examining potential impact by implementing sensitivity analyses if they have quantitative knowledge about factors influencing selection in their study.³⁰

In case-control studies, selection bias can be reduced by sampling controls in a manner to ensure that they will represent the exposure distribution in the population that gave rise to the cases. When determinants of selection or censoring are known and measured, inverse probability weighting can be used to address structural selection biases through the creation of sampling weights or censoring weights.³¹ Approaches to addressing missing data are described below.

3. Immortal Time Bias

Author: Renoux C

Description

While several time-related biases have been described in pharmacoepidemiologic studies,³² immortal time bias is the most common of these biases in studies of drug effectiveness and safety, especially in the context of COVID-19.¹⁶ Latency considerations are also relevant when evaluating vaccines against COVID-19.

The study of drug effectiveness and safety presents unique challenges that stem from the time-varying nature of drug exposure. Moreover, the use of previously collected data enables design flexibility that may, if some elements of the design are not adequately implemented, introduce time-related biases. Properly defining and analyzing treatment status over follow-up time is important. Indeed, inappropriate accounting and classification of exposure over time can introduce immortal time bias.^{33–35} Immortal time corresponds to a period of follow-up during which, by design, the outcome of interest (death or another outcome) cannot occur. In cohort studies, immortal time is typically introduced when exposure status is defined based on a treatment administered at some point during follow-up. The time period between disease diagnosis or cohort entry and the first treatment is “immortal” because the patient has to survive or be outcome-free (owing to censoring of events in the analysis) to be classified as treated. Immortal time bias is then introduced when this immortal period between diagnosis or cohort entry and the first treatment is either misclassified as exposed or excluded from the analysis rather than correctly accounted for as unexposed. Similarly, requiring a minimum number of prescriptions or duration of treatment for the definition of exposure but considering patients as exposed from

the first treatment introduces immortal time bias. Given that individuals move in and out of health systems or insurance plans, it can also be tempting to require patients to have a certain amount of enrollment in follow-up (e.g., one year), which also may create immortal time.

What does it look like in practice?

Several recent cohort studies assessing the effectiveness of various drugs in patients hospitalized with COVID-19 defined exposure on the basis of treatment received at any time during follow-up or within a limited time period (such as the first 48 hours of hospitalization) in their primary analysis.^{23,26,36–39} However, patients were considered exposed as of the date of admission (cohort entry), thereby introducing immortal time bias (Figure 3.2a). The time period between cohort entry (date of hospitalization) and the first prescription or exposure for the treated patients corresponds to immortal time, as patients must survive or be event-free (i.e., not censored) to receive their first treatment. This immortal person-time should be classified as unexposed until the first exposure (prescription), at which point the patients are classified as exposed. Similarly, a cohort study where only patients with a minimum of 3 days of treatment were included in the analysis but cohort entry was defined as the first day of treatment also introduces immortal time bias.⁴⁰

In other cohort studies of patients hospitalized with COVID-19, cohort entry was defined as the date of the first treatment during the hospitalization for treated patients and as the date of hospitalization for those not treated, also introducing immortal time bias (Figure 3.2b).⁴¹ In this situation, the immortal time period is excluded rather than misclassified.

Why is it a problem?

Immortal time bias is particularly problematic in cohort studies of drug effects because it tends to systematically bias the results downward in favor of the treatment under study. As such, a treatment may appear protective when it is ineffective, or neutral when it is actually harmful.^{33–35} The latter is illustrated in a study evaluating the effectiveness of hydroxychloroquine and azithromycin in patients with COVID-19, where both the primary analysis with misclassified immortal time and a sensitivity analysis correctly classifying exposed and unexposed person-time, thereby preventing immortal time bias, were conducted. In the primary analysis with immortal time bias, the hazard ratio was 1.³⁵ (95% CI 0.76–2.40) while in the correct sensitivity analysis, the treatment was

associated with an increased rate of death (HR 1.83; 95% CI 1.02, 3.28).³⁹ The magnitude of the bias and its impact on the results depends on the number of patients exposed in the cohort, the amount of immortal time misclassified or excluded, the duration of follow-up, and the number of events.³³⁻³⁵

How to handle it

Immortal time bias, as described above, is introduced by the investigator at the design or analysis stage and can thus be easily avoided. A simple first approach at the design phase is to define exposure at the date of cohort entry, in a cohort of patients defined by a first diagnosis or hospitalization for COVID-19. Exposure could also be defined based on treatment initiation during a specific time period, such as in the first 48 or 72 hours of hospitalization, with start of follow-up accordingly moved to 48 or 72 hours after the date of hospitalization. A second approach is to use a time-varying exposure definition at the analytic stage, with each day of follow-up classified as either exposed or not exposed to the drug of interest. Finally, a design approach aimed at emulating a target trial (see Chapter 2) in this setting can be used, such as the prevalent new-user cohort design or the creation of a series of sequential cohorts at predetermined time intervals.⁴²⁻⁴⁴

Latency considerations

When evaluating effectiveness of vaccines against COVID-19, latency may be considered in the exposure definition. The latency time period takes into account the biologically relevant timing of exposure. Thus, for a vaccine fully effective >14 days after being injected, patients may be considered unexposed for the first 14 days following vaccine receipt and exposed thereafter. This latency period must be applied to all exposed patients and not only to those with the event of interest during follow-up. The same latency considerations apply when studying the effectiveness of vaccines requiring 2 doses, where patients move from unexposed time period to partially exposed and fully exposed during follow-up. These latency considerations may not apply to all outcomes, and may be irrelevant when studying safety,⁴⁵ for example.

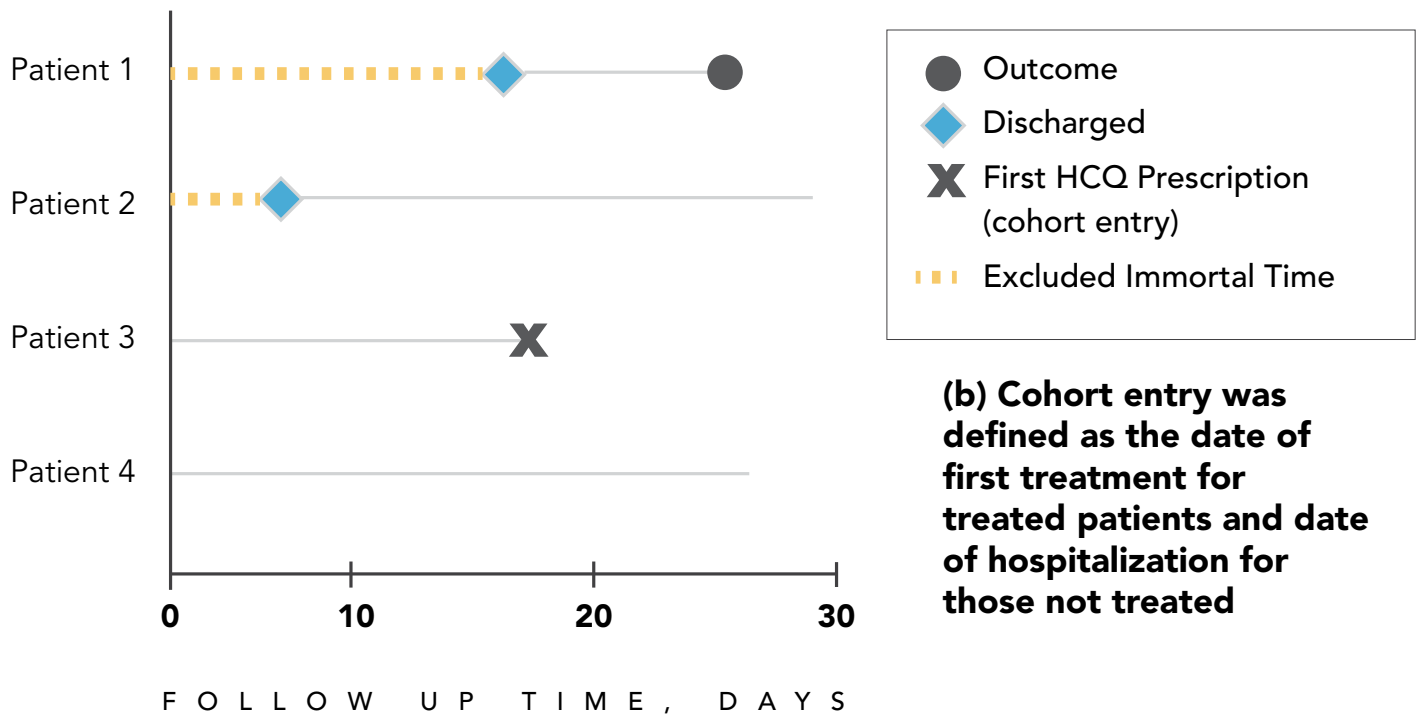
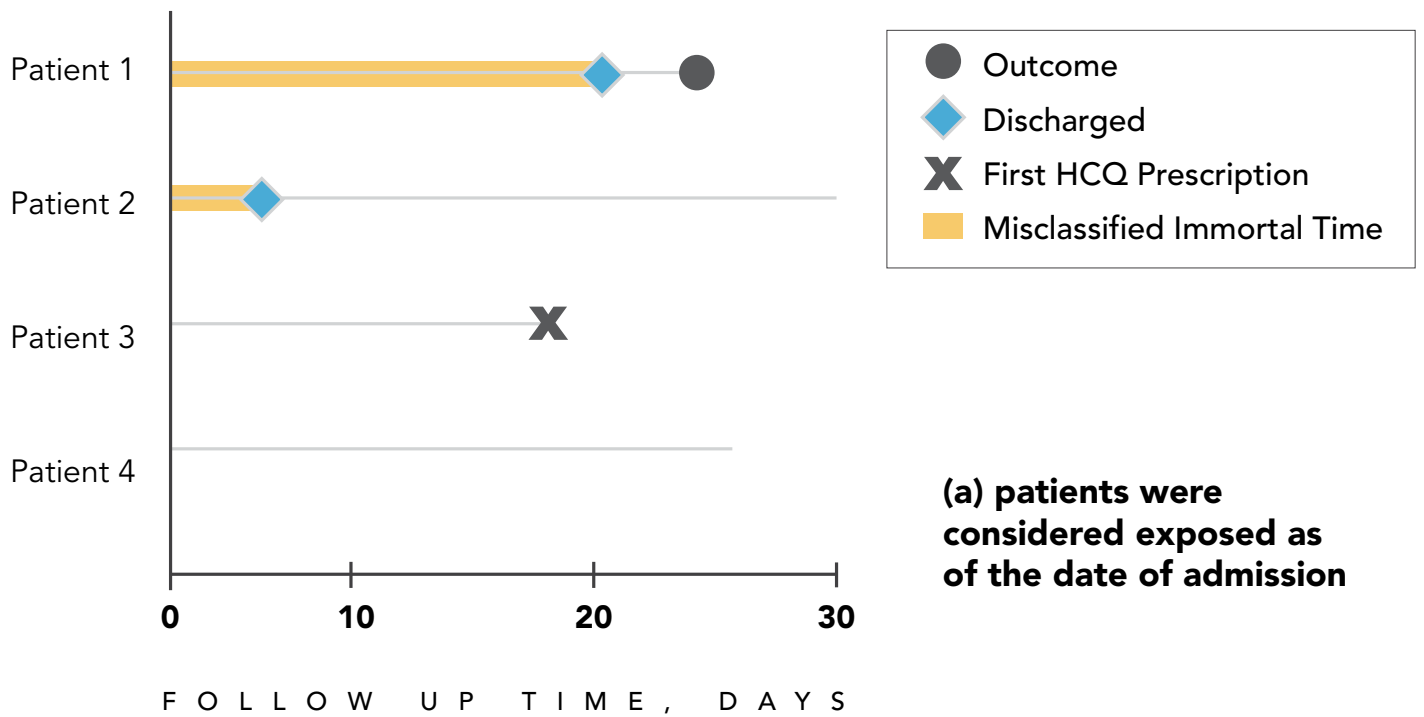


Figure 3.2. Illustration of immortal time bias in a hypothetical cohort of patients hospitalized with COVID-19

Panel A. Patients 1 and 2 receive a first prescription of hydroxychloroquine at some point during hospitalization, but are considered exposed from the date of hospital admission (cohort entry), thereby introducing immortal time bias caused by exposure misclassification (red line).

Panel B. Cohort entry for patients 1 and 2 is defined by the first drug prescription and by the date of hospital admission for the unexposed, thereby introducing immortal time bias caused by excluded unexposed person-time (red dashed line) that should be accounted for in the unexposed group. **Abbreviation:** HCQ = hydroxychloroquine

4. Misclassification

Author: Winterstein AG

Description

While the concept of confounding is broadly appreciated as a major threat to causal inference studies by epidemiologists and even non-epidemiologists, measurement or misclassification bias is less recognized. Likewise, while the value of randomization to ensure balanced comparison groups is intuitive, clinical trial features that address measurement bias may be more subtle. We understand that blinding may enhance objective assessments of outcomes by patients or clinicians, but other trial features are equally important including:

- **protocol-based outcome ascertainment:** This dictates what and how study outcomes are assessed, thus reducing the chance that outcomes are missed or misdiagnosed.
- **prescribed patient assessments at study entry:** This ensures that key characteristics are captured to assess whether comparison groups are balanced with regard to baseline risk for the primary study endpoint and to define the level of generalizability of study results.
- **monitoring of patient adherence to treatment assignments:** This aims to prevent contaminated exposure groups where patients switch or discontinue treatment, thus diluting the observable treatment effect.

What does it look like in practice?

Clinical trials aim to impose a tightly controlled environment that includes prevention of measurement biases. RWE studies that rely on routinely collected data, in contrast, have no ability to prescribe what and how baseline conditions, exposures, and outcomes are collected. Thus, measurement in RWE studies (i.e., the process of converting the available data into key study variables) is as important as the choice of an appropriate study design. To illustrate, consider how information in electronic health record (EHR) or billing records is generated. Each step, from a patient's decision to seek health care to a health care provider's decision about how to evaluate the patient and what treatment to prescribe to a patient's decision to use the prescribed treatment and seek follow-up care is not protocol based and is not random (see Figure 3.3).

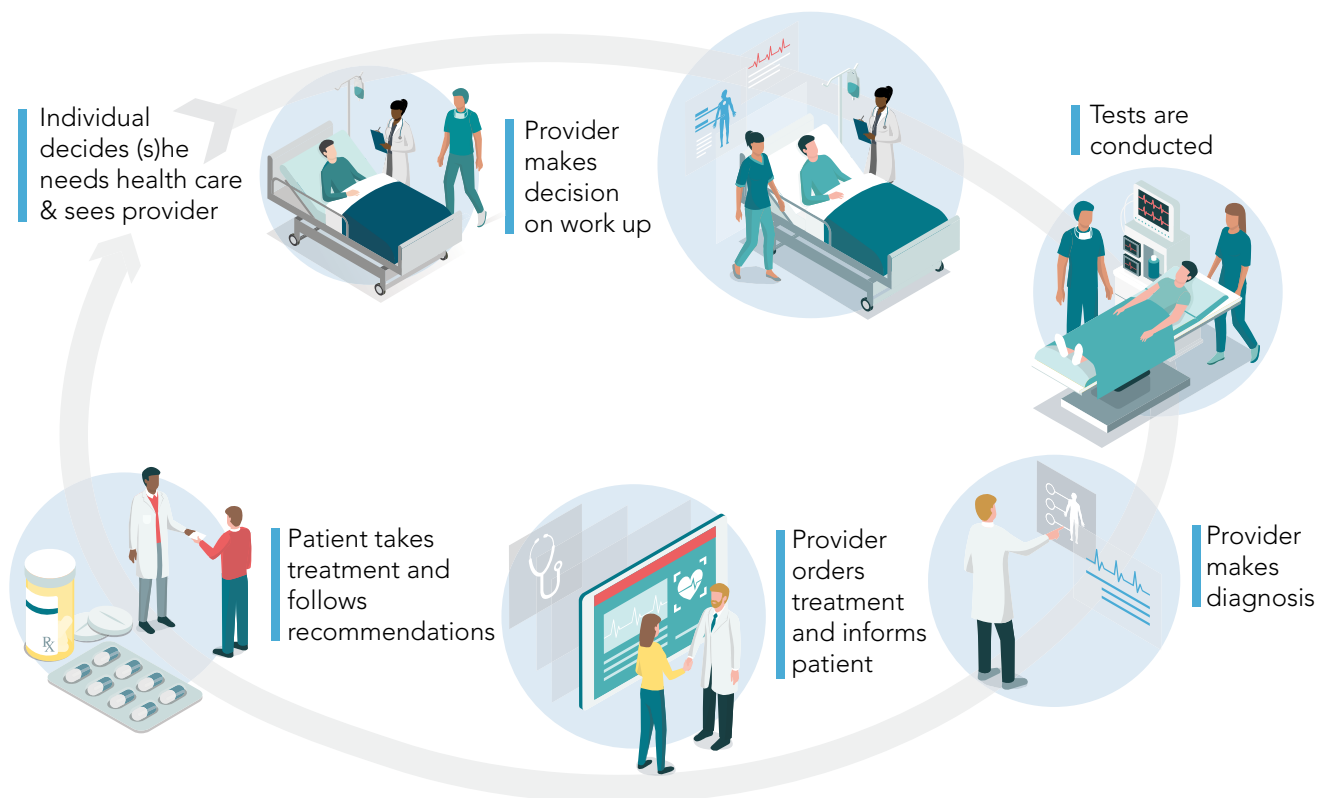


Figure 3.3. Patients who are available in a real-world data (RWD) database may be systematically different from the underlying population of patients we assume they represent. Diagnostic workups may be incomplete or flawed and result in incorrect clinical assessments. Patients may fill their prescription, but they may never consume the dispensed medication. Patients may have certain comorbidities that are not documented during a clinical visit or otherwise missed, leading to potential unmeasured confounders.⁴⁶

In addition to this **non-differential misclassification** (i.e., error in measurement that affects both comparison groups to the same extent), researchers need to be aware of differential misclassification. For example, the propensity to get evaluated for a particular disease, leading eventually to its diagnosis, may be directly related to certain patient characteristics or their treatment. In this scenario, exposure groups will have a different probability for the detection of the outcome. Thus, for each exposure-outcome pair that is evaluated in a RWE study, it is critical to understand the process that generated the data (i.e., to understand what factors determine the validity of measurement).

Without understanding the process that generated the data (i.e., without understanding the health care system, patient and provider decision-making, and documentation and coding practices), we cannot show that:

- Patients who take medications to treat diabetes have more diagnoses of depression than patients who don't (because patients with chronic medication use see their providers more often and have a higher probability of being evaluated for other diseases)
- Patients who take a newer brand of medication have better outcomes than those who take the older generic drug for the same indication (because socio-economic status is oftentimes not available in a database, affordability of the brand of medication becomes an unmeasured confounder)
- Patients who stop statins die sooner (because preventive medications are typically discontinued in end-of-life situations and patient prognosis may not be available in the database to address this issue of reverse causation)
- Patients who have regular refills of the prescription medication have less hospitalization than those who don't (because hospitals usually don't use patients' home supply, hospitalized patients will have fewer refills)

None of these scenarios are causal. They rather reflect measurement biases, a different type of bias than confounding, which accordingly cannot be addressed with standard methods to adjust for confounding such as propensity scores.

Why is it a problem?

The above examples touch on scenarios where bias is introduced based on the sheer availability of data in the data set. To better understand the impact of such measurement biases, we can consider simple epidemiological 2x2 tables that describe differential or non-differential misclassification of binary outcomes, exposure, and confounders.^{47,48}

Outcome misclassification

Outcome misclassification occurs if outcomes are missed (which signifies a sensitivity problem of the measure and is illustrated by the right-pointing arrows in Table 3.1) or outcomes are erroneously diagnosed (which signifies a specificity issue and is illustrated by left-pointing arrows).⁴⁹ The examples in Table 3.1 show true values and the effect of non-differential misclassification of the outcome (i.e., similar measurement error in both exposure groups). The left scenario assumes 90% sensitivity (i.e., 10% of the true outcomes are missed) and the right scenario assumes 90% specificity (i.e., 10% of the patients without an outcome are misdiagnosed as having the outcome). The true risk ratio (i.e., assuming we are evaluating the results of cohort study and follow-up time is fixed) is calculated as:

$$\frac{20 / 100}{11 / 100} = 2.0$$

Table 3.1. Outcome misclassification

	<i>Outcome +</i>	<i>Outcome -</i>		<i>Outcome +</i>	<i>Outcome -</i>
Exposure +	20-2=18 →	80+2=82		Exposure +	20+8=28 ← 80-8=72
Exposure -	10-1=9 →	90+1=91		Exposure -	10+9=19 ← 90-9=81

The observed risk ratio considering measurement bias is:

$$\frac{18 / 100}{9 / 100} = 2.0 \qquad \frac{28 / 100}{19 / 100} = 1.47$$

Thus, in this scenario (i.e., a cohort study with binary outcome classification), reduced sensitivity would not bias the risk ratio (note the same is not true for case-control studies and a variety of other scenarios of outcome misclassification where sensitivity does matter), but a reduced specificity biases the risk ratio towards the null hypothesis (no exposure effect).

Similar simple calculations can be conducted for scenarios with differential outcome misclassification, i.e., where sensitivity and / or specificity or both vary between exposure groups. It can be appreciated from the 2x2 tables that this will almost always result in bias.

Common issues with outcomes measured from routinely collected health care data arise when the diagnosis requires screening, such as with the manifestation of diabetes or testing for COVID-19, especially in populations that may remain asymptomatic. Screening procedures could be erroneously coded with the diagnosis, creating false positive cases and thus a specificity issue. Screening could also be omitted or delayed, creating false negative cases and a sensitivity problem. The latter is a typical scenario that can create differential misclassification inherent in systematic differences in clinical evaluations: for example, patients who use a drug that is known to cause diabetes (e.g., antipsychotics) will be more frequently evaluated for diabetes than a potential comparison group of non-users of antipsychotics.⁵⁰ Likewise, in the pandemic we have observed enhanced screening efforts in high-risk groups such as health care workers, which will have likely biased population-based infection estimates. If the data for the exposure and comparison groups originates from different data sources, the risk for differential misclassification is often amplified and requires particularly careful assessment. To extend the COVID-19 example above, an investigation of the effect of vaccines on COVID-19 infections in real-world data would have likely shown a reduction of infections among vaccinated individuals early after vaccinations were accessible, even if the vaccine were in fact entirely ineffective. This is because the propensity to test for COVID-19 might have been reduced in anticipation of a protective effect of the vaccine. Of course, we have now learned that breakthrough infections may still occur, and accordingly, testing may have increased again.

As a general rule, outcomes that result inevitably in health care utilization because of their severity, such as hospitalizations, are typically less prone to misclassification errors than outcomes that require patient and clinician decisions for evaluation, but the ability of the database to capture and correctly classify any outcome should still be evaluated. For example, even though the diagnosis of myocardial infection is unlikely to depend on patients' decisions to seek health care or clinicians' decisions to order the appropriate tests, evaluation of myocardial infarction based on hospital admission records will be incomplete if death records are not accessible.

Exposure misclassification

Issues with exposure misclassification can be quantified using the same 2x2 tables. In Table 3.2, the left table illustrates again the effect of non-differential misclassification of exposure based on 90% sensitivity and the right table illustrates the effect of 90% specificity.

Table 3.2. Exposure misclassification

	Outcome +	Outcome -		Outcome +	Outcome -
Exposure +	20-2=18	80-8=72		20+1=21	80+9=89
Exposure -	10+2=12	90+1=91		10-1=9	90-9=81

Note that the denominators, i.e., the total number of exposed and unexposed (initially 100 in each group), change as result of misclassification as well. Both scenarios bias the risk ratio and again, the contingency tables facilitate assessments of the impact of any other scenarios, e.g., where sensitivity and specificity problems occur simultaneously or where misclassification is differential, i.e., varies between those patients with and without outcome.

$$\frac{18 / 90}{12 / 110} = 1.8$$

$$\frac{21 / 110}{9 / 90} = 1.91$$

Specificity problems are prominent with exposure measurement in routinely collected health care data because of patient non-adherence issues and missing end dates in utilization (e.g., a prescription may have been written but not filled, or filled but not taken, or prematurely discontinued). Specific to COVID-19, the capture of vaccination data is a concern for exposure measurement as capture is fragmented and longitudinal data for the full dose series may not be available in a single database. This is especially difficult and more unusual than typical health care data because the setting varies from receiving a vaccine at the pharmacy to receiving the vaccine at a mass vaccination site such as a football stadium where reporting of the data may not be consistent or complete. Other challenging constellations include scenarios where the outcome

follows soon after drug discontinuation or switching from one study drug to the other, where outcomes may have induction or latency periods or where drug effects continue after discontinuation.⁵¹ Understanding of the underlying pharmacology to guide assignment of exposure times, defined as the time period during which a drug effect could be expected, is critical to avoid misclassification and biased exposure effect estimates. A particular challenge is protopathic bias where drug exposure is discontinued because of early signs of outcome manifestation, which, if not considered in the design and measurement, will inevitably result in an underestimate of the drug effect.³²

The effects of the pandemic on drug utilization are yet to be described, but one might expect greater gaps with drug refills due to reduced accessibility to health care providers in the outpatient setting. Problems in assignment of outcomes to distinct exposures might also occur in analysis of patients in acute or intensive care settings where different treatment approaches were tested empirically, leading to frequently changing regimen.

Confounder misclassification

While confounding and measurement bias are two separate mechanisms and require different approaches for mitigation, bias can occur in the measurement of confounders as well, potentially exaggerating the confounding bias. To calculate the impact of confounder misclassification, contingency tables can be used again, this time by stratifying by the confounder. Intuitively, it makes sense that a poorly measured confounder will result in poor adjustment for that confounder, but adjustment may not only be incomplete but may produce even more bias. Consider for example a scenario where a confounder is measured more completely (i.e., with better sensitivity) in the exposed than in the comparison group. This would create a false assessment of the presence of this confounder in the 2 comparison groups and thus, adjustment for this confounder would not balance the comparison groups but potentially amplify the imbalance. Related scenarios that can be encountered in RWD include more comprehensive assessments in the exposed than the comparison group (e.g., because certain tests are required before a drug is initiated). Another common clinical scenario is the documentation and coding of a disease during an office visit that presents the indication for a newly prescribed medication (e.g., obesity is coded if anti-obesity treatment is initiated, but omitted otherwise).

How to handle it

From the above it is clear that measurement bias can be introduced by any variable that factors into the final analysis of the (causal) effect of the exposure on the outcome. The impact of measurement bias can be severe and cannot be addressed with common approaches that are used to address confounding. In fact, in the case of misclassified confounders, adjustment for confounding may actually exaggerate bias. Such as with confounding, in order to anticipate measurement bias, it is critical to understand the process that generated the data and what factors have influenced whether a certain variable is present or not present in the data set or measured correctly or incorrectly. This includes an understanding of factors that influence patient decision-making, diagnostic processes and related coding practices, and reimbursement policies, to name a few.

No database will be optimal for the measurement of all necessary study variables with perfect validity, but careful review of each potential data source is the first step to avoid misclassification bias. It should be clear and accepted that every RWD researcher will encounter research questions that cannot be answered with the available RWD sources, and moving ahead and conducting such studies regardless is irresponsible. In those cases where we feel that measurement bias might be an issue but is addressable and does not preclude our ability to make valid causal inferences, there are several steps that can help in mitigating such bias.

Measure validation

Well-conducted pharmacoepidemiologic studies will aim to use measures that have been validated against a gold standard. This is commonly seen with claims-based outcomes measures that have been validated against medical charts, but to a much lesser extent with measures of exposure and confounders. The importance of metrics to operationalize validity (e.g., specificity or sensitivity) might vary based on the particular scenario that is addressed with the measure.⁵² It should also be noted that the suitability of a medical chart to serve as gold standard may vary across scenarios and thus, EHRs may need further evaluation against prospective protocol-based assessments, especially to ensure data completeness. Furthermore, validation studies should be generalizable to the data source, patient population, and other relevant factors that may affect the degree of measurement error that we would expect in the study at hand.

Simple bias / sensitivity analysis

The contingency tables above illustrate how the effect of misclassification errors on exposure effect estimates can be quantified. The same can be done post-hoc, after analyses have been completed to quantify the impact of potential measurement bias.^{53,54} Estimates of measurement error that can be tested may originate from validation studies (e.g., using published estimates of sensitivity or specificity) or be based on other assumptions such as expert opinion. Common examples for sensitivity analyses where the robustness of results across a range of values is tested include scenarios where the duration of assumed drug exposure is varied, or where look-back periods are increased to enhance the sensitivity of confounder measurement.

Probabilistic bias analysis

An extension of the contingency table approach is the use of probabilistic bias analyses, which can assess the impact of multiple measurement errors involving several study variables simultaneously. Using validation studies or other assumptions about the size of measurement errors, several study variables can be updated at the level of individual study participants and outcomes analyses redone with these new updated data sets.

Multiple imputation

As illustrated, measurement bias can occur because of incorrect or incomplete measurement (the topic of missing data is discussed further in the next section). The latter is often addressed with multiple imputation approaches that model the probability to have a potential variable (e.g., disease) or variable value of interest. As briefly touched upon earlier in this section, study variables in RWD are often not missing completely at random (MCAR) and thus, complete case analyses where patients with incomplete measures are excluded commonly introduce bias.^{55,56} Especially if there is reason to believe that absence of a variable does not reflect absence of disease (e.g., because of delayed diagnosis), multiple imputation might be an important means of completing missing data elements. Other approaches to addressing missing or incomplete variables, such as propensity score calibration and regression calibration, are based in similar approaches where richer information for a subset of patients is used to enhance the entire data set.⁵⁷

In summary, even though a range of approaches to address measurement bias exist, they are not as widely integrated in RWE studies as approaches to adjust

for confounding. This notwithstanding, measurement bias can be equally severe and greatly affect the ability to make causal inferences.⁵⁸ Therefore, good pharmacoepidemiologic study practices require that potential sources of measurement bias are carefully examined, validation studies of key study variables are presented, and the direction of potential bias is addressed and ideally quantified.⁵⁹ A well-conducted and presented RWE study will allow the assessment of whether the RWD source was appropriate (fit-for-purpose) for the research question at hand, and whether the processes that generated the data were appropriately considered in the study design and analysis.^{60,61}

5. Missing Data

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Description

The most commonly used RWD sources, insurance claims data and EHRs, could have missing data when used for COVID-19 pharmacoepidemiology research. For patients with mild COVID-19 disease, supportive care has been the preferred management strategy;⁶² pharmacological treatments with possible antiviral effects have been primarily used for patients with moderate to severe disease requiring hospitalization.^{63,64} Insurance claims data generally do not capture detailed information on inpatient medication use, vaccines or treatments not reimbursed by the insurance provider or investigational drugs, or certain clinical data elements, limiting their utility for addressing some questions.⁶⁵ In studies relying on claims, missing information generally translates into misclassification of study variables, which can lead to bias. In contrast, EHR data often enable ascertainment of certain clinical covariates that are not usually measured in claims data, such as vital signs, laboratory test results, smoking status, body mass index (BMI), and code status. However, these factors can have a substantial amount of missing data in routine-care EHR, which can also lead to bias.⁶⁶ In addition, EHR-discontinuity, defined as receiving care outside of the reach of a given EHR, can result in incomplete capture of medical information in the study EHR, which is another form of data incompleteness that can lead to misclassification of key study variables.⁶⁷ It is critical to examine and address missing data in study outcomes, exposures, and covariates.

What does it look like in practice?

For routinely evaluated health metrics or biomarkers, such as laboratory results, vital signs, or body mass index, missing data are presented as having no values recorded in the timeframe of interest (e.g., one year prior to a drug dispensing). If longitudinal recording of multiple values of the same biomarkers is used to monitor disease course, such as a change in glycosylated hemoglobin (HbA1c) or inflammatory markers, having a recording of the biomarker at some time points (e.g., at cohort entry) but not others (e.g., at certain visits or time interval during follow-up) also creates a scenario of missing data (e.g., change of the value since baseline). This is in contrast to what is typical in randomized trials in which measurements are made on a specific schedule according to a study protocol. For health outcomes, such as those defined using diagnostic codes, missing data often result in misclassification of study variables (i.e., false negatives) with EHR or claims data. For example, if a patient has COVID-19 but does not have a medical encounter during the study period in which a COVID-19-related code is recorded, it will appear in the data as though this individual does not have COVID-19. It will not be known that the data point is missing, but the patient's COVID-19 status will be misclassified. This creates an issue between a true negative versus an unknown, as the absence of the value may be the result of the patient not having the condition, the value not collected, or the patient being seen outside the system.

Why is it a problem?

The mechanism or reasons causing missing data will determine its propensity for biasing effect estimates.⁶⁸ "Missing completely at random" (MCAR) means the probability of missingness is independent of exposure and/or outcome (e.g., missing a batch of laboratory results due to a fire). Under MCAR, using only people without missing data (i.e., complete case analysis) will not lead to bias. "Missing at random" (MAR) means the probability of missingness depends only on observed variables (e.g., missing prostate specific antigen values in females). Under MAR, complete case analysis will be biased, so proper implementation of statistical methods is needed to yield unbiased results. "Missing not at random" (MNAR) means the probability of missingness depends on not only observed but unobserved information (e.g., people with better renal function tend to miss serum creatinine values that measure renal function). Under MCAR, bias caused by missing data is expected, and an effort to quantify the impact on the study validity should be made.

How to handle it

Assessment of missing mechanism: The first step is to examine the frequency and patterns of missingness in the database.⁶⁹ Then the missing mechanism should be determined based on domain knowledge or empirical data whenever available.⁷⁰ Under the assumption of MCAR, complete case analysis is unbiased, but statistical power may be reduced. We will now briefly survey strategies to reduce potential bias due to missing data under MAR and MNAR.

Three commonly used statistical methods to handle missing data under MAR—multiple imputation, maximum likelihood methods, and inverse probability weighting:^{68,71} Multiple imputation (MI) relies on a correctly specified imputation model that uses observable information to replace the missing value with a predicted value and repeats such imputation process multiple times to account for the uncertainty of the imputation process. While there is no magic cut-off of missing proportion for reliable imputation, generally imputing data when missing data >40% should be avoided.^{72,73} The implementation of MI can be computationally intensive for large data sets.

Maximum likelihood methods use an iterative algorithm that fits different sets of parameter values for an assumed probability distribution until it identifies what maximizes the log-likelihood value (i.e., what fits the observed data the best). It leverages all the observed information and often yields estimates with optimal efficiency. However, sometimes incomplete likelihood functions have a complicated form or require special computational techniques (e.g., expectation-maximization algorithm).⁷⁴ Therefore, the implementation of maximum-likelihood-based methods may be problem-specific and require special software.

Inverse probability weighting methods weight patients without missing data by the reciprocal of the probability of having complete records to adjust for factors underlying missingness.⁷⁵ Weighting does not use those with missing data in the final outcome model but rather emphasizes (with larger weights) those patients with complete data but with similar characteristics as the patients with missing data. Weighting is sometimes affected by extreme weights, both of which may compromise statistical efficiency.

Strategies to reduce bias due to missing data under MNAR: Sometimes researchers may be able to obtain additional information through linkage with other data sources.⁷¹ For example, in a study of patients with atrial fibrillation (AF), the investigators originally had access only to international normalized ratio (INR, a blood test that quantifies anticoagulation effect) values for tests performed in hospitals, and it is possible that INR values done in the hospitals are higher than in ambulatory settings due to higher medical complexity of hospitalized patients. Under the assumption of MNAR, the investigators linked the data set with anticoagulation management clinic data, where the INR results were available even if the tests were performed outside of hospitals.⁷⁶ Another strategy to reduce missing data is to supplement the structured data with variables derived from natural language processing (NLP) of the free-text notes to improve missingness. For example, in the same cohort of AF patients, using NLP to extract additional information from the free-text notes reduced missing smoking information from 54.4% to 7.8%.⁷⁶ For data with residual missing data under MNAR, the investigator should conduct a sensitivity analysis varying plausible values of the missing data to test the robustness of the study findings.⁷⁷

Methods to handle missing data due to EHR-discontinuity: Except for some systems where the EHR system is explicitly integrated with the payor system (claims), many EHR systems do not have well-defined enrollment dates and are subject to data leakage outside of the study EHR (i.e., EHR-discontinuity).⁷⁸ The causes and patterns of EHR-discontinuity may vary by type of EHR system (e.g., general hospital vs. specialty EHR or a metropolitan vs. suburban systems). For example, EHR data from a general hospital might lack information from encounters at unaffiliated specialty facilities. The information bias due to EHR discontinuity can be reduced by an externally validated algorithm to identify a sub-cohort with high data completeness.^{67,79,80} In select empirical examples, it has been found that patients with high EHR-continuity had a similar comorbidity profile compared to those with low EHR-continuity, so restricting analyses to those with high EHR continuity seemed to confer a desirable trade-off between validity (reducing misclassification of the study variables) and generalizability (drawing inference in the sub-population).⁸⁰ However, these findings may not generalize to all settings and should be carefully considered on a case-by-case basis.

Empirical example: In an observational study aiming to determine the effect of hydroxychloroquine with or without azithromycin on COVID-19 mortality using EHR data from the United States Department of Veterans Affairs,⁸¹ there was a notable amount of missing data in lifestyle factors (e.g., ranging from 2% in alcohol consumption to 38% in smoking status), vitals (e.g., ranging from 3% in blood pressure to 6% in oxygen saturation), and labs (e.g., ranging from 7% in serum sodium, 19% in HbA1c, to 86% D-dimer). Missingness at random was assumed, and multiple imputation was used for most variables before incorporating these variables in a propensity score model for confounding adjustment. Exposure misclassification was unlikely to be a major concern as the study focused on the short-term use of inpatient medications that were well-captured in the study EHR. For outcome ascertainment, to capture out-of-network deaths, the investigators linked the EHR data with the Beneficiary Identification Records Locator Subsystem and Social Security Death Index data.⁸²

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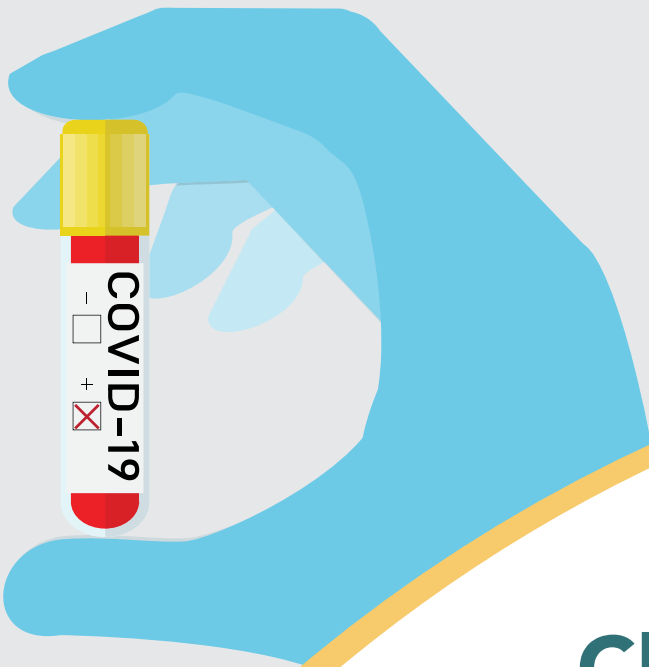
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Chapter 4: Examples of COVID-19 Real-World Evidence Studies

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This chapter provides select examples of COVID-19 studies that used real-world data (RWD) to generate real-world evidence (RWE) that addresses public health questions during the pandemic. The studies presented include:

- target trial emulation
- cohort study
- case-control study
- self-control case series
- drug utilization study
- diagnostic test evaluation study

Each study summary includes the study name; citation details; study objective; population, intervention, comparison, and outcomes (PICO); data source(s), and study period. For each study, we highlight how authors handled key potential sources of error.

Target Trial Emulation

Study citation: Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernán MA, Lipsitch M, Reis B, Balicer RD. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med.* 2021 Apr 15;384(15):1412-1423. doi: 10.1056/NEJMoa2101765. Epub 2021 Feb 24. PMID: 33626250; PMCID: PMC7944975.1

Study objective: The objective of this study was to rapidly characterize and evaluate the effectiveness of the BNT162b2 mRNA vaccine in a real-world setting based on emulation of the target trial of the causal effect. As noted by the authors, COVID-19 vaccination is expanding globally, and understanding vaccine performance in a real-world setting is of paramount importance to patients, public health officials, researchers, and other stakeholders.

PICO: The study population was derived from Clalit Health Services (CHS) which includes 53% of the insured population in Israel. The outcomes of interest were occurrence of documented SARS-CoV-2 infections, symptomatic COVID-19, related hospitalizations, severe COVID-19, and death from COVID-19 among both vaccinated and unvaccinated populations. The intervention was receipt of the BNT162b2 mRNA vaccine, based on availability and individual agreement to receive a vaccination. Patients were matched 1:1 based on clinical and non-clinical characteristics.

Data source: CHS is a large health care organization in Israel, covering approximately four million citizens—just over half of Israel’s total population.

Study period: December 20, 2020, to February 1, 2021

Key sources of error and how they were handled: This study, using the target trial paradigm, is one of the largest population-based studies available and allows for insight into the real-world effectiveness of the BNT162b2 mRNA vaccine. COVID-19 diagnoses were confirmed with gold-standard polymerase chain reaction (PCR) testing, which is an important element of case definition for other large real-world studies as

there can be significant clinical overlap between COVID-19 and other viral respiratory illnesses resulting in potential outcome misclassification. To mitigate the potential for confounding, the authors were able to balance a wide range of factors, including described risk factors for severe COVID-19 disease, by matching patient cohorts on demographic and clinical characteristics. A number of sensitivity analyses were performed, accounting for potential biases. Date of symptom onset was unavailable for this study and presents a minor limitation. There was limited race and ethnicity data appropriate to the region of the study population and the ability to assess treatment effect heterogeneity across other populations is limited. Additionally, several patient populations (those without documented addresses, health care workers, etc.) were excluded from the study for concern of skewing results in the case these individuals were exposed to a greater degree than the general population. Overall, 34% of the otherwise-eligible vaccinated population was excluded due to the rigorous matching performed. This is important to consider when extrapolating these data to other population groups.

Cohort Study

Study citation: Rentsch CT, DeVito NJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, Schultze A, Hulme WJ, Croker R, Walker AJ, Williamson EJ, Bates C, Bacon S, Mehrkar A, Curtis HJ, Evans D, Wing K, Inglesby P, Mathur R, Drysdale H, Wong AYS, McDonald HI, Cockburn J, Forbes H, Parry J, Hester F, Harper S, Smeeth L, Douglas IJ, Dixon WG, Evans SJW, Tomlinson L, Goldacre B. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. *Lancet Rheumatol.* 2021 Jan;3(1):e19-e27. doi: 10.1016/S2665-9913(20)30378-7. Epub 2020 Nov 5. PMID: 33349815; PMCID: PMC7745258.2

Study objective: This study sought to understand the potential effectiveness of hydroxychloroquine in preventing COVID-19 mortality in the general population. Early in the pandemic, there was interest in repurposing pharmaceuticals for the prevention of SARS-CoV-2 infections. Hydroxychloroquine was quickly thrown into a global spotlight after it garnered simultaneous praise and criticism from a number of high-profile sources. At the time of this study, most randomized clinical trials and observational studies showed no evidence of a benefit of hydroxychloroquine as a treatment for patients admitted to hospital who already have COVID-19. However, there

remained uncertainty whether routine ongoing use of hydroxychloroquine in people without SARS-CoV-2 infection protected against new infections or severe COVID-19 outcomes.

PICO: This was an observational, population-based cohort study analyzing electronic health records for individuals over the age of 18 years who were established with a primary care provider in England, United Kingdom (UK). Patients who carried a diagnosis for which hydroxychloroquine was indicated (systemic lupus erythematosus or rheumatoid arthritis) and were on hydroxychloroquine therapy for at least 6 months were selected to be compared with those with systemic lupus erythematosus or rheumatoid arthritis but not treated with this medication. Death due to COVID-19 was studied as the primary endpoint, with non-COVID-19 mortality used as a negative control outcome.

Data source: The OpenSAFELY platform, a new, secure, transparent, open-source software platform for analysis of electronic health record data and linked SARS-CoV-2 testing, hospitalization, and death records for approximately 40% of the population in England.

Study period: March 1 and July 13, 2020

Key sources of error and how they were handled: Because the OpenSAFELY platform collects longitudinal data from routine clinical practice, it enabled an examination of previously approved indications and real-world use of hydroxychloroquine in COVID-19 with adjustment for confounding by indication. The authors developed a directed acyclic graph to inform the selection of potential confounders to include in multivariable regression. The data source had substantial inclusion of patient medication data but was limited by a lack of information on medications prescribed by specialists, such as biologic treatments for rheumatological disease. Therefore, the authors calculated bias-adjusted effect estimates using quantitative bias analysis to assess how adjustment for biologic treatments (as a proxy for disease severity) might have produced different results. Sensitivity analyses were conducted to assess the potential of exposure misclassification, including shortening the exposure ascertainment window from 6 to 3 months prior to baseline to be more sure patients were prescribed hydroxychloroquine closer to baseline. Multiple imputation was used to address missing ethnicity data for 23% of individuals. The

authors pre-specified and published an open-source protocol prior to analyzing the data, which reduced the potential for subjectivity in decision-making during analysis. All code for data management and analyses was archived with version control on GitHub for review and re-use to promote reproducibility of research findings.

Case-Control Study

Study citation: Thompson MG, Stenehjem E, Grannis S, Ball SW, Naleway AL, Ong TC, DeSilva MB, Natarajan K, Bozio CH, Lewis N, Dascomb K, Dixon BE, Birch RJ, Irving SA, Rao S, Kharbanda E, Han J, Reynolds S, Goddard K, Grisel N, Fadel WF, Levy ME, Ferdinands J, Fireman B, Arndorfer J, Valvi NR, Rowley EA, Patel P, Zerbo O, Griggs EP, Porter RM, Demarco M, Blanton L, Steffens A, Zhuang Y, Olson N, Barron M, Shifflett P, Schrag SJ, Verani JR, Fry A, Gaglani M, Azziz-Baumgartner E, Klein NP. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. *N Engl J Med*. 2021 Oct 7;385(15):1355-1371. doi: 10.1056/NEJMoa2110362. Epub 2021 Sep 8. PMID: 34496194; PMCID: PMC8451184.3

Study objective: Understanding the effectiveness of COVID-19 vaccines, particularly in populations disproportionately affected by the disease, is of paramount importance to improving health outcomes. Three vaccines were initially authorized for emergency use in the United States (US) by the Food and Drug Administration (FDA): BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COVS.2 (Johnson & Johnson/Janssen). The objective of this study was to evaluate the real-world effectiveness of the 3 vaccines.

PICO: This is a case-control study of adult visits in an ambulatory clinic and emergency department setting who were tested for COVID-19 within a multicenter health care system network. This study took place across 187 hospitals across the US, with study dates before and after the widespread availability of COVID-19 vaccines. A test negative design was used to study comparative effectiveness for test positivity between unvaccinated and vaccinated individuals. In this study, the ability of each of the 3 vaccines to prevent hospitalization, admission to an intensive care unit, or an ambulatory care visit (emergency room and urgent care) was characterized.

Data source: Electronic health record data from the VISION network, a consortium of 7 academic and private medical centers, were used for this study, with linkage to statewide and local immunization registries, claims, laboratory results, and other diagnostic data where available.

Study period: January 1 through June 22, 2021

Key sources of error and how they were handled: Data derived from several disparate sources (i.e., electronic health records, city and state immunization registries, and claims data) were used for vaccination verification, which reduced potential exposure misclassification. This study had a particularly robust analysis of results as they pertain to racial and ethnic demographics, which is important for COVID-19 (and other diseases), as there are differences in clinical course and outcomes among minority communities.

Self-Controlled Case Series Study

Study citation: Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet*. 2021 Aug 14;398(10300):599-607. doi: 10.1016/S0140-6736(21)00896-5. Epub 2021 Jul 29. PMID: 34332652; PMCID: PMC8321431.4

Study objective: As the science and understanding of COVID-19 has evolved, its effect on specific organ systems (e.g., vascular) requires study. This study sought to characterize the risk of both myocardial infarction and ischemic stroke for those infected with SARS-CoV-2.

PICO: This study used two methods for its analysis: a self-controlled case series (SCCS) and a matched cohort study of patients in Sweden who received a prior diagnosis of COVID-19, and later received diagnosis codes related to a myocardial infarction or ischemic stroke. At most time points of the study, prior laboratory confirmed SARS-CoV-2 infection was identified as a risk factor for these 2 vascular events.

Data source: Patient data were derived from SmiNet at the Swedish Public Health Agency (including all patients registered as having COVID-19 until September 14, 2020) and linked with registries administered by the Swedish National Board of Health and Welfare. Like many other public health databases, SmiNet has been used to help track COVID-19 in Sweden since February 2020, as COVID-19 has been a notifiable disease in Sweden, and diagnosed individuals are reported to SmiNet (Swedish Public Health Agency) daily. The source has suitable coverage for the population of interest.

Study period: February 1 to September 14, 2020

Key sources of error and how they were handled: All individuals in Sweden were eligible for inclusion, which is a particular strength of this nationally representative study, given the comprehensive population level data capture in this RWD source, and making it the largest study evaluating this association at the time of publication. Another strength was the use of 2 different designs (SCCS and conventional matched cohort), which rely on different sets of assumptions and address different types of biases. The use of the 2 designs contributed to the ability to control for bias using different assumptions about pathways for biases. This study also adjusted for income, education level, and country of origin, which are important demographic and socioeconomic factors to consider in real-world evidence studies of COVID-19 sequelae. Generalizability from a single country study may be limited, and RWD studies of COVID-19 outcomes will also benefit from understanding race and ethnicity when available. Additionally, the authors noted that there was a peak of vascular events on day 0 (date of vaccination). A sensitivity analysis that excluded patients with events on day 0 found similar results to the main analysis. This speaks to the robustness of the study results.

Drug Utilization Study

Study citation: Prats-Urbe A, Sena AG, Lai LYH, Ahmed WU, Alghoul H, Alser O, Alshammari TM, Areia C, Carter W, Casajust P, Dawoud D, Golozar A, Jonnagaddala J, Mehta PP, Gong M, Morales DR, Nyberg F, Posada JD, Recalde M, Roel E, Shah K, Shah NH, Schilling LM, Subbian V, Vizcaya D, Zhang L, Zhang Y, Zhu H, Liu L, Cho J, Lynch KE, Matheny ME, You SC, Rijnbeek PR, Hripcsak G, Lane JC, Burn E, Reich C, Suchard MA, Duarte-Salles T, Kostka K, Ryan PB, Prieto-Alhambra D. Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study. *BMJ*. 2021 May 11;373:n1038.5

Study objective: Early in the COVID-19 pandemic, there was great interest in understanding how repurposing of already available therapeutics might be useful, particularly prior to the authorization of antiviral treatments. The primary objective of this study was to understand the most common drugs being used as adjuvant treatment across multiple countries.

PICO: This multinational network cohort study focused on drug utilization, and included electronic health record and administrative claims data from 4 countries (US, South Korea, Spain, and China). Patients were identified by either a diagnosis of COVID-19 or a positive PCR test. Drugs that these patients received were studied as either adjuvant therapies for mitigation of sequelae or repurposed drugs meant to directly serve the purpose of COVID-19 treatment.

Data source: This large study used a mixture of claims and electronic health record data from 4 countries. The data were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Study period: January 2020 to December 2020

Key sources of error and how they were handled: Understanding usage patterns of therapeutics throughout the time course early in the COVID-19 pandemic has important public health implications and can guide investigators toward opportunities for further real-world evidence generation related to the outcomes of these medications. This study found several interesting trends, including usage of drugs that varied widely by country as well as time. Presumably, this was due to the rapidly evolving evidence within the COVID-19 pandemic as well as local drug availability. Specifically, earlier in the study period, hydroxychloroquine was found to have been prescribed broadly, despite lack of evidence of its clinical effectiveness. Prescription of hydroxychloroquine tapered off in later months after observational studies and clinical trials found no clinical benefit in addition to a questionable safety profile.⁶ Conversely, dexamethasone and remdesivir experienced increases in widespread use in later months of 2020. This is another important aspect of drug utilization studies—their ability to demonstrate the impact of implementation and de-implementation of clinical guidance and detection of changes in therapeutic recommendations.

As with all studies relying on diagnosis codes to identify COVID-19, there may have been misclassification of disease, particularly for those with minor illness, who may therefore have been underrepresented.

Diagnostic Test Utilization Study

Study citation: Mack CD, Osterholm M, Wasserman EB, Petruski-Ivleva N, Anderson

DJ, Myers E, Singh N, Walton P, Solomon G, Hostler C, Mancell J, Sills A. Optimizing SARS-CoV-2 Surveillance in the United States: Insights From the National Football League Occupational Health Program. *Ann Intern Med.* 2021 Aug;174(8):1081-1089. doi: 10.7326/M21-0319. Epub 2021 Jun 15. PMID: 34125571; PMCID: PMC8252091.7

Study objective: Evidence to understand effective strategies for surveillance and early detection of SARS-CoV-2 was limited throughout the first year of the pandemic. Limited data have been available describing frequent testing for SARS-CoV-2 in a closed population. The purpose of this study was to describe a large COVID-19 testing and surveillance program.

PICO: The National Football League (NFL)/NFL Players Association (NFLPA) COVID-19 Testing and Surveillance Program instituted routine testing in a closed population of NFL players and team staff, most of whom were tested daily. Several diagnostic tests, including point-of-care (POC) antigen testing and reverse transcription polymerase chain reaction (RT-PCR), were used. Test results were compared against final clinically adjudicated case status, as well as across diagnostic machines (e.g., Roche Cobas compared to Hologic Panther and antigen POC compared to RT-PCR). Outcomes were the agreement of test results and descriptive statistics of test results, including Cycle threshold (Ct) values.

Data source: This large observational study included 11,668 NFL players and staff who underwent testing as part of the program between August 1, 2020 and November 14, 2020. Individual characteristics, symptom data, longitudinal testing data, and case adjudication associated with 632,370 tests were included.

Study period: NFL Season, August through November 2020

Key sources of error and how they were handled: This study drew from a real-world program performing daily RT-PCR tests in a large, closed population with almost complete clinical follow-up for all individuals testing positive, serial testing after an initial positive result, and case adjudication. This, combined with frequent testing and same-day testing on multiple platforms for those with positive tests, provided transparency into the utility of newly authorized diagnostics, notably showcasing the ability of RT-PCR testing to detect early and asymptomatic or presymptomatic infection. Ct values are not often used in real-world application, and high values are often

disregarded as not true infection; this study showed that quantitative values proved useful for understanding test results and that high Ct values can signal early infection. Importantly, because antigen POC tests were often administered on the same day as RT-PCR tests and positive results were clinically adjudicated with serial testing, the frequency of false results for POC testing could be evaluated. This study is limited in its generalizability; notably it was performed within a healthy working population and is not diverse in gender (largely male). Race and ethnicity data were not collected. Additionally, application to non-daily testing environments should be considered; these real-world results within a surveillance system administering daily testing in an ideal setting may not be applicable to for-cause testing but are useful for understanding the utility of the diagnostic tools.

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Chapter 5: Major Multi-Stakeholder Initiatives — Defining the Future of COVID-19 Observational Research

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Introduction

The COVID-19 pandemic laid bare the limited interoperability capacity of the existing health care data infrastructure for assembling data to quickly address critical questions about a novel disease. Several initiatives have emerged to address this shortfall using real-world data (RWD) for COVID-19 observational research. This chapter features a selection of multi-stakeholder COVID-19 RWD initiatives that have contributed to our understanding of the COVID-19 pandemic and/or are structured to continue to provide opportunities for observational research about emerging issues related to the disease. The authors spoke to and/or emailed with representatives from each of the initiatives for the writing of this chapter.

RWD and real-world evidence (RWE) have never been needed as widely and urgently as in the COVID-19 era. Some initial analyses from RWD were needed for decision-making in real time, despite the known limits of the underlying data. Other questions continue to be explored and refined, and new questions emerge over time. COVID-19 is an ongoing pandemic and its effects will stay with us longer than we had hoped. The methods and resources that have emerged to address COVID-19 will ideally endure and evolve into the future. In turn, the way we think about and perform RWE research using RWD will change.

Perhaps the height of public awareness on the value of RWD sources came in January of 2020 with the [Johns Hopkins COVID-19 Dashboard](#)¹ (more formally the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University), which uses publicly available epidemiological data from aggregated government, national, and regional data sources.² Much has been written about the dashboard—how it came to be, how it was relied on, and how the COVID-19 data were interpreted. Spurred by a global emergency, the Johns Hopkins COVID-19 Dashboard supplied a constantly updating source of aggregated data to track COVID-19 cases, deaths, vaccinations, and more.³ Those raw numbers were and continue to be widely used. The real-time aspect of the dashboard and the public availability of the compiled data allowed both researchers and the general public to monitor the evolution of the pandemic as it occurred, and continues to do so.

Patient-level COVID-19 RWD sources have been used since early 2020 in different parts of the world to further characterize COVID-19 and to evaluate the impact of medical and public health interventions on the disease. Many of these data sources have been made available or established as part of multi-stakeholder consortia and networks, maximizing the use and value of RWD and methods as part of the pandemic response. Some of these have been established with long term goals and with enhanced data infrastructures, software, and tools.

Multi-stakeholder COVID-19 RWD initiatives with the potential to expand the depth of real-world observational studies have been compiled by the Duke Margolis Center for Health Policy ^{4,5} and in a [*compilation of tools to support COVID-19 research produced by the Food and Drug Administration \(FDA\)*](#).⁶ Additional COVID-19 RWD multi-stakeholder initiatives have been added after conducting a targeted review of recent COVID-19 data sources and consultation with other researchers.

Some of the existing RWD initiatives leverage data platforms or distributed data networks to conduct COVID-19 research, while others are efforts newly launched during the pandemic. The initiatives that existed prior to the pandemic are mostly based on the commonly used health care RWD—claims and/or electronic health record (EHR) data. New initiatives evolved during the pandemic expand the types of RWD used to include surveillance data, consumer data, and epidemiological survey data. While most of the initiatives are closed systems with restricted access to their participating organizations/stakeholders, others were set up as open-source platforms or data aggregators, with the goal of making data rapidly available to a broader research community or to the general public in the COVID-19 era.

Six COVID-19 RWD multi-stakeholder initiatives are covered in depth in this chapter, as illustrative examples that may help us understand the future of COVID-19 research—and the future of RWD and RWE. Four of these were initiatives adapted from existing infrastructures, while the other 2 emerged during the COVID-19 pandemic. In our selection of initiatives for detailed description, we considered the need to cover different geographic locations (international, United States [US], Europe) and stakeholders (open science collaborative, government, health care-focused private stakeholders, technology-focused private stakeholders, private-public partnerships). The initiatives are:

- **Observational Health Data Science and Informatics (OHDSI):** an initiative leveraging existing international distributed health care data in an interdisciplinary collaborative that facilitates open-source analyses to conduct observational studies on COVID-19 disease characterization, treatment, and care
- **FDA Sentinel:** an FDA system leveraging a distributed data network with a common data model as well as other standalone data sources to conduct COVID-19-related studies
- **OpenSAFELY:** an initiative that enables the access of multiple United Kingdom (UK) government data sources in a reliable and protected platform to address COVID-19 research needs
- **Vaccine Monitoring Collaboration for Europe (VAC4EU):** an international non-profit association set up with the aim to conduct collaborative real-world analysis on vaccines. The entity was founded as a result of the Innovative Medicines Initiative-funded ADVANCE project that was initiated after the H1N1 pandemic
- **COVID-19 Research Database:** a cross-industry, cross-sector initiative composed of institutions that donate technology services, health care expertise, and de-identified data in the US for COVID-19 observational research. The data repository contains integrated, linked data sets from multiple sources, from the more traditional RWD(claims, EHR) to life insurance claims, consumer data, and mortality records
- **COVIDRIVE:** a public-private partnership leveraging the existing vaccine effectiveness platform in Europe to comprehensively examine COVID-19 vaccine effectiveness across a range of products and assist vaccine companies in fulfilling their regulatory obligations

As we continue through the COVID-19 era, questions to consider include:

- What other epidemiological RWD sources have emerged, expanded, changed, or become more accessible for COVID-19 observational research purposes?
- Which ones will continue to serve as methods to further understand COVID-19 disease and the effects of preventive and therapeutic interventions?
- In what ways has this global health emergency altered the way we approach RWD to generate RWE?

The Observational Health Data Sciences and Informatics (OHDSI), an international network of researchers and observational health databases

Link: [OHDSI – Observational Health Data Sciences and Informatics⁷](#)

Brief description of the OHDSI initiative and data

The Observational Health Data Sciences and Informatics (OHDSI, pronounced "Odyssey") collaboration is an open-science, multi-stakeholder, interdisciplinary community. Its goal is to use large-scale open-source analytics to generate evidence that promotes better health decisions and care. OHDSI incorporates an international network of researchers and observational health databases with a central coordinating center located at Columbia University. As of November 2021, the community included 2367 researchers from 74 countries, and health records for about 800 million people from around the world.

OHDSI's health data network is based on the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), enabling federated analytics amongst collaborators. OHDSI Researchers develop [standards⁸](#) and open-source [software⁹](#) to standardize and facilitate analyses. Research within OHDSI includes characterization, medical product safety surveillance, comparative effectiveness research, personalized risk prediction, and methodological research.

The OHDSI model allows researchers and data partners to contribute data without sharing patient-level information and ensures that common analytical code can be applied across databases. Some data partners collaborate on code and then run that code on the data to which they have [access⁷](#). Other partners collaborate by running the code without having contributed to the writing of code. OHDSI's structure and analysis flow diagram is depicted below (Figure 5.1).

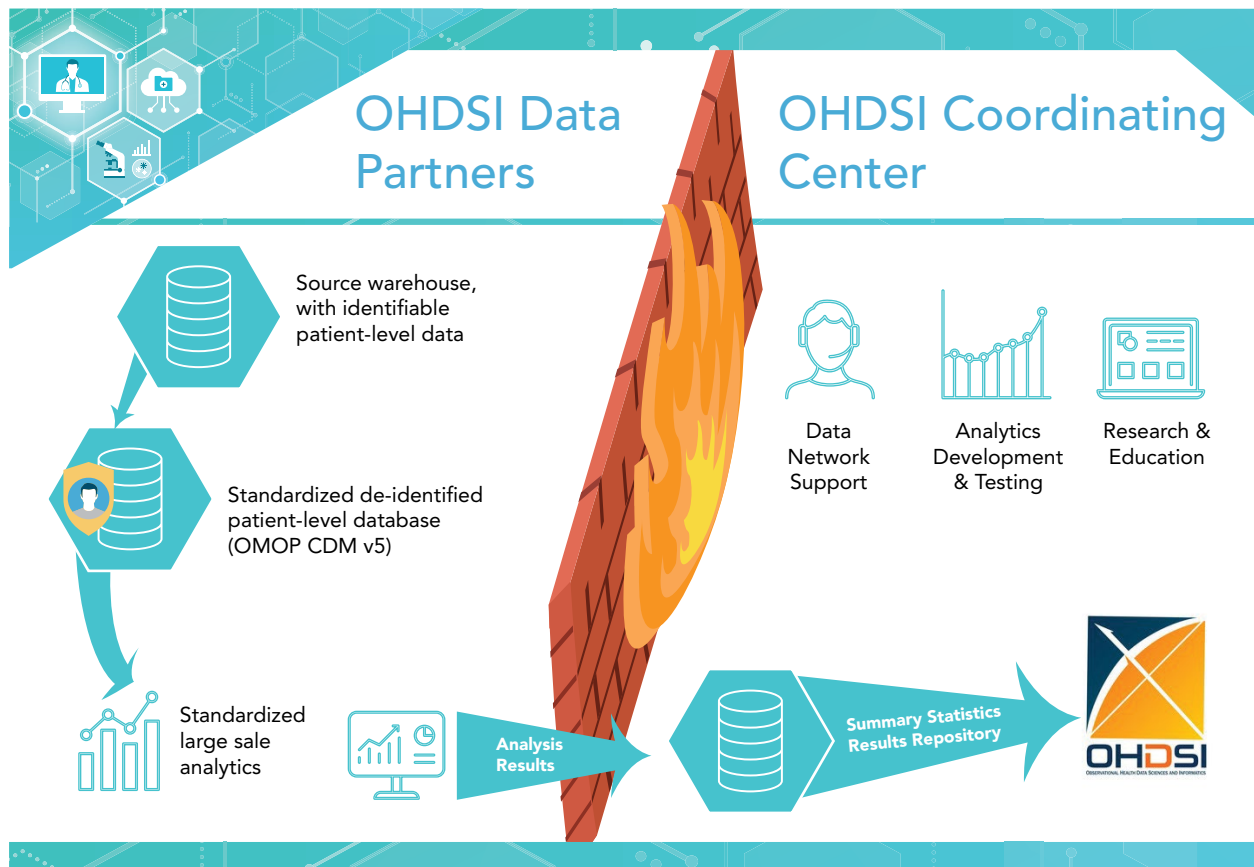


Figure 5.1. OHDSI Structure and Analysis Flow Diagram¹⁰

The OHDSI community is closely tied to the European Health Data & Evidence Network (EHDEN) consortium within the Innovative Medicines Initiative (IMI) in Europe. [EHDEN](#)¹¹ is developing the required infrastructure for observational health research using the OMOP CDM federated network model across Europe, through a community of data partners and small to medium enterprises (SMEs).

OHDSI and EHDEN COVID-19 observational research: International federated data networks and CDM

Early in 2020, OHDSI and EHDEN joined forces to address urgent research questions related to COVID-19 by building on the existing communities, available data sources, software, and infrastructures created by both initiatives.

From March ²⁶⁻²⁹, 2021, OHDSI hosted a COVID-19 virtual 4-day [study-a-thon](#)¹² to inform health care decision-making in response to the global pandemic. Supported by EHDEN, the study-a-thon convened more than 300 researchers from 30 countries, with access to 37 health care databases with COVID-19 patient data.

Fifteen workstream groups were created, each addressing different research questions. Five major milestones were established for each research question: 1) Review relevant literature and develop the study protocol, 2) Develop and evaluate phenotypes, 3) Develop the study packages (these are freely available via the [OHDSI GitHub](#)),^{13,4)} 4) Execute these study packages across the available data network, 5) Review findings by clinical experts and disseminate the results.

Phenotypes and cohorts were also defined, with a total of 355 cohorts created. Of these, 114 were reviewed and validated for use in the study-a-thon studies ([data.ohdsi.org](#))¹³ Execution of studies began almost immediately.

Since March 2020, OHDSI has been focusing on COVID-19 major research in areas which can be systematically examined across the OHDSI network. These include:

- COVID-19 characterization and COVID-19 disease natural history by defining diseases and populations of interest, illustrated by the CHARYBDIS Project (Characterizing Health Associated Risks, and Your Baseline Disease In SARS-COV-2)
- Population level estimation to examine the comparative safety and effectiveness of COVID-19 therapies, addressed by Project SCYLLA (SARS-Cov-2 Large-scale Longitudinal Analyses) which focuses on COVID-19 treatments 1) administered during hospitalization and prior to intensive services, 2) administered during hospitalization after initiating intensive services, and 3) administered after COVID-19 positive testing and prior to hospitalization
- Patient-level prediction, illustrated by study Seek COVER: Development and validation of a personalized risk calculator for COVID-19 outcomes in an international network

Key features characterizing the OHDSI community and related initiatives, such as EHDEN, in their ability to contribute to COVID-19 observational research include:

- Research and data partners multi-stakeholder community with a global geographic reach
- Federated data networks, including EHR, hospital billing data, and insurance claims
- Data harmonization, data using the OMOP CDM
- Established and validated COVID-19 cohorts, with regular data refresh
- Systematic approach to generate evidence on COVID-19
- Open community, open-source ([OHDSI Studies · GitHub](#))¹³

- Protocols, analysis codes, results publicly available ([COVID-19 Updates Page – OHDSI](#),¹⁴ [OHDSI Studies · GitHub](#))¹³
- Pre-prints and scientific publications available
- Possibility to contribute to OHDSI working groups¹⁵
- Possibility to propose research questions and lead studies
- Use of study results to inform health care system and regulatory decision making

OHDSI case studies

The OHDSI data network enabled a rapid baseline analysis of COVID-19 in early hotspots using routinely collected primary care EHR data, hospital billing data, and insurance claims, initially from the US, South Korea, and Spain.

One first study described the characteristics of adults hospitalized with COVID-19 by training a predictive model for influenza and testing it against COVID-19. An analysis of data from 34,128 COVID-19 patients compared to 84,585 individuals hospitalized with influenza in 2014–2019 found that hospitalized COVID-19 patients were more likely to be male, younger, and have fewer comorbidities and less medication use. Their conclusion was that “while protecting groups vulnerable to influenza is likely a useful starting point in the response to COVID-19, strategies will likely need to be broadened to reflect the particular characteristics of individuals being hospitalized with COVID-19.”¹⁶

When angiotensin-converting enzyme inhibitors and angiotensin receptor blockers had been postulated to increase susceptibility to COVID-19, an OHDSI-based study found no clinically significant increased risk of COVID-19 diagnosis or hospital admission-related outcomes, “suggesting users should not discontinue or change their treatment to decrease their risk of COVID-19.”¹⁷

In response to the emergency use authorization of hydroxychloroquine for COVID-19, OHDSI was used to conduct a large cohort study of rheumatoid arthritis patients (without COVID-19) who were taking hydroxychloroquine. The study found that the addition of azithromycin to hydroxychloroquine appeared to be associated with increased risk of heart failure and cardiovascular mortality.¹⁸

Other studies have examined COVID-19 among children and adolescents,¹⁹ patients with prevalent autoimmune diseases,²⁰ patients with obesity,²¹ and patients with a history of cancer.²² The use of repurposed and adjuvant drugs in patients hospitalized with COVID-19²³ was also examined, and the OHDSI framework was used to externally assess the validity of a COVID-19 risk model.²⁴ An updated list of preprints and published OHDSI studies can be found at the [OHDSI webpage](#).¹⁴

OHDSI impact and perspective

OHDSI has contributed to the understanding of key disease knowledge gaps initially posed by the pandemic. Results from studies conducted by OHDSI have informed clinicians, health care systems, and regulators. These results have contributed to better management of COVID-19 patients during the acute phases of the pandemic and have permitted real-time evaluation of COVID-19 therapies by regulators.

Daniel Prieto-Alhambra, a key contributor to OHDSI, describes it as “a very inclusive community in which basically anyone is invited to come and join and work with us. You just join the forums, attend one of the calls, and join a working group. It’s an open science community.” EH DEN, which he finds is often conflated with OHDSI in discussions, has a different but complementary aim “to generate a new transparent, fair, data access network in Europe. They work very nicely together.” Prieto-Alhambra describes a parallel process to OHDSI’s study-a-thon” that he calls an “Evidence-a-Thon.” New data partners in the EH DEN network, are asked to run one study that has already been completed in other databases, review the results, and write up the findings. The process not only tests the CDM, but also engages new data partners immediately.

OHDSI community researchers have defined a “long research agenda” to address future COVID-19 research needs. That agenda includes the characterization of COVID-19 over time (as a condition that changes with vaccinations and variants), long COVID-19 or persistent COVID-19, the sequelae of COVID-19 (organ failure, cardiovascular disease, and thrombotic events), the impact of current treatments, and new treatments that will arise to treat the virus and its complications. It also includes questions related to vaccine safety and effectiveness, plus community-level factors and non-pharmacological interventions.

Food and Drug Administration (FDA) Sentinel System, US

Link: <https://www.sentinelinitiative.org/>²⁵

Brief description of the Sentinel Initiative and data

The US Food and Drug Administration (FDA) leads the [Sentinel Initiative](#),²⁵ which aims to develop new ways to assess the safety of approved medical products including drugs, vaccines, and medical devices. The initiative was created to meet a mandate by the US Congress in the FDA Amendments Act of 2007. Launched in 2009, it has developed into “the largest multisite distributed database in the world dedicated to medical product safety.”²⁶ The Biologics Effectiveness and Safety (BEST) System is also part of the Sentinel Initiative, launched in October 2017 to expand and enhance the [Center for Biologics Evaluation and Research](#) (CBER) “access to new and better data sources, methods, tools, expertise, and infrastructure to conduct surveillance and epidemiologic studies.”

The Sentinel System data consists primarily of administrative claims and some EHRs from US national and regional health plans, integrated delivery systems, and Medicare fee-for-service data from Centers for Medicare and Medicaid Services (CMS). These partners transform their data into the Sentinel Common Data Model, but maintain possession and operational control over their data. During the data transformation, identifiable patient information is removed or masked. The standardized format enables the use of routine analytic programs, enabling rapid analyses without the need for customized code.²⁷ In all, the Sentinel Distributed Database includes claims data on approximately 70 million individuals per year from all 50 US states, covering 800 million person years.

Other [Sentinel partnerships](#)²⁵ include EHR based organizations and networks—HCA Healthcare, a hospital system with over 140 facilities, the National Patient-Centered Clinical Research Network (PCORnet), and EHR data aggregators (TriNetX, Veradigm, IBM Explorys).

The COVID-19 pandemic prompted a rapid expansion and enhancement of Sentinel. In response, Sentinel created the Rapid Distributed Database with a subset of the national health plans and integrated delivery systems. While data in the typical Sentinel Distributed Database is generally 6 months old, allowing for claims to “settle,” the

Rapid Distributed Database is refreshed approximately every 2 months, enabling the FDA to have access to more timely data. The Rapid Distributed Database also maintains the capability to allow for the conduct of targeted chart reviews.

To ensure completeness of information, the inpatient EHR data from HCA Healthcare includes discharged patients only. Importantly, in addition to standardized data on diagnoses, procedures, and medications, nursing documentation notes have been included to supplement diagnosis and procedure codes for identification of oxygen related therapy and non-invasive mechanical ventilation.

The ability of the FDA to quickly use Sentinel claims data and HCA Healthcare data to study COVID-19 was facilitated by past work on influenza in collaboration with the FDA's [Office of Counterterrorism and Emerging Threats](#)²⁸ and an early validation study to assess the performance of an International Classification of Diseases, Tenth Revision (ICD-10)-based algorithm to identify inpatient COVID-19 patients.

As with all studies using RWD, a robust [assessment of whether a study is fit-for-purpose](#)²⁹ is required for every proposed study to determine the best of the available sources for COVID-19 work in the Sentinel System. With the Rapid Distributed Database, the “freshness” of the data comes with challenges, including the need to understand completeness of the data by care setting (e.g., inpatient data lag behind ambulatory data) and claim type (e.g., encounter-based diagnoses lag behind outpatient pharmacy dispensations). Further, investigators now and in the future will have to understand and possibly adjust for changes in general health care utilization during the pandemic, or even issues such as the use of certain specialized wards for isolation of severe COVID-19 cases. As always within Sentinel, data quality review is a high priority and robust methods are in place for the various data sources.

The Sentinel System and COVID-19 observational research

Link: <https://www.sentinelinitiative.org/assessments/coronavirus-covid-1930>,³¹

Sentinel COVID-19 related goals include describing the course and outcomes of COVID-19 illness (including changes over time) in various demographic groups determining prognostic factors for COVID-19 based on data early in the course of illness. These data may allow the examination of determinants of COVID-19-related complications, and provide a benchmark—serving as an external control—for single-

arm trials of COVID-19 treatments in relevant patient populations. Sentinel is also used to study the COVID-19 pandemic in real time.³²

Sentinel developed a COVID-19 Natural History master protocol to serve as a guide for future COVID-19 studies. The master protocol includes translation of inclusion and exclusion criteria and clinical endpoints and definitions that reflect clinical concepts (such as COVID-19 severity categories and complications). Code lists are provided to help define cohorts (including special populations) and pre-existing conditions. This harmonization process allows for the assessment of homogeneity of findings across data sources, regions, and countries, and promotes collaboration and communication across regulatory agencies. This [Master Protocol](#)²⁷ is available on the Sentinel website.³³

Sentinel Initiative COVID-19 case studies

Link: <https://www.sentinelinitiative.org/assessments/coronavirus-covid-19>^{30,31}

Sentinel developed a protocol to estimate the 90-day incidence and risk of death from arterial and venous thrombotic events among patients with COVID-19, and compare their risk of these events to that of patients with seasonal influenza, using propensity score-based adjustment. Within Sentinel, the protocol is being implemented with data from integrated delivery systems and national claims partners. This protocol has been posted on the Sentinel website and was also disseminated through the COVID-19-Evidence Accelerator sponsored by the Reagan-Udall Foundation for the FDA. The European Medicines Agency (EMA) will conduct a parallel study among patients with COVID-19, and a meta-analysis may ultimately be conducted with the EMA- and FDA-sponsored results.^{34,35}

Sentinel's pandemic preparation activities mentioned above were leveraged to develop ongoing surveillance reports of COVID-19 patient census and clinical characteristics in HCA Healthcare, generating bi-weekly reports that examine patient demographic and medical characteristics, treatment and care received, and complications from COVID-19 using inpatient electronic medical record (EMR) data. The work defines markers of illness severity similar to those used in clinical trials. Importantly, the project has examined the capture of oxygen-related therapy. Whereas a code-based approach identified 28% of patients diagnosed with COVID-19 as having received oxygen therapy, adjudicated standardized nursing documentation data revealed that 79% received ventilation or supplemental oxygen (capture of invasive mechanical ventilation did not

significantly change when using nursing documentation). These inpatient EHR data are updated approximately every 2 weeks, and analyses are restricted to discharged patients with complete billing.³⁶

Little information is available to support understanding the natural history of COVID-19 disease in pregnant women, or the impact of COVID-19 treatment on pregnant women or the developing fetus. In order to study the impact of COVID-19 on pregnancy, the FDA has partnered with the EMA on their CONSIGN (COVID-19 infectiOn aNd medicineS In preGNancy) project, which will study COVID-disease in pregnant women across 8 European countries. Sentinel is implementing a parallel study using validated analytic tools to estimate the prevalence of select medicines in pregnant women with and without COVID-19, and in nonpregnant women with COVID-19. The study will also describe disease severity and clinical outcomes of pregnant women with COVID-19, according to treatments received during pregnancy, and compare these data with those of nonpregnant women of reproductive age with COVID-19.³⁷

Sentinel COVID-19 impact and perspective

The success of the Sentinel System goes beyond the ability to have rapid access to COVID-19 related data. The work has successfully demonstrated the ability of the FDA to take on more ambitious protocols (such as the pregnancy study cited above), conduct drug monitoring projects (<https://www.sentinelinitiative.org/methods-data-tools/methods/near-real-time-monitoring-critical-drugs-care-patients-covid-19>)³⁸ on a wide scale, and conduct collaborations with other regulatory agencies. The Rapid Distributed Database will continue into 2022 and will be reassessed to determine whether the initiative will continue.

In May 2021, Acting FDA Commissioner Janet Woodcock, MD, summarized Sentinel and related initiatives as ways that “during this global pandemic, the FDA worked to protect the American public by using every tool at its disposal to quickly review and act on new therapies for COVID-19.” She concluded that in addition to reducing administrative costs and time, master protocols “can also increase data quality and efficiency through shared and reusable infrastructure . . . advantages [that] are of particular importance during a public health emergency such as the current SARS-CoV-2 pandemic, where there is a critical need for efficient drug development. The FDA expects master protocols to continue to play an important role in addressing the public health needs created by the pandemic and in generating clinical evidence in general.”³⁹

OpenSAFELY, UK

Link: [OpenSAFELY: Home](#)⁴⁰

Brief description of the OpenSAFELY initiative and data

OpenSAFELY is a secure, transparent, open-source software platform for analysis of UK EHR data. It allows the user to create a trusted research environment associated with their own database or to add a layer of privacy to an existing database which can then be opened for wider use.

Created with public and charitable funding for the benefit of population health, OpenSAFELY was the product of collaboration between the [DataLab](#)⁴¹ at the University of Oxford, the [London School of Hygiene and Tropical Medicine EHR Research Group](#),⁴² The Phoenix Partnership (TPP) and EMIS Health EHR systems, National Health Service (NHS) England, and NHSX (a joint unit of NHS England and the Department of Health and Social Care). Development of the initiative was planned before COVID-19, but when the pandemic emerged, the initiative sped up rapidly and was quickly deployed within the secure data centers of the two largest electronic health record providers in the UK NHS—TPP and EMIS. This allowed researchers to access NHS records while minimizing the sharing of confidential patient information.

How does OpenSAFELY work?

Without access to raw data, the platform allows researchers to build a “dummy” data set (of any size, but typically of 100,000 records) that is modelled from the real data. The dummy data set contains the same structure, variable names, and variable types that would be created if the same code was submitted to run on the real data. For each variable, the researcher can set expectations for the distribution of that variable in the dummy data (e.g., 15% of records should have an asthma diagnosis). Researchers then develop their analysis code for statistical testing, graphs, tables, and dashboards against this dummy data, using open tools and services including GitHub. When both the data management code and data analysis code are capable of running to completion on the dummy data, the user can securely send the code into the live data environment to be executed against the real patient data. Outputs generated by the code are stored on the secure server until at least 2 trained output checkers review the outputs for any privacy concerns, including redacting tables or figures that have counts less than 5. The redacted tables are then released back to GitHub for the researcher to review and use in publications.⁴³

Every time a researcher subsequently changes their code, it is automatically checked by built-in algorithms to ensure it can be run without errors. This design enforces the principle that no analysis should happen without being prespecified in code. This clean separation of study design and execution makes undisclosed “p-hacking” impossible. This also means the code can be shared so that interested stakeholders can see what was done, and patients, professionals, and policymakers can confirm that this vast store of data has only been used for intended purposes.

Although some code may remain private while an analysis is in development, all code and results executed via OpenSAFELY are published, and the results of the analysis (with disclosure controls applied) are made publicly available at the time of journal submission or at 12 months after the first code was executed. In addition, [code lists](#)⁴⁴ are available open-source for inspection and reuse the moment they are created for analysis at <https://www.opencodelists.org>. After completion of each analysis, only minimally disclosive summary data are released (in summary tables or figures) outside the secure environment after strict disclosure checks and redactions.

Common research tasks such as data aggregation, case matching, time-based numerator/denominator pairs, low number suppression, and statistical summaries are provided as libraries (called “actions”) that are reusable in any supported language (currently Python, R, and Stata). Actions are tested and improved over time. Anyone can contribute new actions to the action library.

OpenSAFELY and COVID-19 observational research: UK big data, shared code
The OpenSAFELY platform can be used on NHS data (currently under an emergency authorization) to support research that will deliver urgent results related to the global COVID-19 emergency. That means approved researchers can execute code against the pseudonymized primary care records of over 58 million people via OpenSAFELY-TPP and OpenSAFELY-EMIS. The records are also linkable to pseudonymized person-level data sets from other data providers using a salted hash (a securely pseudonymized identification key) generated from NHS numbers.

Under certain conditions, and after review and approval of their project, individual researchers have long been able to gain access to specific NHS data sets. But the

COVID-19 pandemic meant that a wide range of questions needed to be asked across a large body of data as quickly as possible. The OpenSAFELY approach allowed for analysis of patient data without moving it out of the secure environments where it already resides—or even granting access to the raw data at all.

Beyond EHR data, OpenSAFELY incorporates many external national data sets. Data are available from the Secondary Uses Service (SUS) (the main repository for health care data in the UK), Hospital Episodes Statistics (HES), the NHS Emergency Care Data Set, and death certificate information from the Office of National Statistics. The platform also has access to data collected by the [Intensive Care National Audit & Research Centre](#)⁴⁵ and the [International Severe Acute Respiratory and emerging Infection Consortium](#).⁴⁶ COVID-19-specific information comes from the COVID-19 Patient Notification System (standardized data to underpin national death analysis), plus the [Second Generation Surveillance System \(SGSS\) and COVID-19 Hospitalizations in England Surveillance System \(CHESS\)](#).⁴⁷

Gaining appropriate research ethics approval is a prerequisite for using the OpenSAFELY platform. (Information governance for OpenSAFELY-TPP and OpenSAFELY-EMIS is handled by NHS England.) Research proposals are assessed by NHS England and the OpenSAFELY collaboration to ensure they support relevant research and planning activities in response to the COVID-19 emergency. As of September 2021, the collaborative is creating a [public dashboard](#)⁴⁸ that lists all approved projects, including purpose, contact information and affiliated organization of researchers, the date when the first code was executed, and links to published material. Participant consent is not required under regulation 3(4) of the Health Service Regulations for Control of Patient Information (2002),⁴⁹ and legal gateways involved for General Data Protection Regulations do not require consent.

OpenSAFELY case studies

Within 6 weeks of the launch of the initiative, a group of 30 researchers had completed and submitted their first analysis of NHS data for pre-print: “OpenSAFELY: Factors associated with COVID-19 death in 17 million patients”⁵⁰ (appearing in final form in Nature in July 2020). On behalf of NHS England, the OpenSAFELY team had used the platform to quantify a range of potential risk factors for COVID-19-related death. It was the largest cohort study conducted by any country to date—one that covered 40% of adults in the UK. The underlying population included all adult patients registered with

a general practice using TPP software who had at least 1 year of data history prior to February 1, 2020. Of the 17,278,392 individuals meeting this definition, 10,926 deaths from COVID-19 had been reported in Office for National Statistics (ONS) data by May 6, 2020. Findings of the analysis included associations between COVID-19 death and older age, male sex, non-White ethnicity, lower socio-economic status (SES), and many factors related to comorbid conditions and medical history: respiratory, cardiovascular, cerebrovascular, neurological, hepatic, renal, immunosuppressive conditions, recent cancer history, and diabetes. The final paper included an age-stratified analysis and a model with age as an interaction term to inform more accurate risk prediction.

The collaborative followed up on the topic with a more sophisticated model for predicting COVID-19 related death (relative and absolute estimates of risk in the context of changing levels of circulating virus) and factors associated with deaths due to COVID-19 versus deaths due to other causes in the same time period.⁵¹

Later in 2020, the OpenSAFELY Collaborative published “Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids” in *Lancet Respiratory Medicine*.⁵² An observational cohort study investigated the association between inhaled corticosteroids (ICS) and COVID-19-related death among people with chronic obstructive pulmonary disease (COPD) or asthma. Early reports of hospital admissions during the COVID-19 pandemic showed a lower prevalence of asthma and COPD than might be expected for an acute respiratory disease such as COVID-19, leading to speculation that ICS might be protective. The paper found no association, and the National Institute for Health and Care Excellence (NICE) responded by noting the study in their rapid guideline for severe asthma during COVID.⁵³

Other OpenSAFELY studies published in 2020 addressed issues that were being actively discussed and debated at the time. One investigated the effectiveness of routine hydroxychloroquine use for prevention of COVID-19 mortality (not for treatment of COVID-19).⁵⁴ No evidence of benefit or harm was found after adjustment for patient characteristics including existing health conditions. Another assessed the association between routinely prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and deaths from COVID-19, finding no harmful effect.⁵⁵

OpenSAFELY researchers also investigated ethnic disparities in COVID-19,⁵⁶ risks for people with learning disabilities,⁵⁷ and risks for people with or without children in their household.⁵⁸

When the SARS-CoV-2 variant B.1.1.7 emerged in England, a rapid analysis was done to estimate the case fatality risk for variant to non-variant cases, adjusting for demographic factors and comorbidities. Early vaccination trends were examined. The collaborative also published observations on how to identify care home residents in the data and trends in the clinical coding of long COVID-19 in primary care.⁵⁹

OpenSAFELY impact and perspective

Alex Walker, a lead DataLab researcher, says the rapid expansion of the initiative was born out of urgency: “We needed to know what groups of people were most vulnerable, how the virus affected them, which drugs might help or hinder when treating patients, and what happened to patients who recovered from infection. To answer these questions quickly, we needed an unprecedented amount of clinical patient data.” Walker says that now that those data have been gathered, “OpenSAFELY gives us the power to quickly respond to emerging clinical population health and policy challenges with precise data and open methods.” With this tool, “researchers can continue to provide immediate answers to extremely urgent questions in any future health emergency.”⁶⁰

So what is the impact on the future of RWE? Ben Goldacre, the Director of DataLab and joint principal investigator for OpenSAFELY, says, “COVID-19 could—and should—be the turning point; however, it all hangs on modern, open, reproducible techniques.” He refers to OpenSAFELY as an example of a “collaborative data science ecosystem.”⁶¹

Sebastian Bacon cites DataLab’s roots in evidence-based medicine, saying that the goal was to “do evidence-based medicine better by getting epidemiologists, clinicians, researchers, and software engineers all working together.” In personal correspondence (September 2021), Bacon wrote that OpenSAFELY “is best practices encoded in software . . . you are forced to do things safety and efficiently.”

In most analyses of EHR data, even on the same database, data management tasks are achieved by a wide range of individualized methods, using different tools, platforms, and programming languages. (Ben Goldacre equates this with “building a fridge every

time you need a cold beer.”)⁶¹ By restricting the user to OpenSAFELY tools, variable definitions and code are created so they can be read, understood, and adapted by other users. Differing variable definitions can be seen and tested against one another. Activity on the platform is publicly logged and any code used for data management and analysis is shared to enable scientific review and efficient reuse. In this way, reusable code and “reusable knowledge objects” are created.

When asked if it was inconvenient to be restricted to a set of tools and kept at a distance from the data, Bacon says, “Yes. But that’s exactly the reason there have been poor security practices in the past—or poor privacy practices—because it’s not convenient . . . people use the word ‘password’ for their password, because it’s not convenient to have strong passwords. That’s the central problem we’re trying to solve. Yes, some aspects of OpenSAFELY are slow compared to doing it the easy but unsafe way, so we aim to solve that by creating additional tools and services that make it easier for people to choose to do the right thing. To the OpenSAFELY team, the tradeoff is access to powerful data sets, to open-source code, and to features that can be added as requested.”

Regarding complex study designs and machine learning, Goldacre says “It’s all theoretically possible, but not all fully implemented yet—we are implementing functionality for our users as the requirements come up.”⁶¹

Goldacre claims we are at the point of a culture shift: “In the past it was quite natural—because data management and data collection was such a laborious and uncommon business—for people to assert monopolies . . . that the person who collected and managed the data would be the only person who would analyze it. It is only since computational tools have become more widely accessible that it has become more common for lots of people to expect to . . . reproduce things and examine the methods that were used.”⁶¹ He compares this period to 10-15 years ago, when clinical trial reporting practices were changed, requiring public registration for all clinical trials (and all interventions within those trials) and strongly encouraging result reporting. That was a shock at the time—but is now an accepted norm.

Vaccine Monitoring Collaboration for Europe (VAC4EU)

Link: <https://vac4eu.org>

Brief description of the VAC4EU initiative and data

VAC4EU, a not-for-profit international association, is a research driven infrastructure (RI) that is creating a major and highly necessary leap in advancing knowledge about vaccines after licensure in the EU market by using novel and existing real-world data. Its governance and sustainability solutions are built on the blueprint that was written by the European Center for Disease Control as part of the European Commission funded ADVANCE project (2013–2019). The ADVANCE project was funded by the European Commission and comprised ⁴⁷ organizations including EMA.

The influenza A/H1N1 pandemic in 2009 lessons showed that the monitoring of vaccine benefits and risks in Europe had potential for improvement if different public and private stakeholders would collaborate better.⁶² Stakeholders recognized that there were clear benefits for an EU collaborative approach, and the ADVANCE project showed this was possible. During the project, the foundations of the VAC4EU legal entity were established, and the entity was established in October 2019 and signed by the King of Belgium in January 2020.

As of January 2022, VAC4EU has 25 organizations as members and provides access to a large network of experts in the area of vaccinology, medicine, data science, public health, pharmacovigilance, and data and regulatory science. As members, these experts have access to routine health data on more than 150 million European citizens, as well as access to the tools to analyze these data in a federated manner for a wide variety of questions. The mission of VAC4EU is to access, characterize, and analyze available and newly collected health data to allow for evidence-based decisions by people who need to regulate, advise, prescribe, or decide on vaccines.

VAC4EU uses the ConcePTION common data model⁶³ as a basis, a generic common data model that was designed by ConcePTION and VAC4EU partners after 10 years of lessons learned around collaborative studies in Europe.⁶⁴ It requires syntactic harmonization of local data through an extraction transformation load process (ETL). The data analytics pipeline conducts semantic harmonization in a transparent manner.

VAC4EU creates standards, builds community, facilitates sharing knowledge and conducting studies, and provides tools and infrastructures. Its governance is described in statutes and bylaws. VAC4EU is a partner in the EU Pharmacoepidemiology & Pharmacovigilance research network (EU PE & PV) and has boosted much of the EMA-tendered research into the COVID-19 vaccines. EU PE&PV is a consortium of more than 20 ENCePP centers coordinated by Utrecht University that holds framework service contracts with EMA since 2015 for the conduct of pharmacoepidemiological studies.

VAC4EU works according to a federated system in which data stay local, and open source analytics, developed in R programming language by its members, are sent to participating data partners. The organization allows for rotation and flexibility of roles and responsibilities across studies, which allows for scaling up and sharing of knowledge. Access to the infrastructure and tools is provided by the VAC4EU secretariat.

VAC4EU and COVID-19 observational research

The ACCESS (vACcine Covid-19 monitoring readinESS) project under VAC4EU was funded by EMA through the EU PE & PV research network to ensure that a European infrastructure was in place to effectively monitor COVID-19 vaccines in the real world, once these were authorized in the European Union. The project started May 2020 and ended July 2021. The ACCESS project produced the following deliverables which went through EMA and stakeholder review:

- A list of 37 events of interest with definitions, ICD-9, ICD-10, Read, International Classification of Primary Care (ICPC), and Systemized Nomenclature of Medicine (SNOMED) codes (available on VAC4EU Zenodo community (<https://www.zenodo.org/communities/vac4eu/?page=1&size=202>))
- Background rates of 41 adverse events of special interest (AESI), including the AESI Background rates of AESI protocol (EUPAS 37273), results of background rate calculations (<https://vac4eu.org/covid-19-tool/>), and report with 41 AESI plus data⁶⁵ on 10 data sources across 7 countries in Europe
- Eight template protocols for different types of studies to be adapted for full implementation to local situation: (<https://vac4eu.org/covid-19-vaccine-monitoring/>)

- Signal detection based on cohort event monitoring
 - ▶ Cohort event monitoring to assess safety of COVID-19 vaccines using patient-reported events, a protocol template from the ACCESS project

- Rapid assessment of new safety signals based on electronic health record data
 - ▶ Rapid assessment of COVID-19 vaccine safety concerns through electronic health records: a protocol template from the ACCESS project

- Safety signal evaluation studies (EHR or hospital based)
 - ▶ Safety evaluation of COVID-19 vaccines through electronic health records: a protocol template from the ACCESS project
 - ▶ Safety Protocol for Hospital Case-Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project

- Effectiveness studies (EHR or hospital based)
 - ▶ Protocol for COVID-19 vaccine effectiveness studies (test-negative design studies): a protocol from the ACCESS project
 - ▶ Assessment of effectiveness of COVID-19 vaccines through electronic health record: a protocol template from the ACCESS project

- Coverage study (EHR/registry based)
 - ▶ Estimation of COVID-19 vaccine coverage using registers and EHR: a protocol template from the ACCESS project

- Feasibility assessment of countries to participate in studies, including a final report

VAC4EU also organized monthly scientific webinars to discuss different aspects of the ACCESS work which were open to the public. Webinars are publicly available from the VAC4EU website [Early-Covid- Vaccine-Monitoring](#).

VAC4EU case studies

The Early-Covid-Vaccine-Monitor project under VAC4EU was funded by EMA through the EU PE & PV research network from November 2020–November 2021 and monitored COVID-19 vaccines in 8 countries using 2 complementary methodologies which have been described in the EU PAS register:

- A prospective cohort event in which more than 100,000 vaccinated persons across 6 countries were included and monitored through apps/internet
- A retrospective cohort study in 4 countries with short lag-time, monitoring the incidence rates of adverse events of special interest and COVID-19 prior to vaccination and post vaccination (<https://www.encepp.eu/encepp/viewResource.htm?id=44372>)

The project was focused on monitoring of incidence, and not signal detection nor signal evaluation. VAC4EU provided expertise and tools.

In addition, VAC4EU leads a COVID-19 Vaccine Monitoring Study (CVM) project funded by EMA through the EU PE & PV research network from April 2021–April 2023. This project aims to:

- Conduct prospective cohort event monitoring across 10 countries, focusing on special populations (children, immunocompromised, pregnant), general population, and booster doses
- Conduct retrospective cohort studies and self-controlled studies in 10 data sources ready to assess safety signals. Studies on Multi-Inflammatory Syndrome and Myocarditis have been conducted (<https://www.encepp.eu/encepp/viewResource.htm?id=42637>)
- Conduct methodological research on comparators and designs related to COVID-19 vaccine studies

VAC4EU is a member of the Global Vaccine Data Network (GVDN) and participates in dedicated studies on associations of COVID-19 vaccines and myocarditis, Thrombosis with Thrombocytopenia Syndrome (TTS), and Guillain-Barré syndrome (GBS) funded by the US Centers for Disease Control and Prevention (CDC).

Finally, VAC4EU supports its members to contract and implement post-authorization safety studies on COVID-19 vaccines for several manufacturers using the VAC4EU tools and governance, the ConcePTION data model and pipeline, and the VAC4EU member organizations.^{66–69}

VAC4EU impact and perspective

Lessons from the 2009 pandemic led to the initiation of a collaboration in Europe, which was designed, tested, and implemented by the VAC4EU. VAC4EU was established as an entity just before the 2019 pandemic was declared, and was able to start its work to support the European PE & PV network and the European Medicines Agency in time to prepare for large scale collaborative studies. VAC4EU member organizations form a vibrant community leveraging the expertise and knowledge from all of its member organizations. VAC4EU supports more than 10 official post-authorization safety studies on COVID-19 vaccines, protocols, and materials, which are all in the public domain.

COVID-19 Research Database, United States

Link: <https://covid19researchdatabase.org/>⁷⁰

Brief description of the COVID-19 Research Database initiative and data

The goal of the COVID-19 Research [Database](#)⁷⁰ is to provide public health and policy researchers with access to RWD to better understand and combat the COVID-19 pandemic. The COVID-19 Research Database was born out of the urgent need to better understand the effects of COVID-19 and streamline the challenges of managing data provider partnerships, patient privacy, and technological integration.

Set up in the spring of 2020, the COVID-19 Research Database consortium is a cross-industry, cross-sector collaborative composed of institutions that donate technology services, health care expertise, and de-identified data in the US. The data repository constructed by the consortium contains integrated, linked data sets from multiple sources, enabling public health and policy researchers to access RWD. The collaborative includes: Medidata (providing the engineering, hosting, and technical services), Datavant (providing the linking software), data providers (e.g., Healthjump, Change, Veradigm, OfficeAlly, and others), academic and non-profit partners (including Health Care Cost Institute), and technology partners (including Snowflake).

In all, 12 de-identified US data sets have been donated by consortium institutions and are integrated into a single repository. Data were de-identified using a technology that replaces identifiable patient information with an encrypted token; patients with data across select multiple data sources were linked using this tokenization process. Linking data in this way allows researcher access to a wide breadth of patient data. The data

sets are loaded into cloud database management software, and researchers access a secure workspace containing analytical tools (e.g., SAS, SPSS, R, Python).

Records from 250 million unique persons and over 5 million patients with COVID-19 were loaded onto the platform. Data types include medical claims, pharmacy claims, EHRs, demographics, life insurance claims, consumer data, and mortality records. The longitudinal, patient-level data sets are HIPAA-compliant (de-identified and limited). The linkages among the data sets allow for a more complete view of clinical care. The linking techniques are also privacy-preserving. All included data are structured. Depending on the source, data are refreshed weekly to quarterly.

Each consortium member is represented on a governance committee that makes consortium-level decisions and ensures all stakeholder interests are protected. Expert advisory groups are consulted on privacy, patient advocacy, legal issues, and strategy. A scientific steering committee, comprised of academics and clinical researchers, reviews research proposals for scientific rigor and peer-review standards. The database itself can be accessed by academic, scientific, and medical researchers. Although the researchers themselves may come from any sector, the projects themselves must be non-profit, non-commercial, and related to COVID-19.

Data workflow and technology features are outlined below in Figure 5.2 and Figure 5.3.⁷¹

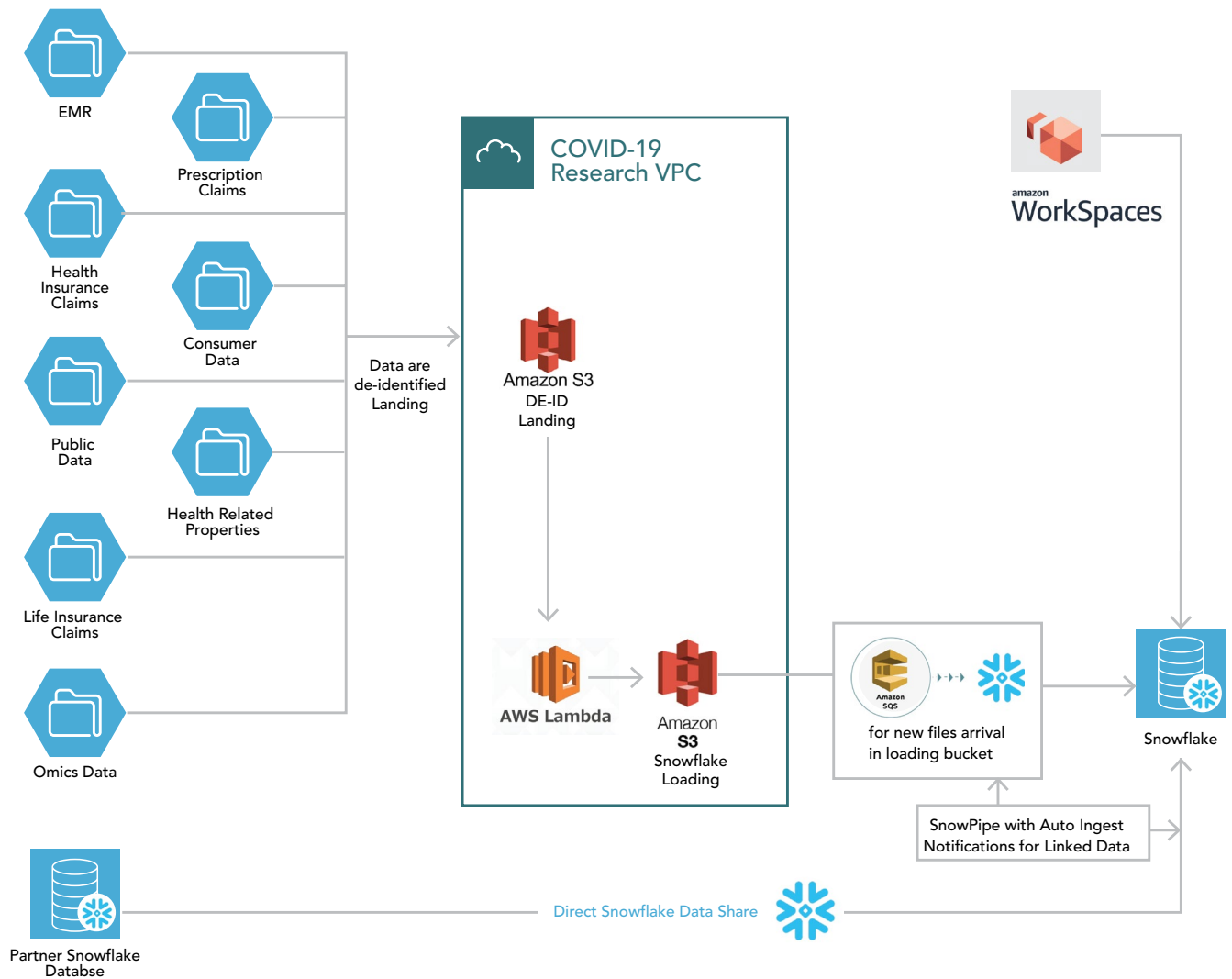


Figure 5.2. COVID-19 Research Database — Data Workflow



De-identified cross-source linking

De-identified of data through HIPPA-compliant, certified tokens

Combination of irreversible PII hashing (to source specific encryption (to dramatically extend ability to link new datasets

Problematic matching on multiple token-group derived from different PII subsets to increase match rate

Highly flexible software package with ease of modification of configuration to fit evolving data pipelines and workflows



Integrated Data Cloud

Single copy of source data, supporting multiple workloads with gated access

Dynamic scaling at both data store and user level to accommodate undependable and spiky demand

Maintenance as a service to reduce cost and keep technical team lean



Certified Privacy Protection

Independent, third-party certification on both individual data sources as well as linked data sets to validate de-identification

Pre-certification of data at source to hasten access to data while preserving privacy

Figure 5.3. Covid-19 Research Database — Technology Features

Researchers interested in accessing the database can submit a proposal to the Scientific Steering Committee. After scientific, privacy, and governance review, approved researchers have access to de-identified data, a knowledge base for the data sets, and tools (including R, Python, and SAS) at no cost. Record-level joins can be made among data sets. All linked data sets are de-identification certified before release for research use. Data cannot leave the secure environment, but an analytical report may be exported to use in published findings. All results must be made publicly available, preferably through peer-reviewed publications.

COVID-19 Research Database observational research: Dynamic, extensible, scalable data integration design

Consortium publications have ranged from disease understanding (e.g., risk factors) to resource utilization (e.g., impact on preventive care) and epidemiology (e.g., social determinants of risk). Examples of projects that have been conducted include

prediction of severity of COVID-19 infection, COVID-19 and social determinants of health, risk factors for COVID-19 infection, and implications of policies related to the COVID-19 pandemic. Potential longer-term projects include understanding the spread of COVID-19 variants, post-vaccination health implications, and understanding of long COVID. Findings are intended for practitioners, to help them understand the disease, as well as policy makers and public health officials, to help drive informed decision-making and improved understanding of the impact on different populations.

COVID-19 Research Database case studies

The below examples of peer-reviewed publications highlight the range of research topics addressable by the diverse array of data assets available in the consortium, in topics including risk factors, testing patterns, resource utilization, and primary care impacts:

- Racial Disparities in Ischemic Stroke Among Patients with COVID-19 in the United States⁷²
- Assessment of Filled Buprenorphine Prescriptions for Opioid Use Disorder During the Coronavirus Disease 2019 Pandemic⁷³
- Charges of COVID-19 Diagnostic Testing and Antibody Testing Across Facility Types and States⁷⁴
- Trends in Filled Naloxone Prescriptions Before and During the COVID-19 Pandemic in the United States⁷⁵

Beyond data diversity, it is the ability to join disparate data sets, in a privacy-compliant manner, that sets apart the COVID-19 Research Database consortium. One example of this is ongoing work by researchers from Northwestern University, Johns Hopkins, and Datavant exploring the intersection of race, income, and mortality due to COVID-19. Traditional RWD sources, such as EHR and insurance claims data, are often missing detailed information on patient attributes and mortality. To address this gap, a medical claims data source, Office Ally, was augmented with mortality data and consumer data. Mortality data were obtained from a curated source drawn from government agencies, online newspapers, funeral homes, online memorials, direct submissions, and other sources that collectively cover over 80% of annual US deaths. Data on demographics and income were obtained from a consumer data source, AnalyticsIQ, with consumer attributes across >120 million households. In the words of the authors, “the key elements utilized in the study were (i) fact of death, which was pulled from the

mortality data set, (ii) the physician diagnosis information from the medical claims data, and (iii) the racial and income attributes drawn from the consumer data.”⁷⁶ Through the consortium, this study was able to match patients across the 3 data sources, confirm privacy-preservation of the linked data, leverage confirmed mortality data, and incorporate modeled consumer attributes.

Another case example highlighting the timeliness of research enabled by the COVID-19 Research Database is work by researchers at the University of Pennsylvania and Medidata Solutions on the association of vitamin D deficiency with COVID-19.^{77,78} As the pandemic unfolded, studies emerged suggesting links between vitamin D deficiency and COVID risk.⁷⁹ Using electronic medical records data, the researchers were able to assess associations of pre-pandemic vitamin D deficiency with risk of COVID-19 infection during the pandemic, initially in oncology populations and later in the general population among patient groups at elevated risk for vitamin D deficiency.

COVID-19 Research Database impact and perspective

The consortium enables an ongoing flow of research questions to be addressed as the COVID-19 pandemic evolves. As of May 2021, over 350 academic, scientific, and medical researchers have accessed the repository and produced over 40 publications. At the time of this writing, the consortium continues to support over 100 ongoing project research teams at any given time and is expected to continue at least through Spring 2022.

The success of the consortium has been achieved by enabling a scalable approach to integrating disparate data sets for rapid research, with applications and lessons learned relevant to future related endeavors. According to the organizers, there are several key factors that have contributed to the success of the project that may inform the development of future similar engagements. These include: structured data processing and access workflows, modularized engineering and architecture with pre-defined and validated mechanisms, an agile development methodology, inclusive governance and veto rights for stakeholders (which builds trust and willingness to participate), and sponsorship and involvement from widely respected and “neutral” figures in setting up the consortium. Aniketh Talwai cites data interoperability and governance standards as key aspects, but another “lesson learned is to prioritize scale and speed from the outset.”

Key features of the COVID-19 Research Database are listed below:⁷¹

- Extensible modularity: Structuring data processing and access workflows as independent modules with pre-defined and validated mechanisms to add in new data feeds and end-users
- Security by design: Structuring data access to be locked down by default with physical impossibility of unauthorized extraction mitigates concerns about protection of intellectual property
- Agile methodology: An iterative product development approach with new features and data introduced on a rolling basis reduces time-to-access and prevents roadblocks from derailing broader effort
- Automation to scale: Investing in upfront automation of the data ingestion, linking, and provisioning processes allows for rapid growth in both users and data
- Structured onboarding: Proactively anticipating challenges in end-user experience and mitigating them through comprehensive onboarding process and collateral
- Stakeholder rights: Inclusive governance committee and veto rights on core interests builds trust and willingness to participate
- Credible convener: Sponsorship and involvement from widely respected and “neutral” figures in setting up the consortium ensures openness to engage
- High-bar wide-scope for applications: Allowing end-users latitude to explore a wide range of use-cases and research topics, but enforcing bar on quality of output

COVIDRIVE, Europe

Link: <https://covidrive.eu/>⁸⁰

Brief Description of the COVIDRIVE initiative and data

COVIDRIVE is the newest multi-stakeholder COVID-19 RWD initiative covered in this chapter. Initiated at the end of 2020, this public-private partnership aims to address the need to continuously monitor COVID-19 vaccination programs to assess brand-specific COVID-19 vaccine effectiveness, supporting vaccine companies in meeting their regulatory obligations in a consistent manner as well as public health institutes in Europe.

Core requirements for the Risk Management Plan (RMP) for COVID-19 vaccines for the EMA state that “effectiveness studies should be included” in the RMP and that the Marketing Authorisation Holder (MAH) should “make use of the established EU

efforts that can provide brand-specific, “reliable and timely data.”⁸¹ COVIDRIVE fits this recommendation, leveraging an existing influenza vaccine effectiveness platform: [*Development of Robust and Innovative Vaccine Effectiveness*](#) (DRIVE).⁸² DRIVE is a 5-year Innovative Medicine’s Initiative (IMI) project, conceived as a proof of concept by EMA to develop a public-private partnership platform providing yearly brand-specific effectiveness estimates for all influenza vaccines and to be used by vaccine companies to fulfill their regulatory obligations. Data has been collected in each influenza season since 2017 from an expanding network of hospitals and general practitioners in Europe. Throughout the project, DRIVE has developed a governance framework fostering transparent collaboration between public and private partners for high-quality research and vaccine performance evaluation.

Key assets leveraged in COVIDRIVE are an efficient study platform and a transparent public-private mechanism with functioning governance including shared decision-making, mutualization of resources leveraging public and private capacities and funds, collaboration in methods, independent study conduct and scientific committee for results review, high data quality standards, and regulatory pathways.

As a public-private partnership, COVIDRIVE includes public institutions, small-to-medium enterprises, and vaccine companies. To date (May 13, 2022), non-industry partners include the Foundation for the Promotion of Health and Biomedical Research in the Valencian Area (FISABIO) from Spain, P95 from Belgium, and The Finnish Institute for Health and Welfare (THL). Vaccine company partners include AstraZeneca (UK), CureVac (Germany), GSK (Belgium), Janssen (Belgium), Moderna (US), Novavax (US), Sanofir (France), and Valneva (France). The consortium is open to new partners (e.g., public health institutes, industry, small-to-medium enterprises, academia) and new European study sites. This partnership offers great opportunities to mutualize health care practitioners’ resources between companies and leverage existing public capacities across Europe, joining forces for a better understanding of COVID-19 disease and vaccine performance. The first COVIDRIVE study monitors for variants of concern and helps provide answers to the critical questions relating to COVID-19 vaccine effectiveness, including duration of protection of the different vaccines, impact of additional vaccine doses, and different vaccine combinations. Beginning with initial recruitment of patients in September 2021 from 12 hospitals in Spain and Italy, COVIDRIVE is currently planned for 2 years and is designed to quickly expand to

other countries across Europe. AstraZeneca (UK) and Janssen (Belgium) are the first vaccine companies in this partnership to monitor the effectiveness of their respective vaccines. A study team composed of COVIDRIVE partners supports the study sites in their data collection, and the first interim results are expected within 6–12 months from recruitment initiation. All scientific results will be reviewed by an Independent Scientific Committee.

COVIDRIVE and COVID-19 observational research: European framework and data, vaccine effectiveness

COVIDRIVE data are collected from hospitals and potentially also primary care centers, often building on existing public health surveillance systems and sites. National register data can also be used in countries where it is available. The network for this observational initiative is expected to include more than 40 hospitals and 500 general practitioners in 12 European countries: Austria, Belgium, Croatia, Finland, Germany, Iceland, Italy, Netherlands, Poland, Romania, Spain, and the UK.⁸³

Each study site is responsible for the collection, validation, and management of participant-level study data. Participating sites follow a master study protocol and related study procedures to ensure high quality standards. Because data collection and source documentation will differ across sites, data flow and management are documented in detail. Participant-level data are locally transformed to conform to a study-specific common minimum data set. The study site performs quality checks and processes any findings accordingly, with sufficient documentation to ensure transparency and reproducibility. The study-specific common minimum data set, composed of data uploaded by the study sites, will be stored on a dedicated secure server; the COVIDRIVE Research Server (CRS), following General Data Protection Regulation (GDPR) compliance requirements.

COVIDRIVE Case Studies

COVIDRIVE's initial studies aim at monitoring COVID-19 vaccine effectiveness against severe disease for specific vaccine brands.

These initial vaccine effectiveness studies are using a [hospital-based case-control study](#) with [test-negative control design](#).^{84,85} Additional studies addressing other aspects related to the evaluation of COVID-19 vaccine benefits are envisioned with contributions by study sites and COVIDRIVE partners.

Current areas of interest include: duration of vaccine protection (mid- and long-term), characterization of circulating variants and vaccine effectiveness against disease caused by those variants and newly emerging SARS-CoV-2 strains, effectiveness over calendar time (with date of hospital admission serving as a proxy for changing genetic variants of the virus), effectiveness against severe COVID-19 disease, and effectiveness in special risk groups such as immunocompromised, frail individuals or subjects with chronic conditions or existing comorbidities.

The exposure of interest and vaccination status (including brand information and date of vaccination[s]) are collected via vaccination registries, vaccination cards, and medical records (depending on country/region). Batch information will be additionally collected when available. Context information on public health guidance, national/regional immunization recommendations including vaccines recommended by authorities, SARS-CoV-2 genetic variant circulation, and COVID-19 vaccine label information will also be collected.

Potential confounders and effect modifiers collected at all sites include: age, sex, history of medical diagnosis for selected morbidities of interest (asthma, lung disease, cardiovascular disease, hypertension, chronic kidney disease, type 2 diabetes, cancer, immunodeficiency), body mass index, vaccination against pathogens causing COVID-19 like symptoms (influenza, pneumococcus), calendar time, and previous SARS-CoV-2 infection. When available, information on precautionary health behaviors (e.g., wearing face masks, using hand sanitizer, going to public places), socio-economic variables and/or ethnicity, being a health care worker, residence in a long-term care facility residence, and smoking history will be collected.

COVID-19 vaccine effectiveness will be estimated with random-effects meta-analysis of site-specific estimates or Generalized Estimating Equations (GEE). The site-specific estimates will be obtained in logistic regression models, adjusting for the confounders. A final study report will be written for each of the individual COVID-19 vaccine brands of interest. The protocol and study reports are posted on the [European Union electronic register of Post-Authorisation Studies \(EU PAS register\)](#)^{84,85} and the study results will be published in peer reviewed open-source international journals. Study sites will remain owners of their subject level data.

Study limitations may include low sensitivity and specificity of the Reverse Transcription Polymerase Chain Reaction (RT-PCR) test, with a bias towards underestimating the effectiveness that is proportional to SARS-CoV-2 positivity rates within the patients meeting the case definition. The study [protocol](#)^{84,85} posted in the [EU PAS register](#) provides additional details.

COVIDRIVE impact and perspective

Dr. Javier Díez-Domingo, Head of the Vaccines Research department of the Foundation for the Promotion of Health and Biomedical Research (FISABIO) foundation and COVIDRIVE co-coordinator, says the first priority of the initiative is to examine COVID-related hospitalization as an [outcome](#).⁸⁶ “Hospitalizations were one of the main reasons for national and regional governments to impose public health measures such as shutdowns, social distance, and wearing of masks to relieve the disease burden on the health care systems. Producing accurate and timely information on how well the different COVID-19 vaccines protect against hospitalizations and remain protective over time is essential to successfully manage the pandemic.”⁸⁶

Thomas Verstraeten, co-coordinator of COVIDRIVE and CEO of P95 (a company that provides consultancy services) says “The current COVID-19 pandemic highlights the need for a public-private collaborative environment to generate vaccine effectiveness data to advise the design of national immunization programs and to fulfil the effectiveness requirements established by the regulatory authorities.”⁸⁶

Laurence Torcel-Pagnon, a key contributor to COVIDRIVE and evidence generation partnership expert at Sanofi, indicates that “the consortium strives at developing a framework to leverage the secondary use of the collected data to address future research questions to advance knowledge on COVID-19 disease and related vaccines performance.” She also emphasizes the importance of multi stakeholder partnerships including public health organizations, academia, industry, and research organizations to maximize the value of fit-for-purpose RWD to address today’s and tomorrow’s COVID-19 research questions.

Conclusion

The selected multi-stakeholder COVID-19 RWD initiatives described in this chapter are examples of how best use of data, tools, and networks can greatly contribute to quickly

and adequately addressing critical questions on COVID-19 while creating infrastructures and sustainable platforms to address current and emerging COVID-19 observational research questions. The initiatives presented cover different geographic areas, involve different types of stakeholders, and demonstrate that it is possible to urgently address key COVID-19 research needs in partnership.

There are common elements in many of these multi stakeholder initiatives that have led to their success in COVID-19 research. They are open and multidisciplinary scientific collaborations with a long-term vision to address multiple types of research questions. They build on existing health care data sources and hospital surveillance systems, and often use federated (decentralized) data networks. They share tools and code, some incorporating common data models to improve transparency and efficiency of research.

Some of these resources were operating before COVID-19, but the pandemic has pushed these multi-stakeholder initiatives to move faster, be more efficient, and demand more frequently updated data while ensuring the highest scientific standards. Through initiatives like these, current and new COVID-19 observational research-specific questions can be answered. If the momentum of such collaborations can be sustained, we may also find new ways of enhancing the use and value of RWD and RWE in other disease areas to drive clinical, regulatory, and key public health decision making.

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Chapter 6: The COVID-19 Evidence Accelerator

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Real-world data (RWD) have helped advance the nation's ability to respond to the COVID-19 global pandemic by providing situational awareness and expanding the capacity to conduct post-market studies of the safety and effectiveness of COVID-19 diagnostics and therapeutics. The [COVID-19 Evidence Accelerator](#)¹ is an initiative launched by the [Reagan-Udall Foundation for the Food and Drug Administration](#) (FDA Foundation),² in collaboration with [Friends of Cancer Research](#) (Friends)³ and on behalf of the FDA, to provide a unique venue for major data organizations, government and academic researchers, and health systems to share information about COVID-19 efforts, and to convene a community to urgently address questions about COVID-19. The Evidence Accelerator is just one example of how the FDA is leveraging RWD, which intersects with RWD efforts at the FDA and other government agencies (see Figure 6.1).

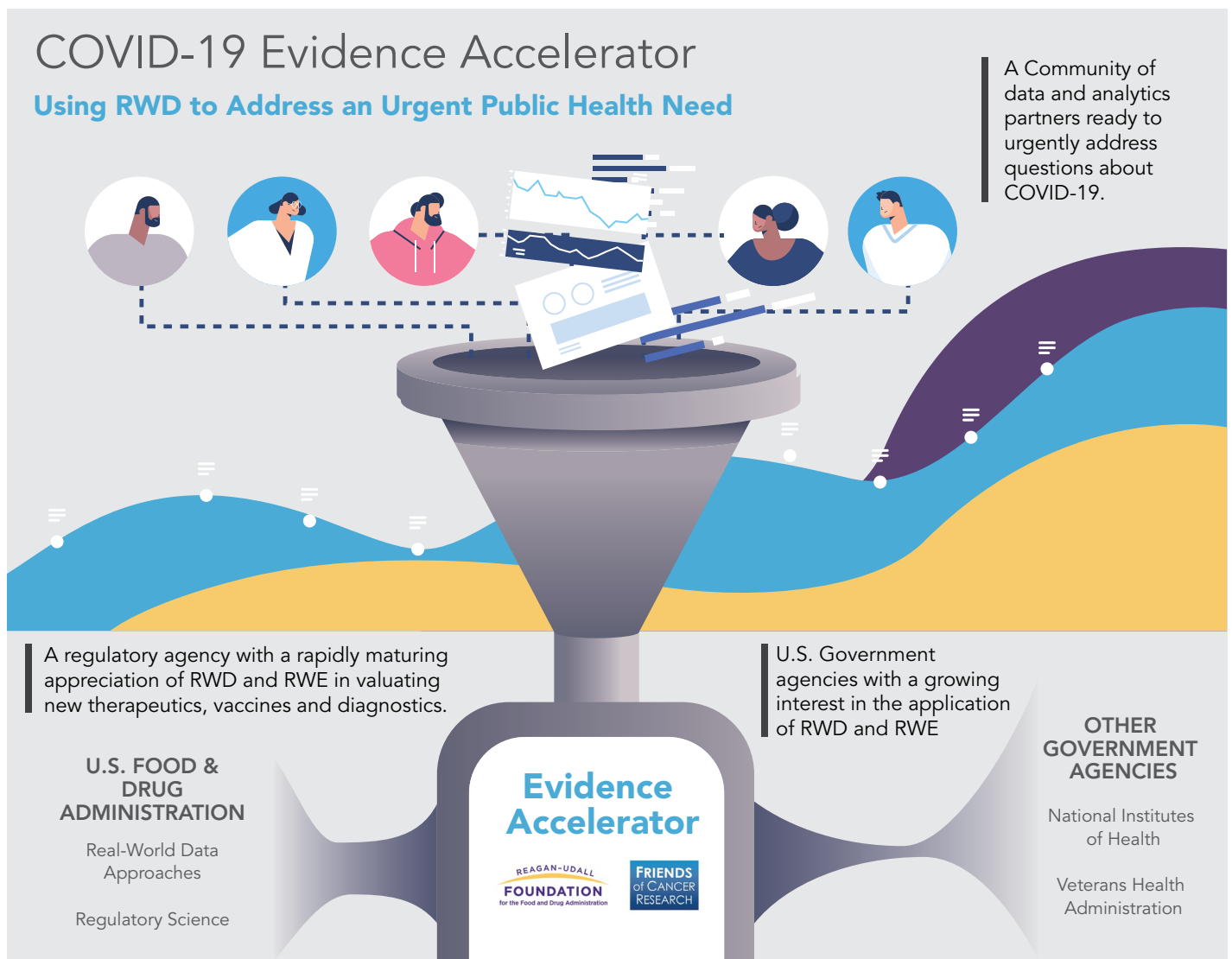


Figure 6.1. Leveraging RWD at the FDA and other government agencies

The Evidence Accelerator includes over 250 organizations that represent health services research, regulatory science, academia, government, regulated industry, technology companies, and health care analytic companies.

The Evidence Accelerator community comes together in two ways on three main workstreams: Therapeutics, Diagnostics, and Vaccines (Figure 6.2). For each of these workstreams, the two pillars of the COVID-19 Evidence Accelerator are Lab Meetings and Parallel Analysis (PA).

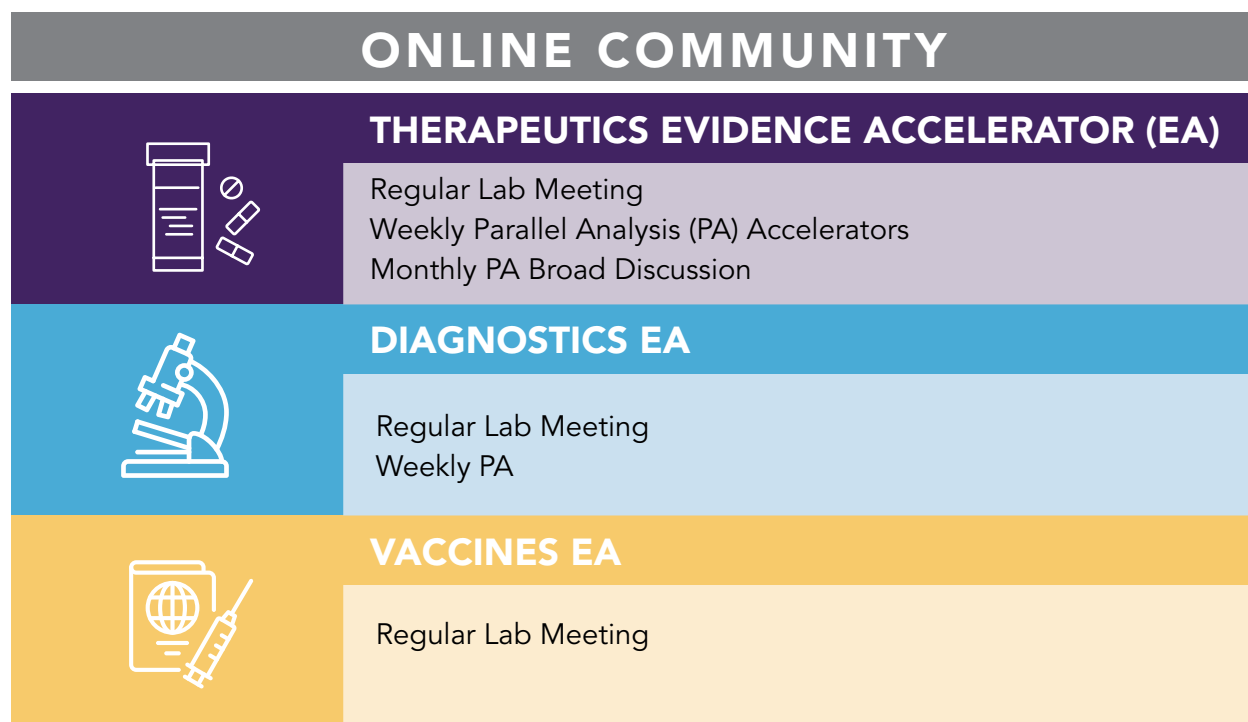


Figure 6.2. The Evidence Accelerator Community

Evidence Accelerator Lab Meetings

The FDA Foundation regularly hosts a Lab Meeting which is named for the popular graduate school lunch-time forum for gathering and sharing information. For the Evidence Accelerator, the focus is on sharing information about COVID-19 and the data needed to better understand its epidemiology, diagnosis, treatment, and prevention. The Evidence Accelerator abides by Chatham House Rules and requests attendants to keep the conversation “in the room” because more often than not, preliminary data are being shared in an informal, real-time peer review. From March 2020 to March 2021, the Evidence Accelerator has hosted 50 Therapeutics Lab Meetings and 45 Diagnostics Lab Meetings.

Evidence Accelerator Parallel Analysis

In parallel analysis workgroups, the [Evidence Accelerator](#)¹ convenes experts in health systems research, regulatory science, data science, statistics, and epidemiology to rapidly collect information related to real-world studies of COVID-19. With leadership and input from the FDA, a foundational task of this parallel analysis is to understand what data are available to answer key COVID-19 questions of interest to public health. In the Evidence Accelerator, we crowdsource the relevance of the research questions

initially developed by the FDA to get a sense of what, where, and when data are available. This exchange fuels the rapid development of master protocols to evaluate the safety and effectiveness of multiple treatments or multiple diagnostic tests in various sub-populations, both in parallel and in succession. Master protocols enable evaluation of the same question across different data systems using a parallel approach to analyses to quickly test reproducibility of results and evaluate data heterogeneity (see Figure 6.3).

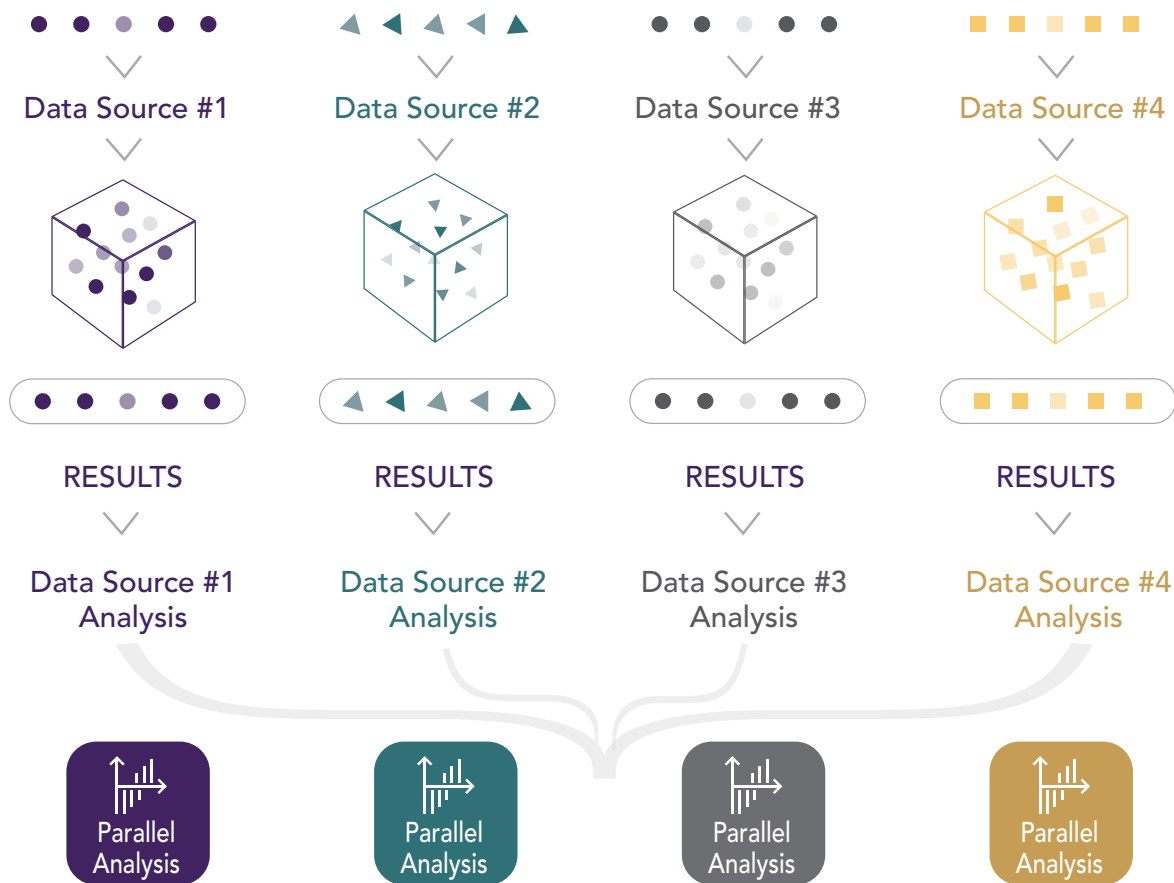


Figure 6.3. Parallel analysis

The parallel analysis groups work collaboratively to determine how data elements are being extracted and how they are being defined to operationalize a platform that can answer current questions, as well as to inform how research activities could be conducted in the future. Repeating analyses in parallel through collaborators using different analytical techniques and data sources helps strengthen findings and learnings. Through a set of community created core principles (Figure 6.4) that underpin all work

efforts, the goal of the Evidence Accelerator parallel analysis is to help validate the role of real-world data as a tool for rapidly learning about patient characteristics, treatment patterns, and outcomes associated with management strategies for COVID-19.⁴

Together, we will create and lead.

- C** **CONTEXT** — tie data to the question, address bias, explain validation strategies.
- R** **RESPECT** — for patient privacy and the patient voice is paramount.
- E** **EARN TRUST** — show processes, analytic approaches, and comparisons. Be open to input. Challenge with productive intent.
- A** **ACT FAST AND DO GOOD WORK** — act with a sense of urgency, but not at the expense of quality or credibility.
- T** **TRANSPARENCY** — ruthless transparency.
- E** **EMBRACE AND EXPLORE** —convergence and discordance to facilitate understanding and generate knowledge.
- L** **LEARN** — continually integrate best practices from **sharing** process, limitations, pitfalls, and successes.
- E** **EXERCISE PATIENCE** — state when a question can't be answered right away and institute action to answer it.
- A** **ACCESSIBILITY AND TRACEABILITY** — document data generation, processing, curation, and analytics.
- D** **DISSEMINATE WORK** — to show what good looks like. *Teach, Don't Preach.*

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Figure 6.4. Community created core principles

Therapeutics and Diagnostics Evidence Accelerator Parallel Analysis Workgroups:

In close collaboration with the FDA, the Therapeutics Evidence Accelerator Parallel Analysis workgroup developed key specific COVID-19 research questions for multiple organizations and teams to address simultaneously. Initial activities include 1) rapidly revising a list of core data elements, 2) identifying those elements critical to answering the primary question, and 3) establishing uniform collection parameters. The Therapeutics Parallel Analysis workgroup has taken on 3 primary research areas to date: 1) effectiveness and safety of hydroxychloroquine (with and without azithromycin), 2) real-world safety and effectiveness of remdesivir for COVID-19, and 3) the natural history of coagulopathy in COVID-19 vs. influenza. This workgroup has met 65 times and presented 3 times to a broader audience. Results from the hydroxychloroquine project were [published](#),⁵ and the results demonstrated across 7 databases that administration of hydroxychloroquine (with and without azithromycin) appeared to have no effect on time to mortality in hospitalized COVID-19 patients. More than 15 organizations have engaged in at least one of the parallel analyses (see Table 6.1).

The Diagnostic Parallel Analysis workgroup incorporates lessons learned from the Therapeutics Evidence Accelerator Parallel Analysis workgroup. It brings analytic partners together to address key research questions about diagnostic testing in parallel. This workgroup conducted the same 3 initial activities as the Therapeutics Parallel Analysis workgroup. These activities are described in detail in a [master protocol](#).⁶ This workgroup operates collaboratively to figure out how data elements are being extracted and how they are being defined. This enables the group to put a platform into use that can answer current research questions.

Table 6.1. Organizations that have engaged in at least one of the parallel analyses.

Therapeutics: (1) Effectiveness and safety of hydroxychloroquine (with and without azithromycin), (2) Real-world safety and effectiveness of remdesivir for COVID-19, and (3) The natural history of coagulopathy in COVID-19 vs. influenza.	Diagnostics: Characterization of the utilization and real-world performance of COVID-19 serology tests
Aetion (with Health Verity (1); Gilead (2))	Aetion (with Health Verity)
COTA (with Hackensack Meridian)	Health Catalyst
Dascena	Optum Life Sciences
Datavant (with Northwestern University)	Mayo Clinic
FDA Sentinel	Regenstrief Institute
HealthPals	University of California Health System
OneFlorida	
Syapse	
Target RWE	
TriNetX	
University of California Health System	
US Veterans Affairs	

The primary research aims were to identify where test data reside in a data ecosystem, and to connect that data to enable researchers to answer key questions: 1) Among persons with molecularly-confirmed SARS-CoV-2, describe serological testing by demographic, behavioral and environmental characteristics, baseline clinical presentation, key comorbidities, and bacterial/viral co-infections, 2) Characterize the timing of serology testing relative to symptom onset or RNA date by demographic, behavioral and environmental characteristics, baseline clinical presentation, key comorbidities, bacterial/viral co-infections, and test characteristics (e.g., manufacturer), 3) Describe demographic, behavioral and environmental characteristics, baseline clinical presentation, key comorbidities, bacterial/viral co-infections, and test characteristics (e.g., manufacturer) associated with positive serology vs. negative serology, and 4) Describe the real-world positive percent agreement of serology compared to positive molecular test for SARS-COV-2.⁷

The Diagnostics Parallel Analysis workgroup has convened 36 times and presented on 3 occasions to the Diagnostics Lab Meeting to report out results from their analysis to characterize real-world data interoperability, use, and performance of SARS-CoV-2 serology tests. To date, one manuscript is under review and two others are in development.

Learnings from the Parallel Approach to Analysis

The Evidence Accelerator Parallel Analysis taught us many lessons that we can use to further the use and effectiveness of real-world evidence beyond COVID-19:

- 1. Collaboration:** The willingness to collaborate with other stakeholders is a key component of the Evidence Accelerator. Finding ways to leverage this attitude beyond COVID-19 to increase knowledge of resources across diverse groups in the health care and laboratory data ecosystem is imperative. Various diverse panels at large health care conferences, including stakeholders from pharmaceutical, regulatory, and health care areas,⁸ have mentioned that the willingness demonstrated by groups working with the Evidence Accelerator to share information and resources is unprecedented. Such collaboration may not easily translate to other disease areas, but it should be considered, especially in areas of high unmet need. The COVID-19 experience highlighted processes that are either duplicative or unnecessary, and we may begin to either do without them or do them more efficiently.

- 2. Data Heterogeneity:** Data from claims and electronic health records (EHRs) have an inherently different capture of the patient experience, which necessitates different approaches to identifying comorbidities and events in order to understand the full clinical history for the event of interest. Researchers often have extensive experience in only one data source specifically. In parallel analysis, we must consider multiple data sources and allow protocols that are flexible enough to accommodate the specifics of each data source and to align where appropriate.⁹⁻¹¹ The FDA Foundation and Accelerators have built catalogues that outline the different study design approaches taken to accommodate these different data sources. We will make this resource publicly available.
- 3. Unifying Case Definitions:** Multiple definitions that represent the same clinical construct abound in scientific literature. In parallel analysis, we have a unique opportunity to align definitions across studies, intentionally point out differences, and describe how they might explain discrepancies in results. Through this work we have catalogued different case definitions (taking validated algorithms where available) and will post them when publicly available.¹
- 4. Ascertainment:** The ability to fully capture events for a given patient will differ based on the data source. Specifically, EHRs only capture events attended within a specific system and have limited capture of events after discharge if they occur in other systems. Similarly, health care claims systems can typically only capture billable events such as procedures and prescription medications and generally lack the granularity available in the EHR. However, some systems are integrated and able to capture data from both the EHR and claims. There is heterogeneity in the granularity of data regarding the care and medical history of a patient, which is generally more available from EHRs than claims.

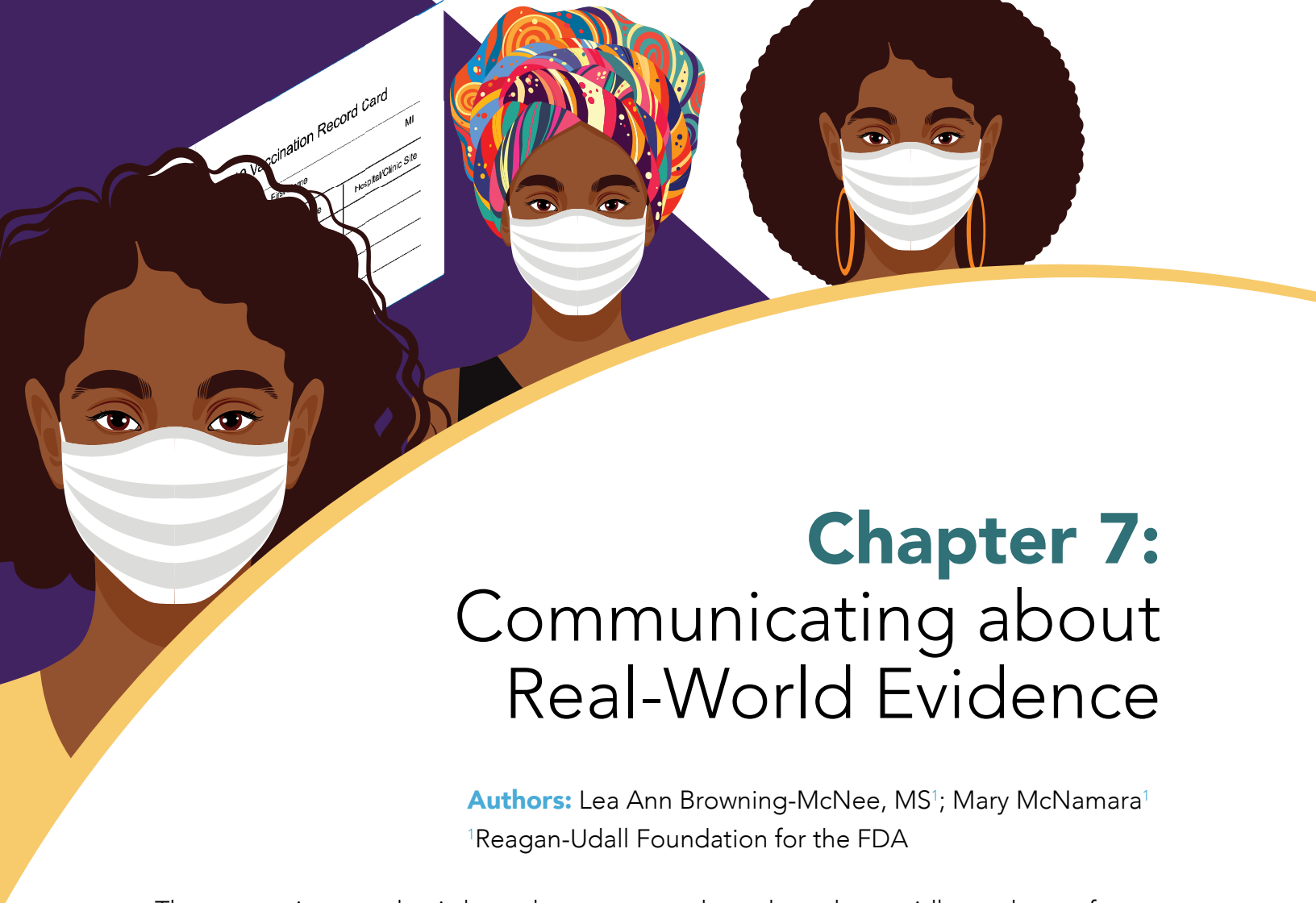
- 5. Disclosure Limitations:** The ability to identify independence across data partners is complicated when data aggregators are prohibited from disclosing the systems included in their network. Disclosure agreements between the aggregator and participating health systems that allow for the identification of the systems for the purposes of public health activities, or by request, would improve transparency. Alternatively (but not as helpfully), independence of samples could be demonstrated by mapping coverage areas for all partners included in parallel analysis in order to understand the amount of overlap and suggest independence of samples across partners.

- 6. Data Flow:** In a fragmented health care system that often involves siloed technologies, assembling the data is the first task toward building real-world evidence. In diagnostics, for example, test manufacturer information is often not integrated with laboratory and clinical data for the instrument. A lack of interoperability impedes public health reporting and the ability to assess the performance of the test post-market. For devices like COVID-19 tests, the experience during emergency situations demonstrates the need for regulatory authorities to require and incentivize the use of device ID, and to integrate these data for public health reporting purposes so that post-market safety and effectiveness can be more readily calculated.

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Chapter 7: Communicating about Real-World Evidence

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The coronavirus pandemic brought an unprecedented need to rapidly produce safe and effective diagnostics, therapies, and vaccines. The demand to accelerate research and development, reinforced by a growing availability of real-world data (RWD), have made the health care community and the larger public more aware and receptive to the use of real-world evidence (RWE). However, there is also skepticism about using RWE to support clinical or regulatory decision-making. In August of 2021, World Health Organization officials reported that misinformation about COVID-19 and vaccines was a factor in vaccine hesitancy and in an increase in cases around the world.¹

Where to Publish

The peer review process helps promote the publication of valid, balanced, and reproducible studies. Additionally, the process can improve the quality of a manuscript and even the study itself. However, the tension between the time it takes to leverage the rigor and credibility that comes from peer review and the need to disseminate findings that may impact public health is even more acute in a pandemic setting.

During the pandemic, some journals have slightly modified their publication procedures to share findings more quickly, but lags still exist in the process. Researchers have options for when they want journal credibility but need to share findings quickly, including:

1. Consider the full spectrum of scientific journal articles for publication. Certain information may be more appropriate for a perspective, editorial, or research letter. Many traditional scientific journals offer narrative or commentary pieces that may be published faster than traditional research articles. These articles still provide credibility for the research and the authors but in less time than traditional research articles take. For example, an urgent call to address gaps in race data when describing COVID-19 vaccination rates may be appropriate for a journal perspective rather than original research. Such information is descriptive, but is critical for future inferences to be made. Case studies may also be a route for publishing research using RWD.
2. Consider open access or open network journals. Many open access journals still adhere to a rigorous peer review process but commonly commit to faster publication than traditional print journals. Even well-established print journals are beginning to offer open access publication options. As with any journal submission, authors should be wary of “pay-to-publish” outlets and select an open access journal that is reputable and geared toward the target audience. Several open access journal directories and databases that publish journal performance metrics such as impact factor are available to help make this determination.
3. Submit for publication as abstract or in proceedings. Some scientific meetings publish abstracts or proceedings documents, which, depending on timing of the conference, may be available more expeditiously.

Once published, dissemination efforts can further include:

- Issuing a press release.
- Sharing with colleagues and thought leaders via email blasts.
- Linking to the publication on social media (and even boosting posts for broader reach). If you leverage social media to disseminate findings or publications, be prepared to monitor and engage the space appropriately. Otherwise, the conversation may introduce inappropriate interpretation.
- Writing guest blog posts.
- Using the paper to spur discussion on podcasts, conferences, and other avenues to connect with interested stakeholders.

Tips for Developing a Communications Plan

Researchers can use crafting a plan to disseminate RWE research to help identify target audiences, refine messages, and select communication pathways to share findings effectively. The foundation of such a plan is clearly defining and prioritizing the audience or audiences that need to be reached. Audiences should typically include internal groups (i.e., colleagues) as well as external groups, such as the scientific community, decision-makers (e.g., clinicians, policy-makers), and the general public. The latter is a commonly ignored but important audience for the communication of scientific evidence, considering the growing reach of misinformation and distrust in science.

Messaging

Once the target audience(s) is/are identified, effective messaging should perform 4 interrelated tasks:

1. Identify the science most relevant to the decisions that people face
2. Understand what people already know
3. Fill the critical gaps between what people know and need to know
4. Evaluate the adequacy of those communications

A clinical audience may want to better understand the nuances of specific treatments with diverse groups, while a general audience may want to better understand the overall risk-benefit.

Methods to increase relevancy of scientific findings include the tailoring of language, illustrations, and anecdotes:

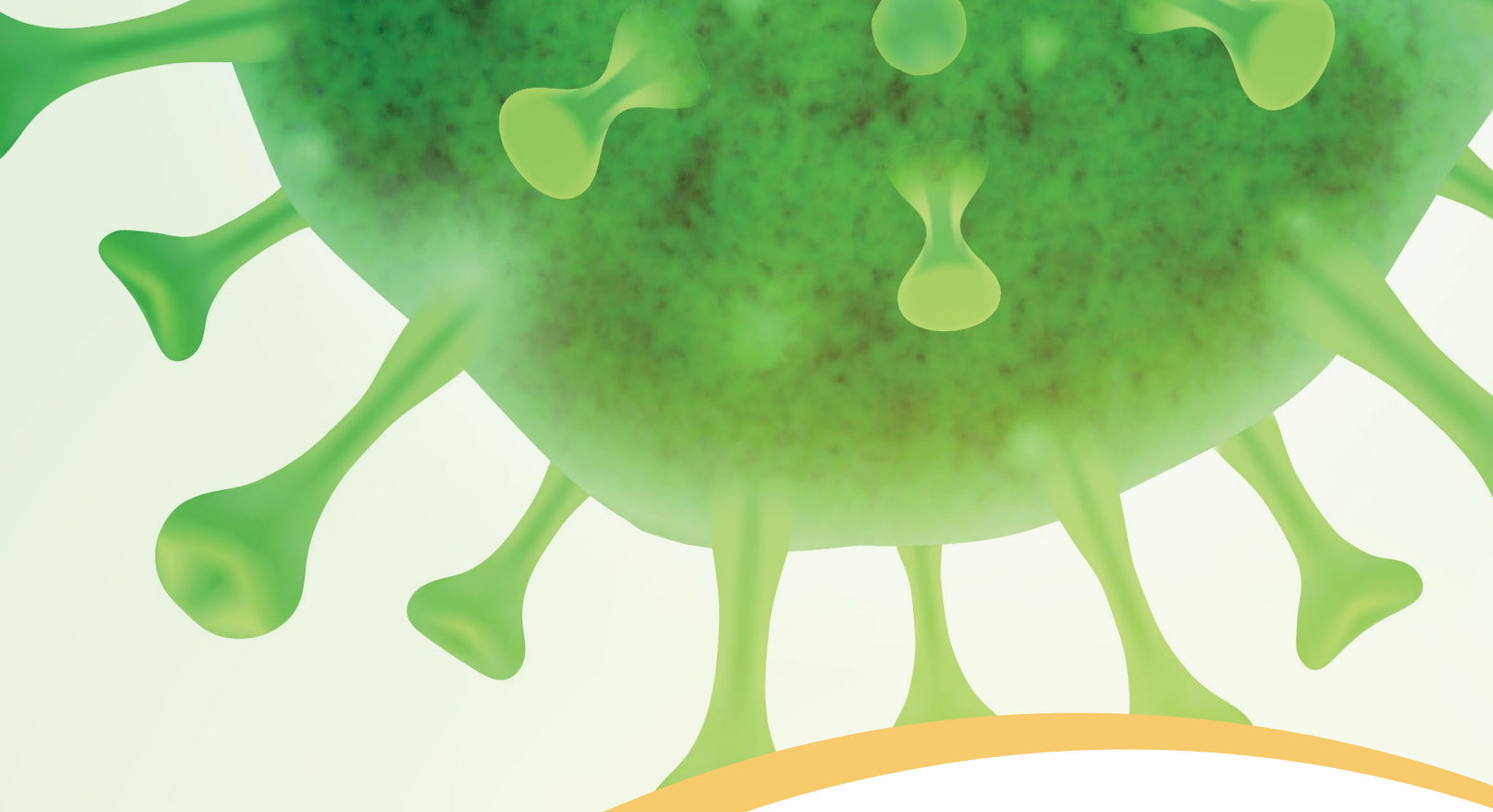
- Use analogies and visuals. Consider the different ways people consume information.
- Address the question, “What’s in it for me?” to keep your audience interested.
- Avoid jargon.

The “elevator speech” is an effective approach to thinking about how to create a positive and memorable impression in a short period of time. It is also a valuable exercise for researchers to ensure effective communications about RWE. When crafting communications about RWE, an author should be able to answer several questions clearly and concisely:

- What is the **topic or focus** of the research?
- What is the core **problem, issue, or question** being asked or addressed in the research? This can be a compelling introduction to the research.
- How is the work **uniquely** addressing this problem, issue, or question?
- Why is the problem interesting and important? In other words, “So what?”
- Finally, what is the **goal or aim** of the communication? Or what is the call to action?

Reference

1. Mendez R. *WHO says Covid misinformation is a major factor driving pandemic around the world*. CNBC. Published August 24, 2021. Accessed January 13, 2022. <https://www.cnbc.com/2021/08/24/who-says-covid-misinformation-is-a-major-factor-driving-pandemic-around-the-world.html>



The Covid-19 Evidence Accelerator fosters engagement, explores new topics, builds collaboration, and advances the use of real-world data to inform our nation's pandemic response. The Evidence Accelerator will continue its evolution to address other public health and regulatory priorities.

Responding to the novel coronavirus pandemic inspired unprecedented collaboration and cooperation in the health and research communities. In March 2020, at the request of the FDA, the Reagan-Udall Foundation for the FDA, in collaboration with Friends of Cancer Research, created the COVID-19 Evidence Accelerator — a forum for stakeholders across the health care spectrum to share real-world data and to generate ideas on how to deal with COVID-19.

