One of these years is not like others: Real-World Data in the times of COVID-19. Did the pandemic change the way we generate and interpret Real-World Evidence?
COVID-19 Will Have a Broad and Lasting Impact on Our Lives

Will COVID-19 affect RWD and RWE for healthcare research?

How we work
Who we live with
How we get care
No: Requirements for high-quality RWE exist

Data Quality and Fit for Purpose

Study Design and Analytic Choices

End-User Requirements
Yes: One of these things is NOT like the others

- RWD Differs by
  - Data collected
  - Analytics to use
  - Outcomes to assess

- Findings
Today’s Debate

1) Will COVID-19 change how we collect, analyze and interpret RWD in future RWE studies?

2) How dissimilar is “too” much? How will you know?

3) Can these differences be mitigated?

4) Will this variances matter to end-users of the research?
Speakers

**Jennifer Graff, PharmD**  
Consultant  
Former Vice President, Policy Research  
*National Pharmaceutical Council (Moderator)*

**Matthew Reynolds, PhD, FISPE**  
Vice President, Real World Evidence, *Real World Solutions, IQVIA*

**John Concato, MD, MPH, MS**  
Associate Director for Real-World Evidence Analytics, OMP, CDER, FDA

**Jeffrey Brown, PhD**  
Associate Professor at the Department of Population Medicine  
*Harvard Pilgrim Health Care Institute and Harvard Medical School*
One of These Years Is Not like Others: Real-World Data in the Times of COVID-19.

*Did the Pandemic Change the Way We Generate and Interpret Real-World Evidence?*

*May 20, 2021*

Matthew Reynolds, PhD – VP, Real World Evidence, Center for Advanced Evidence Generation
The Impact of COVID-19 on Real-World Health Data and Research

Understanding the implications of the pandemic on real-world health research: key considerations and solutions.

MATTHEW W. RYAN, MD, MBA, VP Real-World Evidence, Real World Solutions, IQVIA
NATALIA PETRUSCI-ZVULINA, PhD, Associate Epidemiology Director, Real World Solutions, IQVIA
MELODY SAMANT, MPH, Consultant, Strategy and Innovation, Real World Solutions, IQVIA
VARADE TRIVEDI, MPH, Associate, Life Sciences/Strategy, Real World Solutions, IQVIA
NANCY A. DREVER, PhD, MPH, FIPSP, Fellow OUA, Chief Scientific Officer and Senior Vice President, Head, Center for Advanced Evidence Generation, Real World Solutions, IQVIA
JENNIFER GRAFF, PharmD, VP Policy Research, National Pharmaceutical Council
AMANDA GREEN, MPH, Research Associate, National Pharmaceutical Council
Key Considerations in Pandemic Real World Research

• Shifts in treatment seeking behavior
  - Access to Health-care
  - Delayed treatments/procedures
  - Telehealth
  - Differential impact across patient sub-groups

• Impact on real world outcomes
  - Epidemiology of disease
  - Assessment of outcomes (e.g., hospitalizations, Rx patterns)
  - Direct impact of COVID-19 infection
  - Short-term vs long-term effects?

• Solutions
  - Methodological
  - Analytical
  - Interpretation
IQVIA Institutional & Office Medical Claims: Weekly and Cumulative Year-over-Year Growth

Data for latest week date controlled against prior periods; estimates have been applied to reflect anticipated late-adjudicated claims based on historical rates


Estimated amounts for latest weeks applied based on likely claims still to be received due to data latency or claim processing delays; See Appendix for further details

COVID-19 Market Impact - w/e Dec 4, 2020
Weekly Medical Claims: Office, Institutional, Telehealth vs. Pre-Pandemic Baseline

Total Telehealth Claims Through W/E 10/09 vs. Baseline Period
Weekly Diagnosis Visits Through W/E 10/09 Compared to Baseline Period

Total Visit Claims by Service Type
Baseline Period – W/E 10/09

Data for latest week date controlled against prior periods; estimates have been applied to reflect anticipated late-adjudicated claims based on historical rates

Source: IQVIA: Medical Claims Data Analysis, 2020; Baseline = Average of claims for period W/E 1/10/2020-2/28/2020. Estimated amounts for latest weeks applied based on likely claims still to be received due to data latency or claim processing delays; See Appendix for further details.
Questions?

Please feel free to contact me for more information

Matthew W. Reynolds, PhD, FISPE
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One of these years is not like others: Real-World Data in the times of COVID-19. Did the pandemic change the way we generate and interpret Real-World Evidence?

Lots of Questions and Few Answers

Jeffrey Brown, PhD
Associate Professor
Harvard Pilgrim Health Care Institute and Harvard Medical School
May 20, 2021
ISPOR
Areas of Concern Related to Changes in Health Care Utilization Patterns Related to Covid-19

- Prevalence and incidence rates
- Cohort definitions
- Baseline characteristics
- Incident outcomes
- Vaccination status
- Clinical trial optimization
- And on and on...
Typical Observational Research Study Design

- Inclusion criteria
- Exclusion criteria
- New user/patient (incident) criteria
- Baseline health status assessment
- Health care utilization intensity
- Etc

- Outcome definition
- Censoring criteria (outcome, change in medication use, new diagnosis)
Example from FDA Sentinel

Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: A Propensity Score Analysis

Incident Exposure with History of Heart Failure: Cohort restricted to those with evidence of heart failure in the 183 days before or on the dispensing date.

Baseline Characteristics: Baseline characteristics evaluated in the 183 days before and including the dispensing date. Baseline characteristics of interest: age, sex, race, year of index exposure, combined comorbidity score, ambulatory allergies, serious allergies, diabetes, heart failure, ischemic heart disease, nonsteroidal anti-inflammatory drugs, sirolimus, and everolimus.

If we run this analysis in 2020 will the result be different?

Example from FDA Sentinel
Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis

Inclusion Criteria: Patients with evidence of atrial fibrillation in the 183 days prior to and including the index dispensing date.

Event Outcome: CSVV defined as a diagnosis of hypersensitivity angiitis, vasculitis of the skin, or allergic purpura in the AV, OA, or ED care setting.

Exclusion Criteria: We excluded patients with evidence in the 183 days prior to and including the index dispensing date of any of the following: A) CSVV diagnosis of hypersensitivity angiitis, vasculitis of the skin, or allergic purpura in the ambulatory or emergency department care setting or steroid treatment for CSVV; B) diagnosis of select autoimmune disorders, including rheumatoid arthritis, lupus, Crohn's disease, Sjogren's syndrome, dermatomyositis, polymyositis, and cryoglobulinemia or treatment for these autoimmune disorders; C) cancer or chemotherapy treatment; D) kidney transplant or dialysis; or E) potential alternative indications, including deep vein thrombosis, pulmonary embolism, or joint replacement surgery prophylaxis.

Example from FDA Sentinel
Cutaneous Small-Vessel Vasculitis following Dabigatran, Rivaroxaban, and Apixaban Use in Patients with Atrial Fibrillation: A Propensity Score Matched Analysis

Baseline Characteristics: We evaluated the occurrence of baseline characteristics in the 183 days prior to and including the index dispensing date, including the following: Charlson/Elixhauser combined comorbidity score, health care utilization, drug utilization, autoimmune diseases, hematological blood disorders, viral infections, bacterial infections, anti-infectives, nonsteroidal anti-inflammatory drugs, psychoactive drugs, cardiovascular and diuretic drugs, beta-adrenergic receptor agonists, anticonvulsants, and individual subcategories for each category of interest.

Likely get a different answer if the analysis includes 2020.
Some Additional Areas of Concern

• New clinical or observational studies
• Ongoing clinical or observational studies
• Data quality checking
• Different visit types
• Patient-reported measures
• Impact of validated algorithms
• Impact of comorbidity scores
  • Including Covid-19 infection as a risk factor
• Sensitivity analyses
• Types of methods/ time-varying issues
And What About Studying Covid-19?

- Identification of patients with Covid-19 infection
  - Inpatient algorithms
  - Outpatient algorithms
  - Using laboratory results

- Covid-19 vaccine exposure issues

- Can we study long Covid if we can’t differentiate those infected and those not? Those vaccinated? And if we don’t have any baseline data?

- Covid patients often treated at specialized facilities that have no history for those patients:
  - eg, many patients treated with Remdesivir early in pandemic have no documented medical history because care was “out of network”
So Now What?

- Develop measures to assess the effect of Covid-19 on each study and in each database
  - Patterns of care
  - Issues of missingness
  - Difference in care documentation
  - Difference in reimbursement documentation
- Investigate how remote visits are documented
- New validation studies?
- Other ideas?
Real-World Data and COVID-19 at FDA

International Society for Pharmacogenomics and Outcomes Research (ISPOR) 2021 Annual Meeting
20 May 2021

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics
Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
‘Real-World’ Definitions

from FDA’s Framework for Real-World Evidence (2018):

**Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (e.g., medical claims, electronic health records (EHRs), registries, digital health technologies)

**Real-World Evidence (RWE)** is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD (involving various study designs, such as randomized or externally controlled trials as well as observational studies)
Considerations:

- Whether the RWD are fit for use
- Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements
Representative FDA Activities Related to COVID-19

- Guidance on various COVID-related topics (e.g., *Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency*)
- Extensive discussions with sponsors regarding investigational new drugs and biological products
- Emergency Use Authorizations (e.g., monoclonal antibodies, vaccines)
- Evaluating real-world evidence to inform or support clinical investigations
FDA Guidance on Clinical Trial Conduct During COVID

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Initial release date 18 Mar 2020; multiple updates through 27 Jan 2021
https://www.fda.gov/media/136238/download

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

June 2020
https://www.fda.gov/media/139145/download
• Real-world data continue to accumulate as the pandemic unfolds; valid real-world evidence to inform pandemic response would be beneficial; progress is made from “lessons learned”

• More data aren’t always better; challenges in diagnosing, treating, and reporting on a new disease can create methodological problems; our understanding of COVID-19 evolves over time

• COVID-19 presents an opportunity to leverage real-world data to inform clinical and regulatory decisions, but scientific rigor must be maintained
‘Evidence Accelerator’ for COVID-19


- ‘Parallel Analysis’ activity: Data partners use a common protocol to conduct side-by-side analyses of real-world data on various COVID-19-related topics
Impact of Digital Health Technology

• Emergence of digital health technologies (e.g., sensors and software applications) is changing clinical research

• Decentralized clinical trials involve decentralized trial operations and use technology to communicate with study participants and collect data:
  – faster enrollment and sustained participation in trials
  – greater convenience for participants
  – potential for less missing data
  – increased participant diversity

• Digital health technologies have applications in settings involving clinical trials and observational studies
FDA MyStudies App

- Mobile app – web-based configuration portal
- Secure storage environment
  - 21 CFR Part 11 and FISMA complaint
- Deployed in several demonstration projects
  - collect RWD in randomized trial of patients with pediatric juvenile arthritis
  - collect RWD for registry of patients with inflammatory bowel disease
- Repurposed as COVID MyStudies to facilitate enrollment in clinical trials (https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app)
FDA CURE ID App

- Internet-based repository of RWD on novel uses of existing drugs
- Facilitates evaluation of FDA-approved treatments when used in clinical practice for unapproved uses
- Recently updated to include a focus on COVID-19
- See https://cure.ncats.io/ or download “CURE ID” app
RWE and COVID-19 – A Changing Landscape

• New research approaches are being explored and adopted, including bringing the study to the patient and collecting RWD

• Sponsors can consider appropriate use of RWD in a study by:
  – assessing limitations related to data fitness-for-use, study design, and regulatory requirements
  – discussing with FDA

• All stakeholders can help to shape the research landscape and maximize the usefulness of “post-pandemic” real-world data
Today’s Debate

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2) How much change is “too” much? How will you know?

3) Can these differences be mitigated?

4) Will these differences matter to end-users of the research?
RWD Considerations Amidst COVID-19

Shifts in treatment seeking behavior

Impact on near-term outcomes

Impact on long-term outcomes

Questions?