COVID-19 Evidence Accelerator Collaborative
Lab Meeting #3
Thursday, April 30, 2020, 3:00-4:00 pm ET

Call Summary

Update on Parallel Analysis Workstream

- The parallel analysis workstream is now moving forward by proposing different definitions for the key data elements which will be used to answer questions of interest. We are hoping that by mid-May, we will be populating our data shells with information from each organization.
- The question of interest initially identified is about hydroxychloroquine (HCQ) treatment patterns, the safety of HCQ, and outcomes for patients treated HCQ.
- The work being done to answer this initial question will create a framework that will consist of data variables for future expansion to other questions of interest.
- Organizations interested in joining this initiative or seeing the specific progress which has been made should reach out to either Carla (RUF) or Jeff (FOCR).

Introduction to Lab Meeting 3

The theme for this week's lab meeting was "platform," and, more specifically, understanding how platform approaches can be used to address key COVID-19 research questions. Three presentations were given:

1. Presentation on the Aetion Platform Approach to Creating RWE and Answering Key Questions in the COVID-19 Response in HealthVerity data;
2. Presentation on the COVID-19 Healthcare Coalition coordinated by MITRE; and
3. Presentation on the COVID-19 Research Database by Datavant, HCCI, Symphony Health, Veradigm, and Change Healthcare

The Accelerator hopes to draw learnings from and build off these approaches in its parallel analysis workstream.

Lab Meeting Presentations

Presentation on the Aetion Platform Approach to Key Questions in the COVID-19 Response

- Aetion has built a platform exclusively for the purpose of transforming real-world data (RWD) into real-world evidence (RWE)
- This platform has four key principles for the generation of evidence, which are elaborated upon in a published manuscript titled “Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making” (https://doi.org/10.1002/cpt.512). These four principles are:
    - **Meaningful**—start with the right question and the right data to answer the question

    - **Validated**—apply guardrailed methods for study design, control of bias, and execution of analytics; full scientific validation of all workflows
    - **Expedited**—answer the question when it's most relevant; efficiently run and rerun analytics with fast turnaround and robust sensitivity analyses
    - **Transparent—**full visibility into measures and analytic workflows to enable study reproducibility; comprehensive audit trails
- Sample use cases of the Aetion RWD/RWE platform:
    - Multi-database case study of tocilizumab (TCZ) versus tumor necrosis factor (TNF) inhibitors
        - Randomized studies suggested a potential increase in LDL and triglycerides
        - To demonstrate cardiovascular safety, the sponsor used RWE to compare TCZ against TNF inhibitors for risk of major CV events
        - Results published in a manuscript titled "Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis: A Multi-Database Cohort Study" (https://doi.org/10.1002/art.40084)
    - COVID-19 case study of HCQ users and non-users, and the safety and effectiveness of HCQ
        - This case study was partially motivated by the fact that not fully addressing confounders leads to spurious conclusions.
        - This case study recognized the need to ensure that users and non-users are substantially similar in order to draw conclusions about HCQ:
            - Drawn from the same population, to ensure comparability of patients & information
            - Similar with respect to key risk factors, to mitigate confounding bias by design
            - Equivalency with respect to ability to observe safety events that may occur, to minimize surveillance bias
        - This case study started with a master linked, multi-source dataset from HealthVerity that reflects a complete picture of COVID-19
            - This dataset includes patients defined by treatment, patients defined by labs and procedures, and patients defined by symptoms
        - Within this dataset, a cohort was designed specific to HCQ and noting the following challenges:
            - There isn't necessarily a natural comparator drug
            - Times change quickly, and so a choice made today may not apply equally well to earlier data
            - Patients prescribed HCQ will likely be severely affected by COVID-19, so a comparator group at substantially similar risk must be identified.
        - Risk-set sampling was used to create balance by construction and minimize confounding by design. Sensitivity analyses are being used to verify robustness.

Presentation on the COVID-19 Healthcare Coalition coordinated by MITRE

- About 8 weeks ago, a coalition of the private sector came together to work on questions of interest in the COVID-19 pandemic. Today, over 800 organizations are involved in this initiative (https://c19hcc.org).
- This coalition unlocks large-scale analytics for COVID-19 in three steps:
    - Design and align—agree on study design, cohorts, and definitions
    - Run queries—implement queries and produce minimum viable aggregate results
    - **Analyze and refine**—produce statistics and address issues

  Queries are moved to the data owners; data owners evaluate the queries; and then results are federated.

- This coalition is currently undertaking three COVID-19 drug studies:
    - Hydroxychloroquine—how does the addition of HCQ affect the outcomes of severe disease and inpatient death?
    - Remdesivir – how does the addition of remdesivir affect the outcomes of severe disease and inpatient death?
    - Convalescent Serum (CS)—how does treatment with CS affect the outcomes of severe disease and inpatient death?

Presentation on the COVID-19 Research Database by Datavant, HCCI, Symphony Health, Veradigm, and Change Healthcare

- After recognizing that there was a lack of a central data repository, this initiative sought to establish an open platform for rapid COVID-19 research. This platform required:
    - Real-world data sets that can be joined in a privacy-preserving manner
    - Open, scalable technology to host data, and link to any additional real-world data set
    - Robust governance structure to control access to datasets
- This platform is a pro bono effort and limited to non-commercial COVID-19 related research.
- The qualifications of individual researchers intending to access data through this platform and merit of research are evaluated in a rigorous review process including multiple feasibility and privacy reviews with an average review time of less than 1 week.
- Researchers will be able to perform research on an individual data set, on a joined data set, or on their own data (BYOD) using this platform.
- An open platform will allow multiple researchers to pursue the same question on the same data and to compare the results of different methodologies.
- More information can be found at: covid19researchdatabase.org

Discussion

- As researchers, we must reflect on the importance of balancing scalability with accuracy. We must be thoughtful in designing our studies and methods so as to not hurt the standing of real-world evidence among the broad research community.
- This process begins with choosing fit-for-purpose data and thinking about how best to ask a research question of the data to obtain a meaningful answer. We then must implement our

study in an environment with guardrails. We must also be transparent about our methods and recognize that often we are creating evidence which is evaluated by others.

- As we think about the different kinds of research tools that are being built, we should think about the ability to evaluate and replicate. We should also be sure that, as and when appropriate, we are pointing towards clinical trials.