COVID-19 Evidence Accelerator Collaborative

Lab Meeting # 10

Thursday, June 18, 2020, 3:00-4:00 pm ET

Call Summary

Introduction to Lab Meeting 10

Dr. Amy Abernethy opened the meeting by reviewing a 2016 publication[1] authored by FDA to highlight the application of prospective, randomized study designs in real-world evidence generation. The Evidence Accelerator Collaborative sits within a larger community of organizations and groups working to harness RWD for COVID-19. Today's presentations demonstrate the role of real-world evidence in the context of prospective, randomized trials. Technology enables the convergence of real-world data with clinical trial data to accelerate clinical trial processes and rapidly generate clinically relevant answers to inform practice.

Today's presentations highlight the application of technology and real-world data to expedite prospective pragmatic trials. These presentations exemplify real-world data and real-world evidence in action and demonstrate critical features discussed in the 2016 publication of the use of RWE within clinical trials.

This week's lab meeting presentations highlight additional tools in the toolbox and the urgent need for real-world pragmatic platform trials:

1. I-SPY for COVID-19: Quickly revising a platform trial & RWD infrastructure to address the pandemic—Laura Esserman, MD, MBA - Professor of Surgery, University of California San Francisco
2. The RECOVERY Trial: A Randomised Evaluation of COVID-19 Therapy—Martin Landray, MB ChB, PhD, Professor of Medicine and Epidemiology, Nuffield Department of Population Health, University of Oxford

Lab Meeting Presentations

Presentation on I-SPY for COVID-19: Quickly revising a platform trial & RWD infrastructure to address the pandemic

- I-SPY 2 is one of the longest standing adaptive platform trials in the United States focused on Phase 2 trials for breast cancer

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[1] Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us?. *N Engl J Med*. 2016;375(23):2293-2297. doi:10.1056/NEJMsb1609216

- The rationale for I-SPY COVID was to leverage the optimized I-SPY 2 process to rapidly test Phase 2 treatments for severe COVID-19
- The initial launch is planned for I-SPY 2 sites where contracts are in place, and IRBs are familiar with the platform and its adaptive design process.

Study Design

- The study design includes a screening/eligibility phase that tracked patients admitted to the ICU or "sick enough" for the ICU (e.g., high flow oxygen, mechanical ventilation)
- Patients enrolled onto the study are randomized to one of four arms.
    - Arm 1: Backbone (Remdesivir)
    - Arm 2: Backbone + Tx A
    - Arm 3: Backbone + Tx B
    - Arm 4: Backbone + Tx C
- The study population includes hospitalized patients with severe COVID-19 in a critical care setting
    - Anticipated accrual is around 50-150 patients/arm
- The primary endpoint for this study is time to recovery (WHO COVID status scale ≤ 4 for 48 hours to avoid problems of reintubation which is usually in the first 48 hours). The secondary endpoint is 28 day mortality—This will only be reported for agents that graduate and will not be required to be complete before a decision is made to drop an agent from the trial.
- The primary endpoint was selected for several reasons:
    - Similar to the endpoint used in the ACTT-1 study
    - Fewer days on mechanical ventilation and/or critical care level can be clinically meaningful
    - It is a continuous endpoint, which can have more power than a binary endpoint
    - More patient centered

Key Opportunities and Challenges for the Development of the Master Protocol

- Implementation of a complex trial in a chaotic ICU setting is challenging
    - Therefore, a simplified approach for data collection is necessary:
        - Minimize data elements that were not truly necessary
        - Systematically identify safety signals without having to rely on busy investigators
        - Automatically and systematically grade adverse events for each organ system
- The complexity of multiple agent administration (intravenous enteral, subcutaneous and nebulizer routes) makes double blinding very daunting
    - In the absence of double blinding, the use of multiple sites with variable numbers of patients and a fast-paced trial can help protect against bias
    - Additionally, most of the agents have robust safety data and the administration of placebo agents could compromise the health and safety of health care providers since some agents will be delivered by nebulizers that carries risk to the ICU providers
- There are many standard COVID scales
    - Some status levels overlap and lack clarity
    - Important to have standard outcomes for comparison with other trials

- o Opportunity to map all the scales now ahead of time so additional level of detail can be available if desired
- There is a concern about the rate of adverse events and reporting
  - o Death and organ failure are common in this patient population compared to other studies
    - Renal: 59% with acute kidney injury, 33% requiring renal replacement therapy
    - Hepatic: 59% with transaminase/alkaline phosphatase abnormalities
    - Coagulation: 24% with INR > 1.5
    - Cardiovascular: 67% required vasopressors
    - Neurologic: 44% with encephalopathy
  - o The ascertainment and collection of AEs is hugely time consuming and therefore need to be clear on collection of data versus reporting of data
    - Reported:
      - Severe adverse events related to agent
      - Adverse events of special interest for agents
      - Unanticipated problems
    - Collected:
      - All reported events + all serious adverse events
  - o To systematically assess attribution, the study will look for an imbalance of adverse events among arms

Streamlining Study Management Through EMR Integration

- The I-SPY COVID Study System
  - o Pulls in demographic, medications, and lab data from the EHR system
  - o Sends alerts to investigators for signoff using handheld devices
    - Patient newly enrolled, alert for randomization arm
    - Confirmation of patient outcome
  - o Study report sent back to the EHR system
- This study will implement an approach to only collect data needed for good care and will be mindful of what is essential data to collect directly from physicians or patients

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Discussion Insights

- These studies provide an opportunity to learn about what really matters. Every day a trial is not started is a lost opportunity—We need to focus on what matters most and not collect unimportant data.
- Initial thought was that study design and data collection could be leaner and decrease burden on trial sites due to it being a Phase 2 trial. Currently, there is tension with open label designs and what is considered enough data to collect.

Presentation on The RECOVERY Trial: A Randomised Evaluation of COVID-19 Therapy

- At the onset of the COVID-19 pandemic, there was huge therapeutic uncertainty:
    - Many candidates
    - Many opinions
    - No reliable data (uncontrolled case series, retrospective association studies)
- To address the treatment challenge, a pragmatic platform trial was developed to quickly evaluate treatment effectiveness in the context of COVID-19 (RECOVERY Trial)
    - Unlikely to be a single "big win" but moderate benefits plausible
    - For example, reducing hospital mortality by one-fifth would be important
    - In future, combining several effective drugs may produce big effects
- When selecting therapies, there needed to be some rationale that they were going to work, knowledge of any major safety issues, and the potential for rapid scale up if a treatment was determined to be effective
- Treatments were divided into three broad categories:
    - Anti-viral treatments (lopinavir-ritonavir, hydroxychloroquine)
    - Immunomodulatory treatments (corticosteroid, azithromycin, tocilizumab)
    - Treatments targeted at SARS-CoV-2 (convalescent plasma)

Study design

- Patient must be hospitalized to be eligible for the study (regardless of age, gender, ethnicity, co-morbidity, location) and have SARS-CoV-2 infection (clinically suspected or laboratory confirmed)
- Structured something truly pragmatic: If the doctor felt a particular treatment was not suitable for a patient, they would not be randomized. In analysis, only those patients who could have received the drug are included
- The informed consent contained simple information (2 pages) with an option for witnessed consent (if participant cannot read or sign for themselves or not able due to infection control procedures) or for legal representative (if patient lacks capacity)
- In order to randomize patients, only very simple data was collected (via online entry form)
    - Patient details
    - Inclusion criteria
    - Key co-morbidities
    - Any treatments for which the patient is not suitable
    - Any treatments not available in hospital pharmacy
- The patient is randomly assigned to suitable and available treatments; Doctor prescribes the allocated treatment on usual hospital drug chart
- The primary endpoint for the study was all-cause mortality at 28 days, and secondary endpoints included time to discharge from hospital and use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at baseline)
- Follow-up was conducted using a simple online form completed by research nurses to assess which treatments the patient received; COVID-19 test result; discharge status and date; and use of ventilation
- Patient data was also linked to national health data sources, which will be helpful for long-term follow-up and will have the ability to follow-up via record linkage for up to 10 years

Trial Progress and Preliminary Results

- Currently, 1/6 of patients admitted to the hospital in UK with COVID-19 are enrolled on to the trial (total recruitment of 11,000 people at 176 hospitals)
- Preliminary analysis of hydroxychloroquine:
  - Analysis demonstrated a clear and compelling evidence of no benefit
- Preliminary analysis of dexamethasone:
  - 6 mg dexamethasone was administered once daily (IV or oral) for up to 10 days
  - 2104 patients were randomized to dexamethasone vs 4231 to usual care alone
  - The greatest benefit was observed among patients requiring ventilation
  - Results from this analysis led to implementation in the UK within 4 hours from data presentation

Discussion Insights

- Protocol designed to be accessible and actionable—it is easy to design a protocol that no one can follow. The key to the RECOVERY Trial was to recruit at scale.
  - Results can be put into clinical practice early.
  - The trial and robustness of information did not suffer because we did not include every bit of information. We want to solve a problem and solve it quickly.
- Many may assume that if you do not have large patient numbers then more and more information is needed to be precise and the point of the trial is lost.