COVID-19 Evidence Accelerator Collaborative

Lab Meeting # 28

Thursday, February 18th, 2021 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting #28

Last week's therapeutics lab meeting focused on repurposing drugs to treat COVID-19. First, Dr. Nevine Zariffa, of the Food and Drug Administration (FDA), set the stage for the meeting with an introduction to an evidence framework for drug repurposing. Next, we heard from Dr. Christopher Rentsch of the London School of Hygiene and Tropical Medicine, about a recent study of anticoagulants for prophylactic treatment of COVID-19 patients hospitalized in the US Department of Veteran's Affairs health system. The final portion of the meeting was a panel discussion moderated by Dr. Amy Abernethy of the FDA on the use of real-world data and clinical data for evaluating the efficacy of repurposed drugs for COVID-19. Panelists included Dr. Martin Landray of Oxford's RECOVERY trial, Dr. Chris Seymour of REMAP-CAP at UPMC, Dr. Neil Aggarwal of ACTIV at NIH, and Dr. Susanna Naggie of Duke Clinical Research Institute.

Evidence Framework Repurposing of Drugs for COVID-19
Dr. Névine Zariffa, FDA

Background
- Many ongoing efforts exploring aspects of repurposing drugs to treat COVID-19 (i.e., FDA and external groups, other government agencies, independent efforts, ex-US efforts)
    - Generate hypotheses regarding candidates
    - Establish platform trials
    - Platform trials leveraging RWD
    - Communicating results
- A unified comprehensive framework allows us to be efficient so that multiple parties work in an aligned fashion.

End-to-end Framework Principles
- Outcomes
    1. Fast
    2. Reliable inference
    3. Good use of national and global resources
- How?
    1. Must be actionable now
    2. Diverse views can be expressed and considered
    3. Transparent
    4. Coordinated
    5. Reduce the burden on stakeholders involved in healthcare delivery

Elements of the Framework
- Considers elements before (Steps 1-3) and after (4-7) the definitive assessment, the role of RWD/E in each element, and opportunities.

Key Questions
1. Is an end-to-end process desirable?
2. Any elements we missed?
3. Which elements are the most critical?
4. Where are the opportunities for the RWE community?

Analysis of anticoagulants and COVID mortality
Dr. Christopher Rentsch, London School of Hygiene and Tropical Medicine and VA

Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality in patients admitted to hospital in the United States

Background: Deaths from COVID-19 have been partially attributed to the formation of blood clots that lead to more serious thromboembolic; however, there is limited data-driven evidence that directly addresses whether there is benefit from initiating anticoagulation therapy in patients with COVID-19.

Objective: To evaluate whether early initiation of prophylactic anticoagulation compared with no anticoagulation was associated with decreased risk of death among patients admitted to the hospital with COVID-19 in the US.

Primary Analysis Population: Patients admitted to the hospital between March 1 and July 31, 2020, with a history of care in the US Department of Veterans Affairs, with a lab-confirmed positive COVID-19 test result on or within 14-days of hospital admission, no therapeutic anticoagulation within 30-days before admission, and who were in the hospital at least 24-hours (n=4297).

Doses: Identified anticoagulants and categorized by low or high dose – 99% of patients who received prophylactic anticoagulation therapy received some form of Heparin.

Statistical Methods
- Propensity score model (45 covariates)
- Inverse probability of treatment weighting (IPTW)
- IPT-weighted Cox proportional hazards regression
  - 30-day mortality
  - Inpatient mortality
  - Initiate therapeutic anticoagulation

Absolute and relative risks
- Lower risk of death within 30-days for patients that received prophylactic anticoagulation therapy compared to those that did not receive therapy.

Secondary and post-hoc analyses
- No difference by subcutaneous heparin or enoxaparin
- Some evidence that there is greater benefit in non-ICU patients
- No increased risk for serious bleeding events

Panel Discussion
Amy Abernethy, FDA
Martin Landray, Oxford's RECOVERY trial
Susanna Naggie, Duke Clinical Research Institute, HERO HCQ Trial
Neil Aggarwal, ACTIV trial at NIH
Christopher Seymour, REMAP-CAP trial at UPMC

Dr. Abernethy: How do you go about selecting an intervention for study?

Dr. Landray: Early on in the pandemic, it was clear there would need to be repurposing of medications because there were no novel agents to treat COVID. WHO led a prioritization effort and our selection of treatments for study was largely based on those results (i.e., Dexamethasone). Now, there is the UK Therapeutics Advisory Panel, which has the task of filtering through and selecting the best-suggested agents to study.

Dr. Seymour: Biologic plausibility and availability play a big role in how therapies are selected for study. Some groups have prioritization committees that get together to think through these issues. Labs have taken computers and use algorithms to identify agents/molecules to study as treatments.

Dr. Aggarwal: Largely a human-led effort that is informed by experience with certain treatments. On the ACTIV trial, treatments were scored and weighted based on the class of the agent (i.e. anti-viral, immunomodulatory agent) and its mechanism of action. Those with promising clinical data were weighted higher and prioritized for study. In every case, the drug had to be available and able to be scaled up.

Dr. Abernethy: How might RWD now be used in some of these prioritization decisions? What kinds of sources and studies are available to help identify ideal treatments, what do these sources/studies look like and how do you think about them informing this work?

Dr. Naggie: Clinicians desperate for new options start trying these in clinical practice. Understanding the pharmacology and dosing of these repurposed agents is key as we are developing trials to test them for COVID. It is important to understand the work that has already been done in the real-world space and what showed potential efficacy. I see the real-world functioning as our Phase 1/Phase 2A studies when looking at repurposed agents. RWD can be really helpful for thinking about dose-finding, pharmacology, etc.

Dr. Abernethy: How can RWD help with drug prioritization. Any specific insights from the global perspective of the REMAP CAP Trial?

Dr. Seymour: We have RWD on hospitalized sicker patients. As our clinical focus shifts to the outpatient setting and how to prevent deterioration in these patients, it is important to ask what our RWD source is there and how it can be used to support the causal inference, etc. This is particularly challenging when thinking about merging datasets across countries.

Dr. Landray: From a global perspective there are additional issues around availability and affordability that complicate the prioritization of selection of drugs for study. I still struggle to find a use for real-world data to help prioritize treatments, I'm more swayed by a combination of biology, pre-clinical/early

phase pharmacology around dosing, drug levels, and viral response, and availability. These elements get you to a stronger or weaker hypothesis for each treatment.

Dr. Seymour: When choosing an agent, clinical trialists are hesitant because there is uncertainty about how to prioritize. This speaks to the importance of the design of the platform. They must be efficient, adaptive, randomized, etc. to account for some of the things we are unsure about.

Dr. Abernethy: How can RWD be used after randomization in clinical trials to fill in data variables?

Dr. Seymour: The E in REMAP stands for embedding in the EHR. We've been able to weave in treatment allocation, outcome ascertainment, with healthcare data. The game has changed to allow us to track our patients with data from electronic sources. Although it's harder to collect outcome data once a patient is discharged there are ways of getting it.

Dr. Landray: The smart thing is to combine real-world data and clinical trial data. Get the power of "both worlds" to deal with the bias, get the right sample size, and get the feasibility. This requires a re-imagination of approaches used to study real-world data and clinical data.

Dr. Naggie: I echo that. We must be focusing on high-level, simpler questions right now to have the biggest outcome on patients. The more easily we can align across health systems, countries, etc. to agree on certain things the sooner we'll have more answers. Makes it much more scalable and enables efficiency.

Dr. Seymour: Thinking about after the trial. As we've gone through the pandemic we've gotten more answers, but there are still patients who are not doing well. Right now, it is difficult to know who is receiving what standard of care, and we know some places do not have access to the same treatments as others. How can we build trials to look at this issue and use them to compare outcomes in the future?

Dr. Aggarwal: What happens beyond the timeframe of the trial? What is occurring in the real world that maybe did not occur in the contexts of a clinical trial? We can learn a lot from RWD to answer these questions.

Dr. Abernethy: There is an opportunity to continue to monitor patients with RWD and ask other questions in the context of the monitoring frame. How should we be thinking about what to look at in the future?

Dr. Seymour: Need to bring more collectiveness to monitoring and safety/implementation of these drugs after clinical trials (i.e., project between Kaiser and UPMC linking data from their EHRs).

Dr. Landray: Observational helps for understanding prognosis, things like long-COVID. However, I would say we need to be careful (i.e., with vaccines). Strategy for dosing (i.e. everyone 1 dose first), if you need a trial to say whether a vaccination works, you need one to say whether one dose is better than another.

Dr. Naggie: A lot of opportunity for RWD to be used to examine the evolving nature of the pandemic (i.e., emerging variants, novel agents, how we care for patients, when we discharge patients, etc.).

Dr. Aggarwal: I think RWD can be particularly useful for long-COVID. Being able to tell someone at the time of discharge their risk for various long-term outcomes of COVID would be beneficial. More work needs to be done on this by everybody.

Dr. Abernethy: To summarize, conversations around clinical trials often focus on real-world data OR clinical trial data; however, both are important for answering COVID questions. There is a need for longitudinal work after clinical trials to help understand clinical practice, what clinicians are doing in the real world, what do these things tell us about the future, long-COVID, etc.