SESSION PROPOSAL 4

REAL WORLD EXPERIENCE IN CONDUCTING ADAPTIVE PLATFORM TRIALS

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Description of Session:

Title: Real World Experience in Conducting Adaptive Platform Trials Organizer and Chair : Christina Saunders, Berry Consultants

Platform trials like RECOVERY, SOLIDARITY, REMAP-CAP, TOGETHER, PRINCIPLE, and many others have dominated the COVID clinical trial effort, changing clinical practice with multiple results in The Lancet, New England Journal of Medicine, and the Journal of the American Medical Association. These large-scale international efforts have enrolled tens of thousands of patients and explored dozens of potential therapies for mild, moderate, and severe COVID-19. These trials are the result of a decade of theory and practice building on the experience of oncology platform trials such as I-SPY2. In addition to COVID-19 and oncology, platform trials are now used or planned in Alzheimer's disease, ALS, antibiotics, psychiatry, and many other clinical areas.

Conducting a large-scale platform trial is daunting. While recent platform trial review papers have hundreds of references on the theoretical design issues and research potential of these trials, there is no substitute for the actual real-world experience of implementing an adaptive platform trial, made all the more challenging within a fast-moving global pandemic. This proposed session will investigate the challenges and solutions for successfully executing a platform trial. The proposed speakers bring decades of combined expertise from executing platforms such as ISPY-2, GBM-AGILE, REMAP-CAP, TOGETHER, PRINCIPLE, ANTICOV, HEALEY-ALS, Precision Promise, and others. They will describe many of the challenges specific to these large global platform trials, and the infrastructure and process needs that underpin these complex trials.

The session will consist of 4 speakers with integrated 20 minute talks, followed by a question and answer period as time allows. Dr. Ed Mills will provide an overview of platform trials and their challenges in relation to simpler clinical trials. Dr. Michelle Detry will sharpen the focus on the complexities specific to trial execution and the interactions between various stakeholders, including publication plans that must account for the perpetual nature of many platform trials. Dr. Anna McGlothlin will then discuss the specific requirements and role of the committee performing the actual interim analyses, and finally Dr. Hong Yu will discuss these challenges in the context of the HEALEY-ALS platform trial. All speakers will include examples from their rich real-world experience in implementing complex adaptive platform trials.

Speakers (in proposed order)

Ed Mills, Cytel

COVID-19 has exemplified the utility of platform trials for making clinical and public health decisions in a timely manner. The most useful trials that emerged during the pandemic have been from platform trials. However, with the enthusiasm for platform trials comes the concern that trials should be implemented using methods that many groups are unfamiliar with, such as advanced statistical approaches and implementation of quick changes to the protocols. Challenges exist in interactions with funders, partners managing data sets, and clinical users. This session will use real-world experiences of platform trials in the pandemic to exemplify the utility and challenges of this new approach to clinical evaluation. This talk is for any audience with an interest in clinical trials, and will address strategies to promote the use of platform trials while also highlighting the concerns about the quick adoption of this method.

Michelle Detry, Berry Consultants

Adaptive platform trial designs include interim analyses for pre-specified adaptations, sharing of control arm information, and a perpetual design where investigational agents enter and leave the trial at different time points. This talk will discuss the infrastructure considerations for a perpetual platform trial, ongoing statistical support from both

blinded and unblinded statistical teams, setting clear communication channels and firewalls between blinded and unblinded teams, and the role of Data and Safety Monitoring Committee (DSMC) and their interaction with the independent Statistical Analysis Committee that implements the protocol-specified interim analyses. Additionally, ongoing platform trials face unique challenges in determining “who knows what when”. Dr. Detry will discuss planning for public releases of results, and data sharing in situations where an investigational arm may complete their trial arm participation, but the control arm data will still be used for ongoing investigational arms.

Anna McGlothlin, Berry Consultants

A Statistical Analysis Committee (SAC) is a team of unblinded statisticians tasked with performing the interim analyses for an adaptive trial. The unblinded SAC must have expertise in the statistical methodology being utilized, as well as in the complexities of adaptive designs. This talk will describe the role of the SAC during the preparation and conduct of a platform trial. Responsibilities of the SAC include performing analyses in accordance with the pre-specified design, monitoring each analysis to ensure that the adaptive algorithm is performing as intended, building semi-automated reproducible reports to facilitate quick turnaround of interim results, and partnering with the DSMB to aid in the interpretation of interim results. Additionally, platform trials may have the unique aspect that arms may complete their final read out while other arms continue in the trial. In some cases, the fully unblinded SAC may be the only group that has complete access to the necessary data to perform the final analysis for an arm while other arms continue.

Hong Yu, Massachusetts General Hospital

A complex adaptive platform trial requires complex infrastructure, and many of the challenges are not revealed when conceiving or planning the trial, but only in the face of actual implementation. In this talk we will discuss real world experiences in developing infrastructure for adaptive platform trials, particularly the HEALEY-ALS platform. The specific challenges to be investigated are the required personnel to implement a platform, the system architecture required to support a perpetual trial design beyond the initial set of therapies, as well as the monitoring and management plans required to maintain robust data throughout multiple interim analyses and periodic reporting of results. Platform trials must be nimble to fulfill their goal of efficiently exploring multiple therapies as quickly as possible. These infrastructure solutions allow the trial to adapt to changing arms, maintain data quality as well as trial integrity, and support multiple sets of results and publications throughout the trial's duration.

Contributors:

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