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Technical Report No. 2020-16
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This research was supported in part by National Science Foundation grant DMS 1811818.

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Challenges and Opportunities in Designing Clinical Trials for COVID-19 Treatments

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November 16, 2020

Abstract

We begin with a description of the collaborative public-private partnership, known as Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) initiative and then describe the basic science of SARS-CoV-2 and adaptive clinical trial designs with two recently published clinical trials as examples. We discuss the challenges posed by established practice of adaptive designs to date and the opportunities of using adaptive designs to quickly adapt the fast evolving information about the coronavirus. Finally we discuss some recent advances in adaptive confirmatory trial designs and valid statistical inference methods to ensure reproducible findings from such trials in a highly adaptive setting.

Key words: Adaptive design, collaboration versus competition for patient accrual, economic and time constraints, innovative medicines accelerator, platform trials.

1 Introduction

The April 17, 2020 issue of STAT, an American health-oriented news website, features an article titled "NIH partners with 16 drug companies in hopes of accelerating Covid-19 treatments and vaccines". The public-private partnership, known as Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV), is "orchestrated by the Foundations for the NIH, an intermediary that facilitates partnerships between private companies and federal researchers" (Collins and Stoffels, 2020) The drug companies involved are AbbVie, Amgen, Astra Zeneca, Bristol Myers Squibb, Evotec, GlaxoSmithKline, Johnson & Johnson, KSQ Therapeutics, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, Takada, and Vir Biotechnology, 16 in number. On September 13, 2020, the NIH director Francis Collins described the focus of the collaboration on standardizing the methods, models and endpoints that researchers use to test promising COVID-19 compounds, on (a) providing access to high-level facilities to ensure that different compounds use the same criteria to judge potential medicines and (b) establishing one joint control arm to be shared among all clinical trials. He said, "Now is the time to come together with unassailable objectivity to swiftly advance the development of the most promising vaccine and therapeutic candidates that can help end the COVID-19 global pandemic." In Section 2 we review and discuss this major development that COVID-19 has brought forth to drug and vaccine development plans. The week beginning with November 5, 2020 witnessed a breathtaking series of news items on the success stories of Remdesivir, the Pfizer-BioNTech vaccine, and the Moderna vaccine that also uses the mRNA technology. Section 3 reviews the ongoing clinical trials for these and other COVID-19 drugs and vaccines and the underlying adaptive designs. Section 4 discusses adaptive platform trials, including RECOVERY in the U.K. and WHO's Solidarity trial, as another pathway to implement collaborative partnerships and accelerate drug and vaccine development.

2 Collaborative Partnerships to Accelerate Covid-19 Treatment/Vaccine Development

The high ideal of "establishing one joint control to be shared among all clinical trials" of the participating companies in the ACTIV public-private partnership to accelerate COVID-19

drug/vaccine development has its roots planted in oncology research as part of the Cancer Moonshot Initiative announced in 2016 by President Obama in his State of the Union address, leading to the May 18, 2016 announcement of a new CDISC (Clinical Data Interchange Standards Consortium) and TransCelerate BioPharma for a new CDISC Therapeutical Area Standard for Breast Cancer, so that data for the therapeutic area "can be readily shared among clinical researchers and regulators around the world", thereby providing a platform for more efficient clinical trial designs and more speedy dissemination of the results. TransCelerate BioPharma Inc. is a nonprofit organization whose mission is "to collaborate across the global biopharmaceutical R&D community to identify, prioritize, design, and facilitate implementation of solutions intended to drive the efficient, effective and high-quality delivery of medicines." In its May 23, 2019 press release, it mentioned "20 member companies and 30 initiatives focused on improving the patient and site experience, enhancing sponsor efficiencies and drug safety and, as appropriate, harmonizing process and sharing information." One of the member companies is Allergan, with which Lai has been collaborating in the TransCelerate project of companies sharing data to provide "one joint control" and which was acquired by AbbVie, one of the ACTIV partnership companies, in May 2020. This project has its statistical foundations in the Rubin causal model,[1] which involves potential outcomes in causal inference from comparative clinical trials; see Sections 6.6.2, 6.2.3 and 7.1.2 of Chen et al. (2018). Note that the joint control arm of the planned new trials might be the control or the new treatment in a partner company's previous pre-licensure trial for regulatory approval.

3 Basic Science of SARS-CoV-2 and Adaptive Clinical Trial Design

We begin with the publication of the final report in NEJM (Nov. 5, 2020) by Beigel et al. (2020) for the Adaptive COVID-19 Treatment Trial Study Group on "a double-blind, randomized, placebo-controlled trial of intravenous Remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infections." This report is the first stage of "an adaptive platform trial (consisting of) a series of phase

[1]The causal model is also called the "Neyman-Rubin causal model" as it was introduced by Neyman in 1923.

3, randomized, double-blind, placebo-controlled trials" of COVID-19 treatments (ACTT-1) and was funded by NIAID (National Institute of Allergy and Infectious Diseases) and collaborating institutions such as National University of Singapore School of Medicine, Seoul National University Hospital, Tokyo National Center for Global Health and Medicine Hospital, MRC Clinical Trials Unit at University College London, University Hospital of Cologne, Germany, besides Gilead Sciences that developed Remdesivir with government support under the "orphan drug" designation. The report concluded that "Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory infection." Several statistical issues concerning this finding were raised in the report, which we will discuss further in Section 4.

On Nov. 9, 2020 Pfizer and BioNTech announced that their mRNA-based vaccine candidate BNT16262 against SARS-CoV-2 had demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis of a global Phase 3 study on Nov. 8, 2020 by an external, independent Data Monitoring Committee. Two days later, Moderna which was conducting a clinical trial of 30,000 participants, with half randomized to its vaccine mRNA-1273 and the other to placebo (see Jackson et al. (2020)), announced that the trial hit the threshold of 53 study participants becoming ill with COVID-19, a requirement for authorization considerations of the FDA. Although it does not know how many of the patients who became ill received the vaccine (respectively, placebo), it is preparing the data for the trial's Data and Safety Monitoring Board. Anthony Fauci, director of NIAID, said that Pfizer's promising outcomes were also good news for Moderna, which is working with NIAID to develop the vaccine, as "Moderna has an almost identical mRNA", commenting: "We hope we're going to see a similar kind of result from Moderna. If we do, then we'll have two vaccines in play."

The preceding paragraphs illustrate the importance of basic science (including the genomic and and proteomic structure of SARS-CoV-2, its mechanism of pathogenesis, and the responses of human immune system to SARS-CoV-2 upon infection) and the rapid accumulation of such knowledge following the sudden emergence of COVID-19; see also Gao et al. (2020) and Wrapp et al. (2020). Hence adaptive clinical trial designs that can adapt quickly to evolving information about the coronavirus are in great demand to initiate, execute and

monitor the clinical trials to evaluate safety and efficacy of the therapeutics and vaccines under development, as will be discussed further in Section 4. These adaptive designs also pose new challenges and opportunities for the established practice of adaptive designs to date; see Pallmann et al. (2018) and Stallard et al. (2019). Moreover, the trial designs should be pragmatic in order to generalize the results to "real-world" patients. Pragmatic trials differ from RCTs in several dimensions, such as eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis (Loudon et al., 2015; Ford and Norrie, 2016). Therefore, pragmatic trials allow for rapid recruitment of broader investigators and patient subjects, interpreting evolving data quickly, and testing multiple therapies according to individual physician's judgement on best available treatment options. Therefore, the results of pragmatic trials can readily be generalized to the general target patient population (Branch-Elliman et al., 2020).

4 Platform Trials, Master Protocols and Statistical Inference

Lai et al. (2020) have given an overview of (a) the FDA's draft guidance to industry on adaptive designs, enrichment strategies and master protocols, and (b) recent advances in adaptive confirmatory trial designs and valid statistical inference methods to ensure reproducible findings from such trials in a highly adaptive setting. In particular, their Section 3 describes the "hybrid resampling method" for primary and secondary endpoints and novel methods for statistical inference from multi-armed confirmatory trials for testing biomarker-guided personalized therapies. Their Section 4.1 reviews precision-guided drug development involving advances in multiomics and imaging to study mechanisms and structure (such as cryo EM that won the 2017 Nobel Prize in Chemistry), while their Section 4.2 describes a "fast real-time assessment of combination therapies in immuno-oncology" program that uses master protocol. Lai et al. (2019) describe recent advances in contextual multi-armed bandits and their applications to precision medicine and recommender system. In particular, their Sections 2.2 and 3.1 describe adaptive enrichment designs in precision medicine. Their Section 2.3 provides novel methods for group sequential testing of multiple hypotheses in recommender systems, and their Section 3.2 summarizes an ongoing project on contextual bandits and mobile health. They say: "Just-in-time adaptive interventions (JITAIs) aim to

provide support for health behavior change at times when users most need the support", which is highly relevant during this time of "shelter in place" because of the pandemic. They mention some technical issues in designing JITAIs for mobile health and discuss how the contextual bandits that enable personalization can be combined with the field of interactive machine learning to address these issues.

Acknowledgement

Lai acknowledges support of this research by the National Science Foundation under DMS-1811818.

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