STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2020, VOL. 12, NO. 4, 397–398
https://doi.org/10.1080/19466315.2020.1828692

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Statistical Challenges in the Conduct and Management of Ongoing Clinical Trials During the COVID-19 Pandemic

Toshimitsu Hamasaki[a], Frank Bretz[b,c], Freda Cooner[d], Lisa M. LaVange[e], and Martin Posch[c]

[a]The George Washington University Biostatistics Center, Rockville, MD; [b]Clinical Development & Analytics, Novartis Pharma, Basel, Switzerland; [c]Section for Medical Statistics, Medical University of Vienna, Vienna, Austria; [d]Statistical Innovation, Amgen, Thousand Oaks, CA; [e]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC

The COVID-19 pandemic has influenced the world in a way that none of us could have imagined. Since February 2020 unplanned changes to daily routines due to the mandatory isolation and social distancing requirements have occurred across the globe. It is the greatest global healthcare crisis of our generation. The COVID-19 pandemic presents enormous challenges in particular to medical research, as these disruptions have wreaked havoc on clinical trials in progress as well as those in the planning stages. For example, the COVID-19 pandemic is reducing the ability and willingness of trial subjects and staff to access clinical sites, disrupting timely data collection or necessitating a move to virtual data collection. These challenges may result in difficulties in complying with protocol-specific procedures, including administration or use of the investigational product or compliance with protocol-required visits, efficacy assessments, and laboratory/diagnostic tests. In many situations, these challenges cause delays or halting of clinical trials altogether.

In recognition of these unprecedented challenges, we decided to dedicate a Special Issue of *Statistics in Biopharmaceutical Research* to the statistical challenges in the conduct and management of ongoing clinical trials during the COVID-19 pandemic. This special issue highlights and discusses critically important topics, including the impact on trial integrity and interpretability, issues around trial management and operations, estimands and missing data handling as well as the application of novel trial designs and analysis approaches. This Special Issue consists of peer-reviewed articles and commentaries, reflecting the vibrancy of ideas and discussions around the COVID-19 pandemic.

Meyer et al. (2020) put forward a number of strategies and recommendations to assess and address issues related to estimands, missing data, validity and modifications of statistical analysis methods, need for additional analyses, ability to meet objectives as well as overall trial interpretability. This article has been translated into Japanese by the Data Science Expert Committee of the Japan Pharmaceutical Manufacturers Association (JPMA) and available on their website (JPMA 2020). Collins and Levenson (2020) as well as Hemmings (2020) provide insightful regulatory commentaries on the article by Meyer et al. (2020). Akacha et al. (2020) discuss implications of the COVID-19 pandemic on clinical research methodology aspects and provide points to consider to assess and mitigate the risk of seriously compromising the integrity and interpretability of clinical trials. Reflecting on the impact of the COVID-19 pandemic in oncology trials, Degtyarev et al. (2020) identify key intercurrent events that may occur due to the pandemic in oncology clinical trials and discuss considerations pertaining to the estimand framework introduced in the ICH E9 addendum (ICH 2019). Guo et al. (2020) address some statistical issues and operational experiences in the conduct of clinical trials during the COVID-19 pandemic and share their experiences from remote clinical trials in China. Wiens and Lipkovich (2020) provide recommendations on how sponsors can maximize the chance that a non-inferiority trial conducted during the COVID-19 pandemic gives useful information. O'Kelly and Li (2020) assess the operating characteristics of the World Health Organization (WHO) scale for COVID-19 endpoints via an extensive simulation study. Motivated by four current clinical trials in a variety of disease areas, Kunz et al. (2020) illustrate the challenges faced by the pandemic and sketch out possible solutions using the latest adaptive designs methodologies. One of these case studies embedded a COVID-19 group sequential clinical trial within an ongoing trial, as discussed in more detail by Dequin et al. (2020). Building on Kunz et al. (2020), the article by Stallard et al. (2020) review efficient adaptive designs for clinical trials of interventions for COVID-19. Complementing the above body of work on efficacy analyses, Nilsson et al. (2020) provide guidance on how analyses and reporting of clinical trial safety data may need to be modified, given the potential impact from the COVID-19 pandemic. Finally, Zame et al. (2020) describe the impact that COVID-19 is having on clinical trials, and reveal potential applications of state-of-the-art machine learning approaches, in three areas: ongoing clinical trials for drugs unrelated to COVID-19, trials for repurposing drugs to treat COVID-19, and trials for new drugs to treat COVID-19.

We thank the authors of the articles published in this Special Issue on COVID-19. They have individually and collectively added to the literature on this important topic and have given critical insights into the statistical problems encountered in the conduct and management of ongoing clinical trials during the COVID-19 pandemic. We are deeply indebted to the

CONTACT Toshimitsu Hamasaki *thamasaki@gwu.edu* The George Washington University Biostatistics Center, 6110 Executive Blvd., Rockville, MD 20852.
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

anonymous referees who made great efforts to review all submitted articles, often within a few days, and helped us to select the published articles. This Special Issue would not have been possible without their tremendous efforts and dedication to complete their reviews within very short timelines. We are grateful to Jina Lee and Eric Sampson for their enthusiasm and support for this Special Issue. We also thank Taylor and Francis for the rapid processing and publication of this Special Issue. Following the general policy of Taylor and Francis, all COVID-19 related, peer-reviewed research published in this Special Issue is free to access and available for anyone to read. We sincerely hope that this Special Issue will provide clear, concise guidelines that will help us all navigate an unfathomable scenario.

References

Akacha, M., Branson, J., Bretz, F., Dharan, B., Gallo, P., Gathmann, I., Hemmings, R., Jones, J., Xi, D., and Zuber, E. (2020), "Challenges in Assessing the Impact of the COVID-19 Pandemic on the Integrity and Interpretability of Clinical Trials," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1788984. [397]

Collins, S. H., and Levenson, M. S. (2020), "Comment on 'Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic'," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1779123. [397]

Degtyarev, E., Rufibach, K., Shentu, Y., Yung, G., Casey, M., Englert, S., Liu, F., Liu, Y., Sailer, O., Siegel, J., Sun, S., Tang, R., Zhou, J., and on behalf of the Industry Working Group on Estimands in Oncology (2020), "Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1785543. [397]

Dequin, P. F., Le Gouge, A., Tavernier, E., Giraudeau, B., and Zohar, S. (2020), "Embedding a COVID-19 Group Sequential Clinical Trial Within an Ongoing Trial: Lessons From an Unusual Experience," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1800509. [397]

Guo, T., Chen, C., Chiang, C., Chen, C.-T., and Hsiao, C.-F. (2020), "Operational Experiences in China and Statistical Issues on the Conduct of Clinical Trials During the COVID-19 Pandemic," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1797866. [397]

Hemmings, R. (2020), "Under a Black Cloud Glimpsing a Silver Lining: Comment on Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1785931. [397]

ICH (2019), "Topic E9(R1) on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials," available at *www.ich.org*. [397]

JPMA Data Science Expert Committee (2020), "COVID-19 パンデミック下での臨床試験実施に対する統計的課題と推奨 COVID-19 Pandemic-ka deno Rinshosiken-Jisshi nitaisuru Toukeitekikadai to Suisho (in Japanese) [Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic]," available at *http://www.jpma.or.jp/medicine/shinyaku/tiken/allotment/pdf/covid-19_conduct-clinical-trials.pdf*. [397]

Kunz, C. U., Jörgens, S., Bretz, F., Stallard, N., Van Lancker, K., Xi, D., Zohar, S., Gerlinger, C., and Friede, T. (2020), "Clinical Trials Impacted by the COVID-19 Pandemic: Adaptive Designs to the Rescue?," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1799857. [397]

Meyer, R. D., Ratitch, B., Wolbers, M., Marchenko, O., Quan, H., Li, D., Fletcher, C., Li, X., Wright, D., Shentu, Y., Englert, S., Shen, W., Dey, J., Liu, T., Zhou, M., Bohidar, N., Zhao, P. L., and Hale, M. (2020), "Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1779122. [397]

Nilsson, M., Crowe, B., Anglin, G., Ball, G., Munsaka, M., Shahin, S., and Wang, W. (2020), "Clinical Trial Drug Safety Assessment for Studies and Submissions Impacted by COVID-19," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1804444. [397]

O'Kelly, M., and Li, S. (2020), "Assessing via Simulation the Operating Characteristics of the WHO Scale for COVID-19 Endpoints," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1811148. [397]

Stallard, N., Hampson, L., Benda, N., Brannath, W., Burnett, T., Friede, T., Kimani, P. K., Koenig, F., Krisam, J., Mozgunov, P., Posch, M., Wason, J., Wassmer, G., Whitehead, J., Williamson, S. F., Zohar, S., and Jaki, T. (2020), "Efficient Adaptive Designs for Clinical Trials of Interventions for COVID-19," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1790415. [397]

Wiens, B. L., and Lipkovich, I. (2020), "The Impact of Major Events on Ongoing Noninferiority Trials, With Application to COVID-19," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1788983. [397]

Zame, W. R., Bica, I., Shen, C., Curth, A., Lee, H. S., Bailey, S., Weatherall, J., Wright, D., Bretz, F., and van der Schaar, M. (2020), "Machine Learning for Clinical Trials in the Era of COVID-19," *Statistics in Biopharmaceutical Research*, DOI: 10.1080/19466315.2020.1797867. [397]