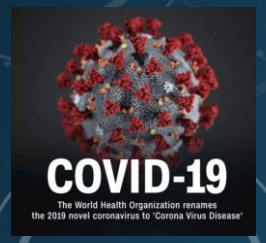

STATISTICAL CONSIDERATIONS FOR CLINICAL TRIALS DURING COVID-19: Article Series Review for BASS XXVII (September 9 and 10, 2020)

FDA Guidance on Conduct of Clinical Trials During COVID-19 states

"Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses."

How to address unplanned changes in clinical trials affected by COVID-19, while still maintaining the integrity of statistical inference and interpretability of study results.

QRMedSci, LLC

A Media | QRMedSci Articles by Qing Liu, Ph.D., ASA Fellow, and Karl Peace, Ph.D., ASA Fellow

OUTLINE

- History of Article Series
- Article Highlights
- What's Missing?
- What do we know now and impacts?
- Plan

HISTORY OF ARTICLE SERIES

- Unprecedented challenge to ongoing clinical trials
- Unplanned events and trial modifications
- Inform clinical trial community timely and broadly
- LinkedIn article platform
- 16 Articles between March 29 and June 6
- Co-authors

  Karl Peace, Ph.D., Alex Sverdlov, Ph.D., Stephan Ogenstad, Ph.D., and Michael Tirgan, M.D.
- Links to the articles chronologically published in real time

  https://www.linkedin.com/in/qliu-qrmedsci/detail/recent-activity/posts/
- Lead article with links to individual articles

  https://www.linkedin.com/pulse/statistical-considerations-clinical-trials-during-asa-fellow-1e/

ARTICLE HIGHLIGHTS

- **1. Background** https://lnkd.in/ed54vzP

  This is the first of several articles on Statistical Considerations for Clinical Trials During COVID-19.

- **2. Blinded Data Review for Adaptive Estimands** https://lnkd.in/gJ2bbpy

  This article describes an adaptive estimand framework for mitigating impacts of COVID-19 affected clinical trials while preserving the integrity of statistical inference and interpretability of study results.

- **3. Steps for Mitigation** https://lnkd.in/ejffMqq

  This article describes six steps to mitigate impacts of COVID-19 on ongoing clinical trials

ARTICLE HIGHLIGHTS (CONTINUED)

- **4. Independent DMC for Blinded Data Monitoring and Analysis** https://lnkd.in/eUUJE9U

  To supplement EMA guidance, this article describes key elements for establishing a data monitoring committee (DMC) and developing DMC charter for blinded data monitoring and analysis.

- **5. Impacts on Permuted Block Randomization and Mitigations** https://lnkd.in/efWmfZR

  This article describes impacts and mitigations of COVID-19 on permuted block randomization for moderately affected clinical trials.

- **6. Impacts on Minimization Randomization and Mitigations** https://lnkd.in/e5igX3j

  This article describes impacts and mitigations of COVID-19 on minimization randomization for severely affected clinical trials in COVID-19 high risk patients.

ARTICLE HIGHLIGHTS (CONTINUED)

- **7. Integrated Analysis of Efficacy with Adaptive Estimands** https://lnkd.in/eA9_aV6

  This article describes a two-stage adaptive design approach with integrated analysis of efficacy to address protocol deviations due to COVID-19.

- **8. Interim Analysis with Adaptive Estimands** https://lnkd.in/eFzvfJQ

  This article describes how to add a unplanned formal interim analysis for futility, early significance and other changes for ongoing clinical trials affected by COVID-19.

- **9. An Adaptive Hybrid Design for Clinical Development in Rare Diseases** https://lnkd.in/exFJN72

  For rare disease drug development, this article describes an adaptive hybrid design to increase power of a randomized controlled trial using data not affected by COVID-19.

ARTICLE HIGHLIGHTS (CONTINUED)

- **10. A Two-Stage Adaptive Design for Clinical Trials with Chronic Conditions** https://lnkd.in/exsQaeT

  This article describes how to a two-stage adaptive design for ongoing clinical trials in patients with chronic conditions affected by COVID-19.

- **11. Natural History Controls for Survival Analysis** https://lnkd.in/enVKuVW

  This article describes a virtual matched controlled methodology for comparative analysis using natural history controls for ongoing clinical trials seriously affected by COVID-19 in patients with serious diseases such as cancer for which overall survival (OS) is of primary interest.

- **12. A Two-Stage Adaptive Design for Clinical Trials in Patients with COVID-19 High Risk for Severe Illness** https://lnkd.in/eDa_Zeh

  This article describes how to a two-stage adaptive design for ongoing clinical trials in patients with COVID-19 high risk for severe illness.

ARTICLE HIGHLIGHTS (CONTINUED)

- **13. Accurate COVID-19 Testing in Clinical Trials** https://lnkd.in/emSQf5T

  This article describes the basics of diagnostic testing and current experiences with COVID-19 test kits and serology tests.

- **14. Phase 1 Cancer Trials** https://lnkd.in/esmEJYN

  This article describes mitigation strategies for phase 1 cancer trials following a dose escalation scheme to identify MTD.

- **15. Confirmatory Adaptive Platform Trial (CAPT) Design for COVID-19 Treatment** https://lnkd.in/eH9rs6g

  This article describes confirmatory adaptive platform trial (CAPT) design for COVID-19 treatment development aimed for regulatory approval.

ARTICLE HIGHLIGHTS (CONTINUED)

- **16. Systematic Bias in a Randomized Trial of Hydroxychloroquine as Post-exposure Prophylaxis for COVID-19** https://lnkd.in/dCyA8BJ

  This commentary describes systematic bias in the University of Minnesota sponsored randomized trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. The trial does not meet the substantial evidence standard of adequate and well-controlled investigations and its conclusions are both scientifically flawed and overstated.

WHAT'S MISSING?

- Statistical Inference with Missing Data
  - ✓ Baseline, missing visits, early dropouts
  - ✓ Multiple imputations under MAR and MNAR
  - ✓ Data dependency of imputed data on observed data
  - ✓ Re-randomization tests
    - Permuted block randomization
    - Minimization procedure

WHAT DO WE KNOW NOW AND IMPACTS?

- No clear distinction between during and post pandemic
- Population at risk, transmission
- COVID testing, NPI, treatment and vaccines
- Sensitivity and supplemental analysis

PLAN

- Additional articles
  - ✓ Inference with missing data
  - ✓ Many-to-1 matched control analysis
  - ✓ Oncology trials
- Trial experience with blinded data analysis
- Journal article and book