Statistical Considerations on Unplanned Clinical Trial Disruptions due to the COVID-19

Lilly Yue, Ph.D.
Division of Biostatistics
FDA/CDRH

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Outline

- FDA's response to the COVID-19
- Valuable insights from industry lead statisticians
- A consideration on mitigating study power loss by leveraging external data source
- Statistical methods for such study power salvage by leveraging external data
- Concluding remarks

FDA's Response to the COVID-19

- FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic.

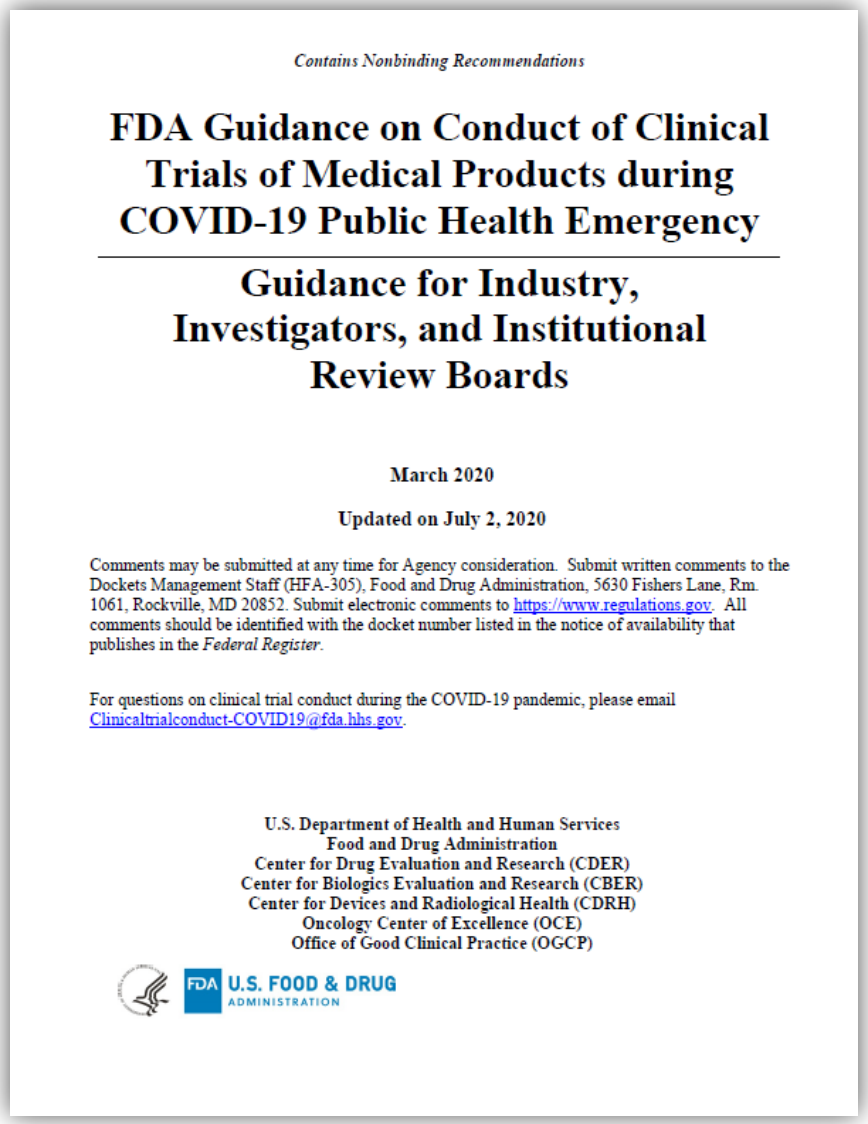
- FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA

Conduct Guidance

Draft: March 2020

Update: July 2, 2020



Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on July 2, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

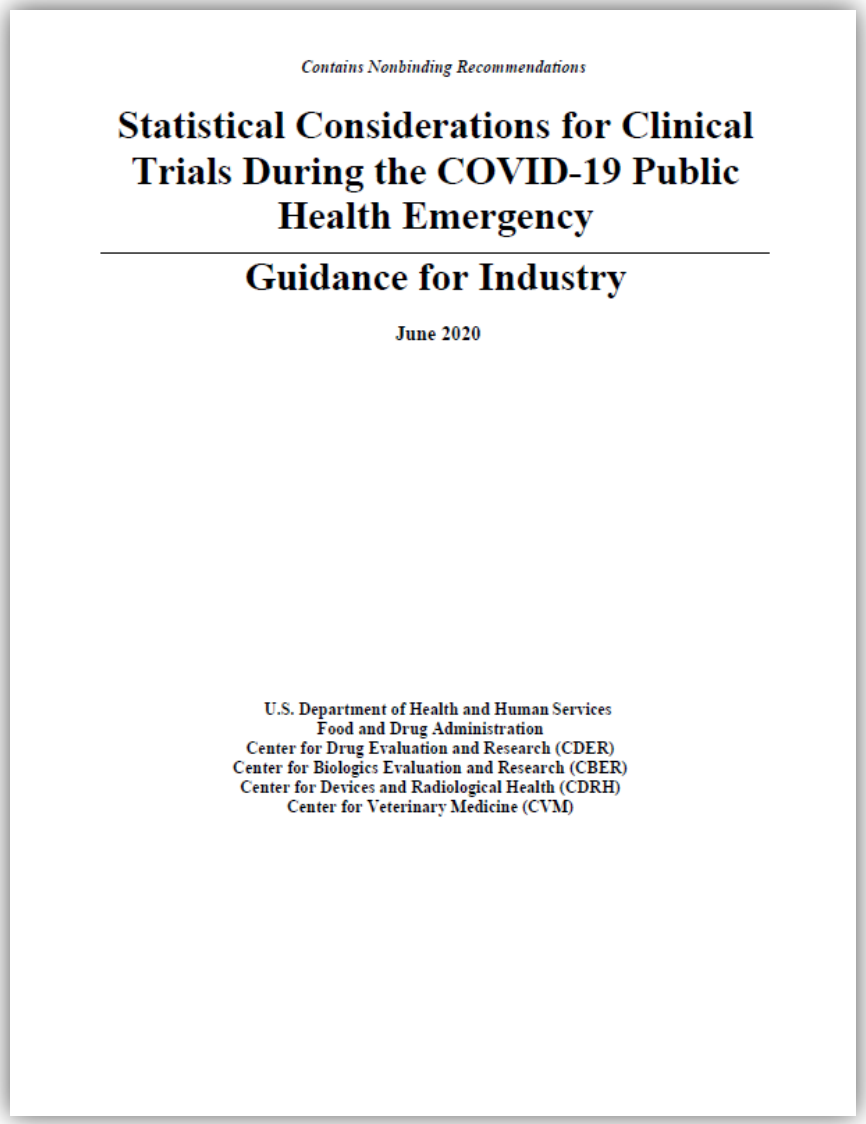
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA

Statistical Guidance

June, 2020



Contains Nonbinding Recommendations

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

June 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)

FDA Conduct Guidance

- FDA recognizes that the COVID-19 public health emergency may impact the conduct of clinical trials of medical products.
- ***Ensuring the safety of trial participants is paramount.***
  - Robust efforts by sponsors, investigators, and IRBs/IECs to maintain the safety of trial participants are expected, and such efforts should be documented.
- The guidance provides general considerations to assist sponsors in
  - assuring the safety of trial participants
  - maintaining compliance with good clinical practice (GCP)
  - minimizing risks to trial integrity for the duration of the COVID-19 public health emergency.
- Appendix – Q&As about conducting clinical trials during the COVID-19 public health emergency.

For all trials impacted by the COVID-19

- **Protocol modifications**
  - FDA recognizes that protocol modifications may be required, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures.
  - Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, are important.
  - Consultation with the appropriate FDA review division regarding protocol modifications is recommended.

For on-going trials

- **Study data integrity**
  - Robust efforts to maintain study data integrity are expected, and such efforts should be documented.
- **Amendment of statistical analysis plans (SAP)**
  - FDA recommends consultation with the applicable FDA review division.
  - ***Prior to locking the database***, sponsors should address in the SAP how protocol deviations related to COVID-19 will be handled for the pre-specified analyses.
- **Info. collection on missing data**
  - It is important to capture ***specific*** information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information.

FDA Statistical Guidance

The guidance

- Provides recommendations on statistical considerations to address the impact of COVID-19 on meeting trial objectives for clinical trials conducted during the COVID-19.
- Outlines considerations for the statistical analysis of the primary and key secondary endpoints to help ensure that the trial will
  - provide interpretable findings
  - with correct statistical quantification of uncertainty.
- Addresses statistical considerations for proposed changes to trial conduct that may impact the analysis and interpretation of the primary or key secondary endpoints in the trial.
- Recommends that sponsors consult with the relevant FDA review division when considering protocol and SAP changes that may impact the analysis and interpretation of these endpoints.

Valuable Insights from Industry Lead Statisticians

- Some recent publications in SBR (2020), including
  - *Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic (Meyer et al)*
  - *Challenges in Assessing the Impact of the COVID-19 Pandemic on the Integrity and Interpretability of Clinical Trials (Akacha et al)*

- Provide some valuable insights on assessing and mitigating the COVID-19 impact on study objectives, design, conduct, analysis and interpretation
  - Integrity and interpretation of clinical trials
  - Intercurrent events, estimands and missing data
  - Sensitivity analyses

A Consideration on Mitigating Study Power Loss by Leveraging External Data Source

- *Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic* (Meyer et al, 2020, *SBR*) (*P*11):

  For some trials, it may not be feasible to increase sample size and the trial will fall short of enrollment target. Given the extraordinary circumstances, we advocate more flexibility to **consider methods for quantifying evidence across multiple trials and sources, including use of historical control arm data and real-world data,** although sources and methodology for selection of such data would need to ***be planned and agreed with regulatory agencies in advance.***

- *Challenges in assessing the impact of the COVID-19 pandemic on the integrity and interpretability of clinical trials (Akacha et al, 2020, SBR)*

  What are the implications (e.g. on trial power) if the trial was to stop early because of COVID-19? Are there other options that would be appropriate and could be considered to mitigate power lost due to COVID-19 complications? For example: increased sample size (perhaps within an adaptive scheme), extended study duration to obtain more events, change from a fixed-time endpoint to a longitudinal approach, **incorporating data from other studies or historical controls,** change to a hypothetical estimand strategy, etc.

A Consideration on Mitigating Study Power Loss by Leveraging External Data Sources (*cont.)*

- **Consultation and agreement with relevant FDA review division are needed in advance.**
- It is critical to assess whether leveraging external data fits for purpose for the specific research question under consideration.
- Sufficient external data quality and integrity are essential for regulatory decision-making – *relevance and reliability.*
- Outcome-free planning is critical – *trail integrity and transparency.*
- Innovative statistical methods are needed.
- Statistical methods exist for leveraging external data.

FDA Voice by Commissioner Scott Gottlieb, M.D.

https://blogs.fda.gov/fdavoice/index.php/2018/07/fda-budget-matters-a-cross-cutting-data-enterprise-for-real-world-evidence

Improving Clinical Trials

The development of such a tool can also make the entire clinical trial process much more efficient. And it can enable us to enroll more patients from more diverse backgrounds into trials.

For example, real world data can be used to more efficiently identify and recruit patients for a clinical trial. Key design considerations, such as randomization, can be integrated across clinical care settings, introducing a much more diverse population into the clinical trial system. Innovative statistical approaches — such as Bayesian and propensity scores methods — can combine information from different sources and potentially reduce the size and duration of a clinical trial while expanding the scope of healthcare questions that we're able to evaluate. This will enable a modern clinical trial system that improves upon trials being conducted in large medical care centers. It could enable more clinical trials at smaller community-based health care providers. Such a system can expand the number of patients we're able to evaluate, and broaden the information that we're able to collect, while at the same time reducing the cost of developing this information. We can have more and better information, and a less costly process.

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Application Examples of Novel Stats Methods

- Propensity score methodology
  - Identify and construct a control group
  - Form both treatment and control arms
  - Augment treatment or control arm

- Bayesian inference
  - Borrow external information for treatment or control arm

- Composite likelihood approach
  - Down-weight patient info obtained from external data source.

Propensity Score Methodology

- A ground-breaking statistical innovation for the *design* and *analysis* of observational studies, developed by Rosenbaum and Rubin in 1983 (Rosenbaum and Rubin, 1983).
- Propensity score (PS): Conditional probability of receiving treatment A rather than treatment B, given a collection of observed baseline covariates.
- Replace the collection of confounding covariates with one scalar function of these covariates: the propensity score.
- Goal: Simultaneously balance many observed covariates between the two treatment groups, and then reduce bias in treatment comparison on outcomes.

Propensity Score Methods

- Commonly used PS methods in the regulatory settings:
  - Matching on propensity scores
  - Stratification on propensity scores
  - Inverse probability of treatment weighting using propensity scores
- All these can be used for both study design and outcome analysis, and can separate study *design* from outcome *analysis*.

Propensity Score Methodology Application

- Yue, LQ., Lu, N. and Xu, Y. (2014, *JBS*). Designing pre-market observational comparative studies using existing data as controls: challenges and opportunities. *Journal of Biopharmaceutical Statistics* 24:994-1010.
  - Uses propensity score methods to identify patients and construct a control group from external data source for a comparative investigational study.
  - Introduces 2-stage outcome-free study design to avoid data dredging and bias, and ensure integrity of study design and interpretability of data analyses.

Bayesian Power Prior

- A power prior is constructed as

$$\pi(\boldsymbol{\theta}|D_0, \alpha) \propto [L(\boldsymbol{\theta}|D_0)]^{\alpha} \pi_0(\boldsymbol{\theta})$$

  - $\boldsymbol{\theta}$ **:** parameter of interest
  - $L(\boldsymbol{\theta}|D_0)$: likelihood of the external data
  - $\pi_0(\boldsymbol{\theta})$: initial prior distribution for $\boldsymbol{\theta}$
  - α: *power prior parameter*, $0 \leq \alpha \leq 1$

- α: control how much external data to borrow
  - $\alpha = 0$: no borrow
  - $\alpha = 1$: full borrow

- Question: how and when to determine α for a prospective investigational study?

Ref. Chen, M-H and Ibrahim, J.G., (2000) Power Prior Distribution for Regression Models. Statistical Science, 15(1): 46-60

Composite Likelihood Approach

- General form (weighted product of probability density functions):

$$L(\theta|Y) = \prod_i f(y_i|\theta)^{\lambda_i}$$

where λ_i is nonnegative weight to be chosen, and can be used to discount patient info from external data source.

- Set:
  - $\lambda_i = 1$, if the patient *i* is from the investigational study
  - $0 < \lambda_i \leq 1$, if the patient *i* is from the external data source
    - E.g. If $\lambda_i = 0.6$, 60% of this patient's info is borrowed and 40% discounted.
- Question: how and when to determine λ for a prospective investigational study?

Ref. Lindsay, BG (1988). Composite likelihood method. *Contemporary mathematics*, 80(1): 221-239.

Varin et al (2011). An overview of composite likelihood methods. *Statistics Sinica*, P5-42.

Propensity Score-Integrated Approaches

- A new methodology for leveraging external data to augment a prospective investigational study, and save sample size required in investigational study.
  - PS-integrated power prior (PS + PP) - Bayesian
  - PS-integrated composite likelihood (PS + CL) – Frequentist
- Used to
  - augment a single-arm investigational study with external data,
  - augment the control arm in an RCT,
  - with the option of down-weighting information from external data.
- PS -> Study design
- PP or CL -> Outcome analysis

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PS-Integrated Approaches – Study Design

- Define PS as the conditional probability of being in the investigational study, given patient baseline covariates.
- Use PS to leverage external data source and design an investigational study:
  - Select comparable patients from external data source
  - Determine the weights used to down-weight information of external patients
- The selection of external patients and determination of weights are based on patient baseline covariates: Outcome free!

PS-Integrated Approaches - Reference

- Wang, C., Li, H., Chen, W., Lu, N., Tiwari, R., Xu, Y., Yue, L. (2019). Propensity Score-Integrated Power Prior Approach for Incorporating Real-World Evidence in Single-Arm Clinical Studies. *Journal of Biopharmaceutical Statistics*, 29 (5),731-748.

- Wang, C., Lu, N. Chen, W., Li, H. Tiwari, R., Xu, Y., Yue, L. Propensity Score-Integrated Composite Likelihood Approach for Incorporating Real-World Evidence in Single-Arm Clinical Studies. *Journal of Biopharmaceutical Statistics*, 30(3), 2020.

- Chen, W., Wang, C., Li, H., Lu, N. Tiwari, R., Xu, Y., Yue, L. Propensity Score-Integrated Composite Likelihood Approach for Augmenting the Control Arm of a Randomized Controlled Trial by Incorporating Real-World Data. *Journal of Biopharmaceutical Statistics*, 30(3), 2020.

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Concluding Remarks

- The COVID-19 has major impacts on ongoing clinical trials, and imposed significant challenges caused by unplanned trial disruptions due to the public health emergency.
- We statisticians have a significant role in assessing and mitigating the impacts of these disruptions, and addressing statistical issues related to the conduct, analysis and interpretation of clinical trials..
- Look forward to future discussions on estimand, missing data and adaptive design, and related novel statistical methodology.

Acknowledgements

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Thank You!