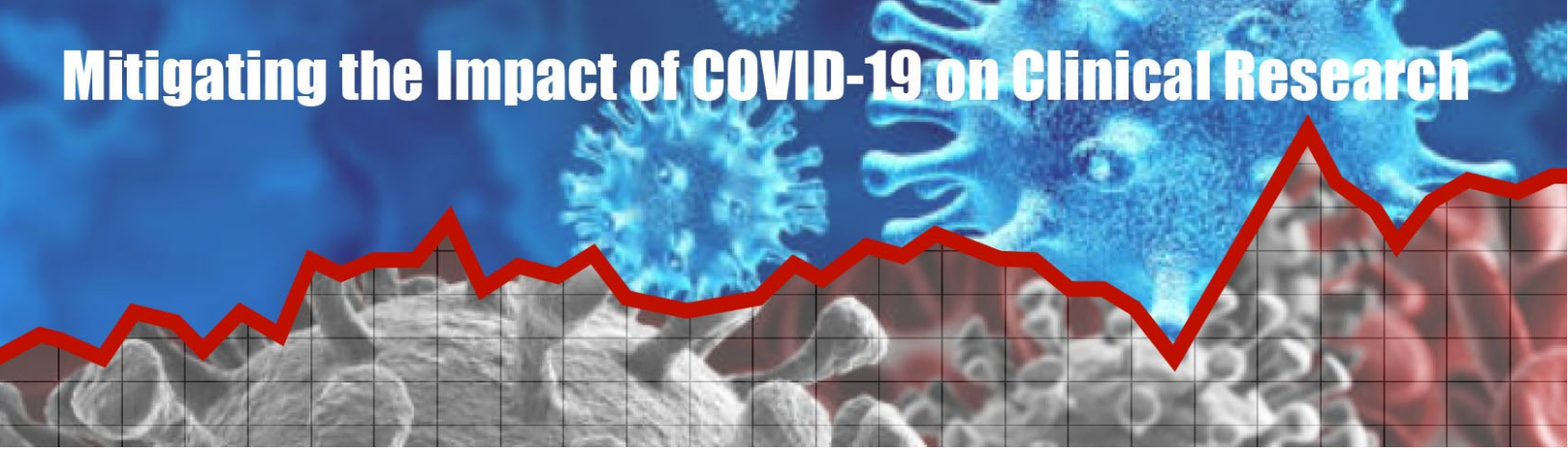


Statistical Considerations on Challenges and Solutions in Clinical Studies During the COVID-19 Pandemic

By Jennifer Schroeder, Ph.D., Statistician, BioStat Solutions, Inc.

April 15, 2020

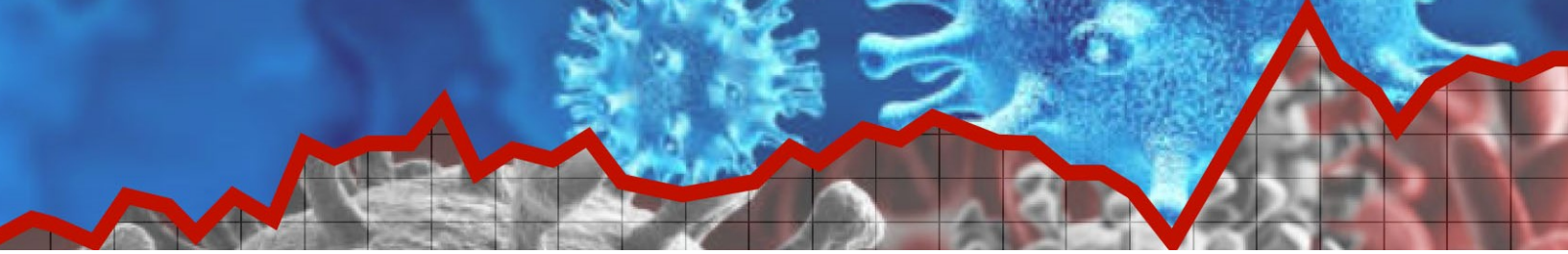
The COVID-19 Pandemic

The current outbreak of acute respiratory illness, named "Coronavirus Disease 2019" (COVID-19) is causing worldwide morbidity and mortality, as well as economic disruption. This illness, caused by the SARS-CoV-2 virus, was first detected in Wuhan City, Hubei Province, China, in December 2019. Its spread has been rapid: on 30 January 2020, the World Health Organization (WHO) declared the outbreak to be a public health emergency of international concern, and upgraded it to pandemic status on 11 March 2020. The first known case in the United States was diagnosed on 20 January; by 17 March, cases had been confirmed in all 50 states and the District of Columbia.

The rapidity of the spread of the virus, coupled with the potential severity of the symptoms, meant that the health care system could easily become overwhelmed by COVID-19 cases' need for care. To "flatten the curve" of the pandemic and reduce the number of incident cases, many containment and mitigation measures that lessen physical contact between people have been implemented by governmental authorities across the world. Non-essential businesses have been closed, schools have transitioned to online learning, and many areas have issued shelter-in-place orders that require individuals to remain at home unless purchasing food or seeking medical care.

Impact of the COVID-19 Pandemic on Clinical Trials

The current COVID-19 pandemic has the potential to impact the conduct of clinical trials of medical products worldwide. Many of the countries that afford access to clinical trials to the most people also have the highest rates of COVID-19 infection. A key consequence is that trial participants may not be able to come to investigational sites for protocol-specified visits, to receive the investigational interventions or to have assessments done and data collected. This could be due to shelter-in-place orders that restrict travel, as well as to the participants' own or household members' illness with COVID-19. Because COVID-19 infection rates



and mitigation measures vary widely by geographic region, multi-site clinical trials will likely find study sites to be differentially affected by the pandemic. An additional challenge may be obtaining the necessary investigational products and personal protective equipment (PPE) for study personnel due to disruptions in the manufacture and distribution of these products.

Many trial sponsors and Clinical Research Organizations have undertaken COVID-19 risk mitigation investigations in response to the pandemic. The safety of study participants and study personnel who interact with them, as well as maintaining data integrity, are of paramount importance. Many studies have suspended screening and enrollment for ongoing studies, and shifted data collection from onsite to remote via telephone or electronic device. Clinical trials are leveraging existing technology to maintain engagement with study participants and timely collection of study data.

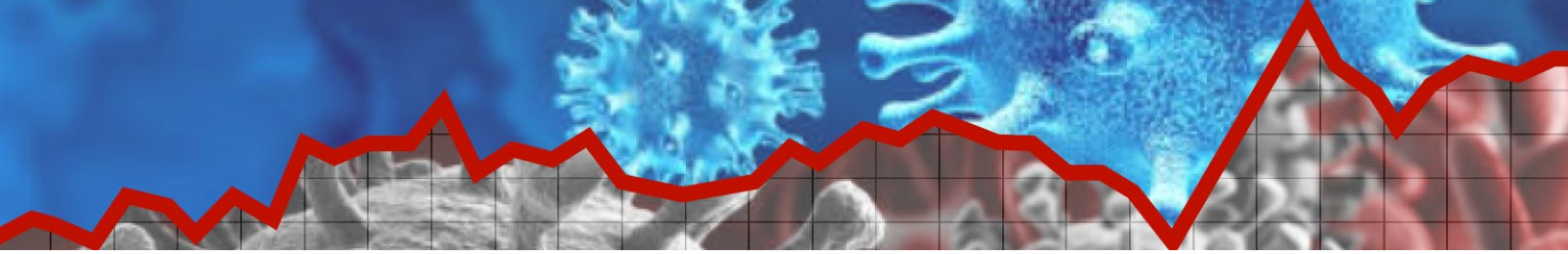
Nevertheless, disruptions to data collection are to be expected in spite of these efforts. This will result in protocol deviations as well as outcome data that are missing not at random (MNAR). Studies that are put on hold for an extended period of time face greater challenges, such as differences in composition of the study sample due to shifts in patient demographics and treatment options pre- and post-pandemic.

Regulatory Guidance

The U.S. Food and Drug Administration (FDA) has responded to the COVID-19 pandemic with guidance for clinical trial conduct (FDA, 2020). This document emphasizes that ensuring the safety of clinical trial participants is the highest priority. Many decisions, such as continuing recruitment, continued use of the investigational product, and switching in-person visits to remote visits must be made on a study-by-study basis. These decisions depend on the unique circumstances of each study, and must consider the nature of the investigational product, the nature of the condition being treated, the ability to conduct appropriate safety monitoring, and the potential impact on the investigational product supply chain.

Highlights of this guidance document include the following:

- Sponsors should consider switching in-person data collection to remote methods, as long as this level of monitoring is sufficient to ensure continued safety of trial participants.
- Sponsors and clinical investigators are encouraged to engage with review boards as early as possible when changes to the study protocol or informed consent are anticipated as a result of COVID-19.
- Any modifications to the study should be communicated to study participants as soon as possible.
- Any alternative procedures should be consistent with the study protocol to the extent possible, and reasons for adopting alternative procedures should be well-documented.
- It is important to capture specific information regarding the basis for missing data, and this information must be summarized in the clinical study report (CSR).
- Prior to locking the study database, sponsors should address in the statistical analysis plan (SAP) how protocol deviations related to COVID-19 will be handled in the analyses.



- All trials impacted by COVID-19 should describe in the CSR:
    - Contingency measures implemented to manage study conduct during disruption of the study due to COVID-19 control measures
    - A listing of all participants affected by COVID-19 related study disruption by unique identifier number and by investigational site, with a description of how the individual's participation in the trial was altered
    - Analyses and corresponding discussions that address the impact of implemented contingency measures on the safety and efficacy results reported for the study

Statistical Considerations

Below are statistical considerations for dealing with these challenges to clinical trial conduct due to the COVID-19 pandemic.

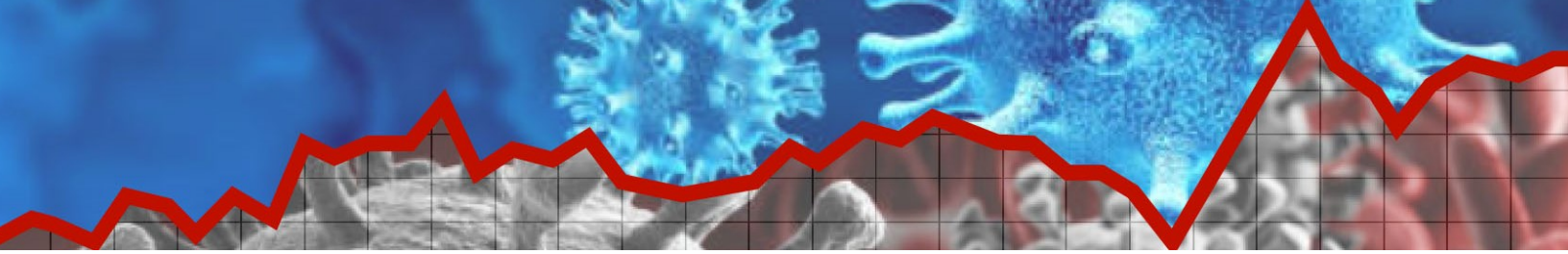
Design

When faced with the decision to change study methods due to COVID-19 mitigations, one consideration is how the introduction of a new method will impact the ability of the study to detect a treatment effect. For example, if remote data collection increases the variability in measurements, how does this impact the power of the study? Conducting a simulation study may help to anticipate how introduction of alternate methods could impact study results. When different methods are under consideration, simulation study results can help the sponsor make an informed choice.

Analysis

Study disruptions due to COVID-19 are likely to lead to increased rates of missing data, as well as higher study dropout rates. Choosing statistical methods that maximize the use of available data (*i.e.,* don't exclude participants with incomplete follow-up) are essential for trials impacted by COVID-19 to reach valid, generalizable conclusions. Methods that require complete data lead to findings that apply only to the select subset of patients that have a high degree of compliance with study procedures, and are not representative of the intended use population (IUP) for the investigational product.

Mixed models for repeated measures (MMRM) is a statistical modeling method that includes observations with incomplete follow-up. It is a form of regression modeling that includes both fixed and random effects, and allows for estimation of subject-level parameters, as well as specifying the pattern of correlation within-subject. The inclusion of random effects and correlation structure enhances the realism of the model and can lead to more precise parameter estimates. An alternative to MMRM is Generalized Estimating Equations (GEE). Like MMRM, GEE allows inclusion of observations with incomplete follow-up. However, GEE does not include random effects and has more stringent assumptions for missing data: GEE requires data to be missing completely at random (MCAR), while MMRM requires data to be missing at random (MAR). For this reason, MMRM may be preferable to GEE. See Diggle *et al.* (2002) for further description of MMRM and GEE.



Another strategy to analyzing repeated measures data is to create a numeric summary of the repeated observations. Calculated area under the effect curve (AUEC) uses all data collected, and can accommodate missing observations and observation times that vary from subject to subject. There is the potential for biased conclusions if treatment groups have different patterns of missing data, because this can lead to systematic group differences in AUEC. Prior to calculating AUEC, treatment groups should be compared in terms of missing data patterns and mechanisms. If group differences are found, a weighted analysis can be performed that gives more weight to participants with less missing data.

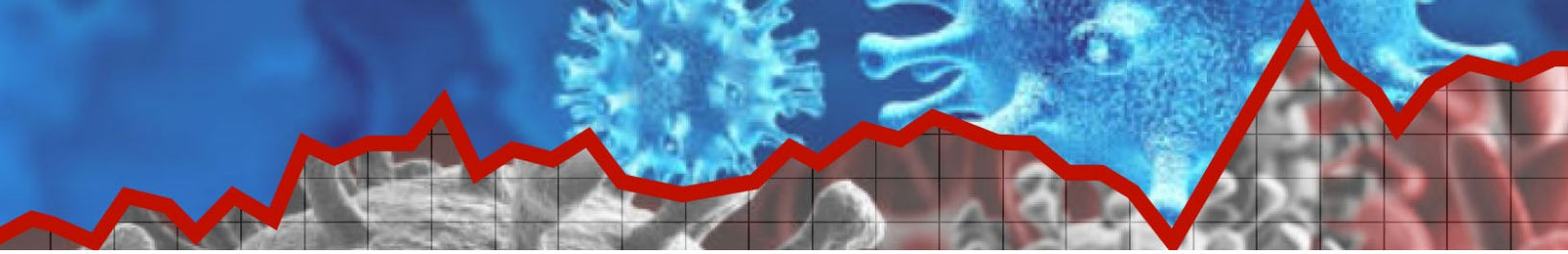
MMRM, GEE, and AUEC are all methods that can utilize incomplete follow-up data without requiring imputation of missing data values. Many data imputation methods can result in biased estimates and lead to incorrect conclusions, so it is preferable to choose a method that does not require imputation. However, if a complete-data method is chosen for analysis, it is critical to choose an imputation method that minimizes the potential for bias. Single-value imputation, such as last observation carried forward (LOCF) can introduce bias as well as artificially increasing precision. Multiple imputation is a procedure in which multiple plausible values are imputed for each missing value, thus simulating the variability that would have been observed had the data not been missing. Multiple imputation performs well in terms of bias and precision, as long as the parametric assumptions behind the imputation are valid. See Hedden, *et al.,* (2008) for a comparison of imputation vs. alternative methods with varying amounts of missing data.

Interpretation

Since COVID-19 is likely to lead to higher rates of missing data than anticipated when a trial was planned, quantifying and characterizing the nature and extent of missing data is an essential first step in interpreting study results. As stated above, regulatory agencies expect this to be included in a CSR. Finding that group differences in missing data rates are not statistically significant is not sufficient to demonstrate that they are not relevant, since it does not prove the null hypothesis that the missingness patterns are the same. Missing data patterns that differ by treatment group should be taken into consideration when interpreting study findings, as this could lead to results that do not generalize to the IUP of the investigational product.

Increased attrition due to COVID-19 may disproportionately affect placebo or negative control groups, as participants in these groups are not likely to experience a treatment effect that could motivate them to remain in the study. In the event that study attrition results in a control group that is not large enough to serve as a basis of comparison for other treatment groups, methods for sparse data analysis can be employed to evaluate whether sparse data bias is likely present, as well as minimize and assess the impact of sparse data bias. Greenland, *et al.* (2016) describe a penalized estimation approach for logistic regression; this method can be adapted as needed to obtain valid treatment effect estimates.

Sensitivity analysis can be conducted to determine the impact of missing data on trial results. Missing data values for primary endpoint(s) can be imputed based on “worst case” (consistent with the null hypothesis) and/or “best-case” (consistent with the alternative hypothesis) assumptions. The analyses for each endpoint can be re-analyzed, combining the observed data with either the worst-case or best-case imputed values, and results compared with those obtained without imputation.



For multi-site studies, COVID-19 may result in site differences, since the pandemic may affect a site's ability to follow the study protocol and/or collect needed outcome data. A poolability analysis to determine if study sites influence the primary outcome(s) is advisable. This can be accomplished using a model for the primary outcome measure that has site, treatment, and site x treatment as independent variables.

Conclusion

The impact of the COVID-19 pandemic on clinical studies already underway will be significant, and many planned studies have been delayed. However, there are statistical methods that can help mitigate the impact of incomplete data, and facilitate valid conclusions.

References

Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data, 2nd edition.* Oxford University Press, 2002.

Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; 353:i1981.

Hedden SL, Woolson RF, Carter RE, Palesch Y, Upadhyaya HP, Malcolm RJ. The impact of loss to follow-up on hypothesis tests of the treatment effect for several statistical methods in substance abuse clinical trials. *Journal of Substance Abuse Treatment* 2008; 37:54-63.

U.S. Food and Drug Administration. *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic. Guidance for Industry, Investigators, and Institutional Review Boards.* March 2020.

Contact: For more information or a free consultation please contact us at info@biostatsolutions.com or call us at 301-829-4001