PharmaSUG China 2021 - Paper SR-055

Statistical considerations in a case study disrupted by COVID-19 pandemic

Kun Li, JIANGSU HENGRUI PHARMACEUTICAL CO., LTD.

ABSTRACT

The outbreak of the COVID-19 pandemic has led to a host of challenges in almost all the industries globally and also in clinical trials. Especially for ongoing studies, it is an urgent task to minimize the impact of this public health emergency such as missed or delayed exposure, missed visits and missed assessments, which may lead to statistical bias on both safety and efficacy analysis. This paper reviews some important COVID-19-related guidance and assesses potential statistical issues in an ongoing study disrupted by COVID-19 pandemic. Furthermore, statistical strategies for addressing these issues are discussed including expanding sample size, capturing COVID-19-related information and modifying analysis sets or censoring rules for analysis on the primary endpoint in the sensitivity analyses as well as making comparisons between different pandemic phases (pre-pandemic phase, during-pandemic phase) and trial subpopulations (enrolled but not completed before pandemic, enrolled during pandemic).

INTRODUCTION

In December 2019, a novel coronavirus first started driving people into hospital and the disease caused by it quickly became a pandemic globally. China has activated first-level public health emergency response to contain the outbreak, including the lockdown of Wuhan city, travel limitations, quarantines of confirmed cases and close contacts, site restrictions, etc. These restrictions succeeded in curbing population flow but also brought difficulties in the conduct of clinical trials such as the supply of investigational medical products and inability of the trial participants to visit the clinical site, and therefore may lead to various challenges to analysis and interpretation of the trial results. This paper reviews some important guidance related to COVID-19 and identifies the impacts of COVID-19 pandemic on statistical analysis and discusses how to handle them in analysis under the influence of these important guidance based on a specific study.

COVID-19-RELATED GUIDANCE

In response to the COVID-19 pandemic, regulatory authorities and agencies in different countries have offered guidance to direct the implement of clinical trials. Two of the most representative authorities are the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Both of them has rapidly issued guidance related to the conduct of clinical trial in March 2020 and statistical considerations in June 2020 separately (FDA. 2020a, 2020b and EMA. 2020a, 2020b). Table 1 outlines some key points of the updated version of aforementioned guidance from FDA and EMA:

CONDUCT OF TRIAL	• Ensuring the safety of trial participants is paramount. • Keep communication with relevant authorities, trial sites, trial participants and other stakeholders. • Perform a risk-assessment of the impact of COVID-19 potentially affecting trial participants directly and COVID-19 related measures affecting clinical trial conduct. • Consider which information is essential for the interpretation of the trial and whether an alternative method of data collection might be warranted. • Establish an Independent Data Monitoring Committee (IDMC) or revise DMC charter accordingly. • Evaluate alternative methods for drug administration (e.g., home nursing). • Evaluate alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers).

STATISTICAL CONSIDERATIONS	• Sponsors can consider increasing enrollment and extending follow-up and can conduct sensitivity analyses to examine differences in baseline characteristics and post-baseline events between the originally enrolled participants and the additional participants. • Pandemic-related information may be useful for incorporating into analysis strategies to address potential biases or for performing sensitivity analyses related to the impact of COVID-19. • Sponsors should consider how to approach the analysis of data from participants who are missing endpoint ascertainment or the investigational product was interrupted because of COVID-19. • Modifications to the definition and ascertainment of trial endpoints should be discussed with relevant agencies and be carefully evaluated in sensitivity analyses. • An analysis of the number and type of deviations periodically to assess whether a protocol amendment or other modifications are needed.

Table 1. Guidance from FDA and EMA

The main principle of all the guidance discussed above is prioritizing the safety of participants and minimizing the potential bias during the coronavirus pandemic. In addition, both FDA and EMA admit that their recommendations in the guidance are not feasible and suitable for all the studies and allow an alternative approach under the current statutes and regulations. The following sections assess the impacts of COVID-19 pandemic from the perspective of statistical analysis and discuss how to handle them in analysis under the influence of these important guidance based on a specific study.

THE IMPACTS OF COVID-19 ON STATISTICAL ANALYSIS

The discussion of the impacts is based on a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial for non-COVID-19 related therapies. Patients were enrolled from June, 2019 to September, 2020, covering the most difficult moment in our fight against the COVID-19 outbreak. The primary objective of this trial is to evaluate the progression free survival (PFS) assessed by investigator between treatment group and placebo group. The primary endpoint of PFS is defined in SAP as the time from randomization until objective tumor progression or death based on RECIST version 1.1. In order to minimize bias in radiological interpretation, an Independent Review Committee (IRC) have conducted a separate tumor assessment.

Pandemic control measures such as quarantines, travel limitations, site restrictions and interruptions to supply chain of investigational drugs have substantial impacts on the conduct of the trial and interpretation of the trial results. The safety of participants is of course our highest priority. A risk assessment is performed by sponsors to assess the impacts of COVID-19 on the safety of participants, treatment adherence, protocol compliance, data collection and the interpretability of the trial results. The following part outlines some major pandemic-related impacts on the example trial that may lead to statistical issues.

- Pandemic has caused a large amount of missed or delayed use of study drugs. The investigational drugs that are normally administered in a clinical site will be significantly impacted. The strict restrictions of visit and increased demands on health service at clinical sites as well as the interruptions to the supply chain and fear from the potential risk of COVID-19 infection all contribute to the delay. Particularly in the period from January 20,2020 to March 15,2020, according to a risk assessment, approximately 20 percentage of subjects did not receive drugs on time and these subjects may need to be excluded from the analysis, which could cause loss of statistical power due to the smaller sample size and less follow-up time. In addition, once the reduction in total drug exposure time increased to some extent, treatment effect is likely to be influenced and could lead to bias on analysis of the key endpoints.
- Similarly, a number of missed assessments on laboratory tests, imaging or other diagnostic tests also come into notice. These diagnostic tests such as blood tests, CT need to be conducted in clinical facilities with professional devices and medical workers as well. On the one hand, the original

site may be unavailable to provide these assessments due to public health control measures. Under these circumstances, participants can choose an alternative site to perform these assessments. On the other hand, participants may be unable or unwilling to receive these assessments because of personal pandemic-related factors. However, the results of these assessments may have significant impacts not only on safety assessments but also on efficacy assessments. For example, the objective tumor progression, which plays a key role in ascertainment of PFS, is assessed based only on radiological assessments conducted by CT or MRI.

- Moreover, COVID-19 has introduced much more protocol deviations than normal. Due to the pandemic, the increase of protocol deviations is understandable. Protocol deviations, such as missed or delayed treatment, visit and assessments, alternative sites and deviations that impact primary and secondary endpoints, need to be taken into account during analysis of the data, and can affect the reliability of the trial results if not documented and communicated adequately (MHRA, 2020).
- In addition, whether the pandemic has the impacts on the occurrence of adverse events is uncertain. Because COVID-19 is a new disease to us, it is hard to identify the relationship between COVID-19 and adverse events (CDISC, 2020). As advised by FDA, adverse event reporting processes as required by statute and regulation should be maintained to the maximum extent possible during a pandemic (FDA, 2020c).

ADDRESS THE IMPACT OF COVID-19

To deal with these pandemic-related impacts in analysis, the planned statistical analyses may need to be updated before database lock and the changes should be well balanced and proportionate as recommended in the guidance. In the example trial, the core analysis methodology remains unchanged. Meanwhile, multiple statistical strategies are conducted for proposed issues and are discussed as follows.

EXPAND THE SAMPLE SIZE

In regard to FDA's guidance, increasing enrollment after COVID-19, extending follow-up to attain more events and conducting a blinded power assessment is suggested (FDA,2020a). A blinded statistical simulation is used in this ongoing trial to re-estimate the sample size based on the actual enrollment and event rate as well as some epidemic-related factors. According to the outcome of the blinded simulation by sponsors and evaluation from the IDMC, sample size of this study is decided to be increased and events of the primary endpoint of progression free survival (PFS) is also expanded. It is no doubt that expanding the sample size can increase the reliability of the trial results. However, for some rare diseases, there are difficulties in increasing enrollment.

CAPTURE COVID-19-RELATED INFORMATION

In order to have a better understanding of the general impacts of COVID-19 on trial outcomes, the main concern for data analysis is how to distinguish between data "affected" and "unaffected" by the pandemic. One way is to capture information describing how events can be attributed to the COVID-19 pandemic. Sponsors should ensure that all required data has been captured and mapped to suitable fields in tabulation datasets. Due to the pandemic-related restrictions, it is hard for site staff to enter clinical sites and collect trial data as usual. Therefore, alternative methods such as telephone calls or telemedicine visits are used in our study for data collection. In addition, the Clinical Data Interchange Standards Consortium (CDISC) has published its reference guidance on how to describe information related to COVID-19 in tabulation datasets in April, 2020. In our study, in keeping with CDISC guidance, pandemic-related information including changes in administration of study products and specific reasons for COVID-19-related protocol deviations is documented with the key words (e.g., "COVID-19") and is represented in standard SDTM variables or in non-standard variables (NSVs). The occurrence of delays in exposure and pandemic-related protocol deviations are summarized separately for safety analyses. This is a relatively standard approach in adjusting pandemic effects. However, the disadvantage of this approach is that data collection during the pandemic is not feasible in some circumstances (Meyer RD et al, 2020).

SENSITIVITY ANALYSES IN A MODIFIED ANALYSIS SET

According to FDA guidance, if recently randomized participants are not able to obtain trial-specified treatment for an extended period of time for an investigational product whose hypothesized effect occurs

only after sustained treatment, it may be reasonable to exclude from the analysis all participants potentially impacted (FDA, 2020a). As discussed above, the delayed use of study drugs is commonly occurred in our study. Once the reduction in total drug exposure time increased to some extent, treatment effect is likely to be influenced and could lead to bias on analysis of PFS.

Therefore, we have tried to use a modified FAS analysis set (mFAS) in sensitivity analyses. The primary analysis on PFS is based on full analysis set (FAS) which includes all randomized subjects following the intention-to-treat principle. The mFAS is defined in SAP as a subset of the full analysis set but excludes the subjects who have more than 7 days of delay in treatment. The sensitivity analyses based on mFAS are consistent with the primary analysis on PFS based on FAS.

SENSITIVITY ANALYSES ON A MODIFIED ENDPOINT

Similarly, after assessment from sponsors, delays in treatment exceeding 7 days are treated as interruption events. Tumor response assessments after the interruption event should not be viewed as valid anymore and hence these patients should be censored. In the example trial, we have tried to perform sensitivity analyses on a modified endpoint of PFS (mPFS) based on the original censoring rules on PFS. If the supply of investigational products is disrupted due to the impacts of coronavirus and the resulting delay is more than 7 days, trial participants will be censored at the last radiological assessment date before the 7-day delay. Notably, if delay occurs prior to any assessment, the censor date is the date of randomization.

SENSITIVITY ANALYSES BETWEEN SUBPOPULATIONS AND PANDEMIC PHASES

Additionally, the EMA points out that study participants within a certain trial will be unequally affected by general (i.e. external to the trial) COVID-19 pandemic control measures (EMA, 2020b). To be specific, some study participants may already have completed all study relevant activities and recorded measurements before pandemic-related issues started impacting the trial; for other participants, the main individual study phase might fall during a time when it can be affected by the COVID-19 pandemic (EMA, 2020b).

In order to deal with such concerns, additional sensitivity analyses are performed in our study to understand the treatment effect among population affected by the COVID-19 during different pandemic periods. The first step is to evaluate start and end dates of pandemic periods based on sufficient information regarding to pandemic-related control measures and their potential impacts. After the evaluation, the period between January 20,2020 and March 15,2020 is defined as “during-pandemic phase” and the time before January 20,2020 is “pre-pandemic phase” and the time after March 15,2020 is “post-pandemic phase”.

The next step is to identify trial patients who are affected by COVID-19 and who are not affected based on these three different phases. Trial patients who have completed all study activities during “pre-pandemic phase” or who were enrolled during “post-pandemic phase” are considered as “unaffected” population because they were not participate in the pandemic periods. Other patients who have enrolled before January 20,2020 and did not finish the trial until January 20,2020 or who were enrolled between January 20,2020 and March 15,2020 are considered as “affected” population. Our sensitivity analyses involve these two subpopulations (enrolled but not completed before pandemic and enrolled during pandemic) among “affected” population.

In our study, delayed exposure to each of the study drugs is summarized by exceeding days (3 days, 7 days and 14 days) and compared between different treatment groups and different pandemic phases (pre-pandemic phase and during-pandemic phase) among different subpopulations (enrolled but not completed before pandemic, enrolled during pandemic) separately. In order to evaluate the impact of the coronavirus on an adverse event with special interest (AESI), the incidence rate of this adverse event is summarized by maximum CTCAE grade and compared between “enrolled but not completed before pandemic” subpopulation and all “affected’ population. Because of the low incident rate of AESI, the sum of the subjects “enrolled but not completed before pandemic” and “enrolled during pandemic” is used instead of subjects “enrolled during pandemic”. Similarly, COVID-19 has caused a number of missed visits and assessments. In the analysis on some critical laboratory tests, the incidence and frequency of missed assessments is summarized by visits between different pandemic phases (pre-pandemic phase

and during-pandemic phase) among different subpopulations (enrolled but not completed before pandemic, enrolled during pandemic) as well.

The use of subpopulations and pandemic periods is a well understood approach and can be simply used in a study conducted in only one region with trial participants relatively equally affected by the pandemic control measures. Whereas, this approach requires the precise and accurate start and end dates of pandemic periods and the influence of the pandemic and relevant control measures on participants is probably not homogenous. In addition, there may be several waves of infection outbreaks which means more challenges in implement (Meyer RD et al, 2020).

CONCLUSION

Regulatory agencies have already provided substantial and valuable guidance for sponsors to deal with the COVID-19 impacts in the conduct of clinical trials. However, pandemic-related impacts vary from studies to studies. All changes to analysis strategies should be carefully evaluated and discussed. In this article, we identify some major statistical issues caused by COVID-19 in an affected trial including missed or delayed use of study drugs, missed assessments, more protocol deviations and uncertainty in the relationship between the pandemic and adverse events. In addition, multiple statistical strategies for proposed issues are discussed with the important guidance including expanding sample size, collecting pandemic-related data and performing additional sensitivity analyses based on a modified analysis set or a modified endpoint or within different pandemic phases (pre-pandemic phase, during-pandemic phase) and subpopulations (enrolled but not completed before pandemic, enrolled during pandemic). Although any analyses accompanying with missing data can be problematic, the results can be more convinced for the similar conclusions in both the primary and sensitivity analyses (FDA,2007). It should be noted that statistical methods discussed above are used only for guiding thinking during the COVID-19 emergency and are probably not appropriate and feasible for other studies. As the pandemic has not been effectively controlled globally, more concerns related to COVID-19 are calling for discussed in the future.

REFERENCES

US Food and Drug Administration. "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency: Guidance for Industry." US Department of Health & Human Services. June 2020a. Available at https://www.fda.gov/regulatory-information/

US Food and Drug Administration. "Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency." US Department of Health & Human Services. March 2020b. Updated January 2021. Available at https://www.fda.gov/regulatory-information/

US Food and Drug Administration. "Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic." US Department of Health & Human Services. May 2020c. Available at Postmarketing Adverse Event Reporting for Medical Products Final 050820 (fda.gov)

Clinical Data Interchange Standards Consortium. Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic Version 1.0. April 2020. Available at https://www.cdisc.org/standards/therapeutic-areas/covid-19

European Medicines Agency. "Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic." Version 4. February 2021a. Available at Good clinical practice | European Medicines Agency (europa.eu)

European Medicines Agency. "Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials." June 2020b. Available at Good clinical practice | European Medicines Agency (europa.eu)

R. Daniel Meyer, Bohdana Ratitch, Marcel Wolbers, Olga Marchenko, Hui Quan, Daniel Li, Christine Fletcher, Xin Li, David Wright, Yue Shentu, Stefan Englert, Wei Shen, Jyotirmoy Dey, Thomas Liu, Ming Zhou, Norman Bohidar, Peng-Liang Zhao & Michael Hale .2020. "Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic." Statistics in Biopharmaceutical Research, 12:4, 399-411.

Shiely F, Foley J, Stone A, Cobbe E, Browne S, Murphy E, Kelsey M, Walsh-Crowley J, Eustace JA. 2021. "Managing clinical trials during COVID-19: experience from a clinical research facility." Trials. 22(1):62.

US Food and Drug Administration. "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics." US Department of Health & Human Services. May 2007. Available at Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics | FDA

Medicines and Healthcare products Regulatory Agency (MHRA). "Guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19." November 2020. Available at Guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19 - GOV.UK (www.gov.uk)

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Kun Li
JIANGSU HENGRUI PHARMACEUTICAL CO., LTD.
kun.li@hengrui.com