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Data Science in Action

Addressing the Impact of the COVID-19 Pandemic on Survival Outcomes in Randomized Phase III Oncology Trials

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Abstract

We assessed the impact of the coronavirus disease 2019 (COVID-19) pandemic on the statistical analysis of time-to-event outcomes in late-phase oncology trials. Using a simulated case study that mimics a Phase III ongoing trial during the pandemic, we evaluated the impact of COVID-19-related deaths, time off-treatment and missed clinical visits due to the pandemic, on overall survival and/or progression-free survival in terms of test size (also referred to as Type 1 error rate or alpha level), power, and hazard ratio (HR) estimates. We found that COVID-19-related deaths would impact both size and power, and lead to biased HR estimates; the impact would be more severe if there was an imbalance in COVID-19-related deaths between the study arms. Approaches censoring COVID-19-related deaths may mitigate the impact on power and HR estimation, especially if study data cut-off was extended to recover censoring-related event loss. The impact of COVID-19-related time off-treatment would be modest for power, and moderate for size and HR estimation. Different rules of censoring cancer progression times result in a slight difference in the power for the analysis of progression-free survival. The simulations provided valuable information for determining whether clinical-trial modifications should be required for ongoing trials during the COVID-19 pandemic.

Keywords *model evaluation; oncology; optimal design; protocol modification; survival analysis; trial simulation*

1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory disease called coronavirus disease 2019 (COVID-19) in infected individuals (Wu and McGoogan, 2020). Since its first outbreak at the end of 2019, COVID-19 has rapidly evolved into a global pandemic (Gates, 2020; Huang et al., 2020). Cancer patients are often immunosuppressed as a result of both their disease and the treatment they receive, which puts them at increased risk of severe complications of respiratory viruses (Hirsch et al., 2013); moreover, many cancer patients have

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additional risk factors for COVID-19, such as advanced age and comorbidities (Wang et al., 2020). Early evidence also suggests that COVID-19 prevalence is disproportionately higher in cancer patients (particularly in those with lung cancer) compared with the general population (Bakouny et al., 2020, 2022; Sessa et al., 2022). Notably, however, cancer treatment itself has been shown not to be a risk factor for COVID-19-related mortality (Serrano et al., 2020; Pinato et al., 2020; Seguí et al., 2020; Tapia et al., 2020; García-Illescas et al., 2020; Joerger et al., 2020).

Since March 2020, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and regulatory agencies around the world published a series of COVID-19 related guidance documents to support rapid COVID-19 response efforts. Particularly, the guidance documents on the conduct of clinical trials during the COVID-19 pandemic (US Food and Drug Administration, 2020, 2021; European Medicines Agency, 2020, 2022) called on trial sponsors to ensure the safety of trial participants and minimize the risks to trial integrity while maintaining compliance with good clinical practice. As difficulties in meeting protocol-specified procedures may lead to protocol modifications, the guidance suggested the impact of such modifications be thoroughly recorded and summarized in clinical study reports. Further, sponsors were directed to proactively plan to address the impact of COVID-19 on the ability to meet trial objectives, e.g., by agreeing any changes to key endpoints with regulatory authorities in advance of database lock, and by assessing the impact of COVID-19 related events in an ongoing, but blinded fashion (Castelo-Branco et al., 2021).

Thus, study sponsors are faced with a dilemma where, although overall trial objectives should remain unchanged, the data gathered from trials ongoing during a pandemic can be used to address these objectives in the context of the pandemic or in a post-pandemic setting; the latter could require longer timelines, additional recruitment, or other study modifications (Degtyarev et al., 2020). For example, an analysis that censors COVID-19-related deaths might mitigate the impact of COVID-19-related mortality on overall survival (OS), and thus describe the effects of treatment with an experimental drug versus control in the same way it would have done in the pre-pandemic world (or will have, in a post-pandemic scenario). In contrast, an analysis of all deaths would provide answers on the benefit of the experimental drug in the presence of the pandemic (including potential benefit on COVID-19-related deaths), working on the assumption that at least some deaths in the trial are directly related to COVID-19. In addition to an increased risk of mortality in cancer patients due to COVID-19 (Bakouny et al., 2020), the travel restrictions and social distancing measures put in place to prevent the spread of the virus, as well as fear of contracting the virus at hospitals and clinics, constitute an important barrier to participation in clinical trials according to protocol, particularly in terms of time off-treatment, missed visits or even dropouts (Wilkinson, 2021). Therefore, the impact of these two factors on survival outcomes also necessitates investigation.

Although the problems of unexpected deaths, time-off-treatment and missing clinical visits happen all the time, the COVID19 pandemic exacerbated these issues. However, there are few literature that have examined the impact of these exacerbated situations. Using simulation, Tang et al. (2022) examined the impact of COVID-19 on the OS and progression-free survival (PFS) analysis in oncology clinical trial design and analysis. Here, we conducted more comprehensive simulation studies that examined the impact of COVID-19 from several alternative perspectives. The objective of the present analysis was to develop a framework of general rules and considerations to assess and understand the risks and implications of the COVID-19 pandemic on the statistical analysis of time-to-event outcomes, i.e., OS and PFS, in Phase III randomized controlled oncology trials with an interim analysis. Specifically, we assessed the impact of

COVID-19-related deaths, excess hazards due to time off-treatment, and different censoring rules due to missed visits during the COVID-19 pandemic. We also provided mitigation strategies to reduce the impact of COVID-19 pandemic.

2 Methods

2.1 Analysis Goals and Case Study

This analysis used simulations to evaluate the impact of the COVID-19 pandemic on the operating characteristics of Phase III clinical trials by assessing the impact of COVID-19-related deaths, time off-treatment due to the pandemic, and missed clinical visits, i.e., imaging assessments for efficacy, due to the pandemic. For each of these three objectives, we examined the effects by varying both the timing of pandemic onset relative to the clinical trial progress and the duration of the pandemic. The analysis was based on the assumption that the COVID-19 cohort was well defined based on the collected data.

The schematic diagram of the trial design is shown in Figure 1. We considered a Phase III randomized controlled trial in patients with non-small-cell lung cancer (NSCLC) during the pandemic. The primary time-to-event endpoints were PFS and/or OS (Supplementary Figure 1). In the study, 530 patients (enrolled into the study according to a quadratic distribution with a recruitment duration of 29 months) were randomized with 1:1 ratio into two treatment arms, i.e., Standard of Care (SoC) and experimental treatment. The primary endpoint was PFS and OS was a secondary endpoint. Overall power was 90% for PFS and final analysis (FA) maturity was approximately 59% for both PFS and OS. The simulated FA time for PFS was at the end of 5 years after first-patient-randomized (FPR) and the FA time for OS was 15 months after the PFS FA time. We assumed that the actual PFS and OS times for the SoC followed an exponential distribution, with a median of 26 months and 38.6 months, respectively. Under the alternative hypothesis, the PFS and OS hazard ratios (HRs) for the experimental arm versus control arm were 0.69 and 0.72, respectively; under the null hypothesis, the HR was 1 for both PFS and OS. The start of the pandemic corresponded with the enrollment stage, with the global pandemic starting approximately 13 months after the first patient was randomized.

The impact on the following parameters was assessed: HR estimate; type I (false positive) error; and power to detect a hypothesized treatment difference. Let Z be the indicator of treatment arm, where $Z = 1$ for the innovative treatment and $Z = 0$ for SoC. The primary analysis is to test whether

$$H_0 : \mu_0(t) = \mu_1(t) \text{ versus } H_1 : \mu_0(t) \neq \mu_1(t),$$

where $\mu_0(t)$ and $\mu_1(t)$ are the hazards of having event at time t for the SoC and treatment groups, respectively. The null hypothesis H_0 implies that there is no treatment effect. The log-rank test is used to test the hypothesis with nominal Type 1 error rate 0.05. Under the proportional hazards assumption, the hazard functions can be expressed as

$$\mu_1(t) = \text{HR} \times \mu_0(t),$$

where HR is the hazard ratio between the two groups. A HR < 1 indicates that the treatment group improves survival compared to the control (SoC) group. The Cox regression model is used to estimate the HR in the analysis.

To assess the impact of COVID-19 in broader settings, we assumed that the pandemic began at 35 or 53 months after FPR, i.e., 24 or 6 months before the FA data cut-off (DCO),

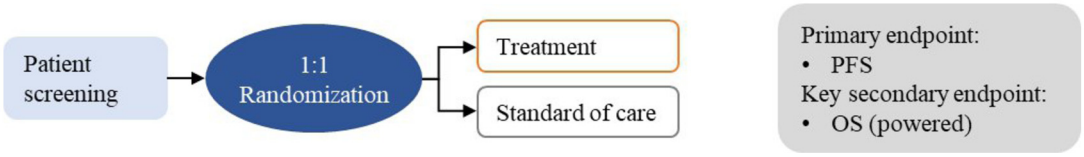

Figure 1: Schematic diagram of clinical trial design in the simulation.

and the pandemic duration was 3, 6, or 9 months. We assumed that scheduled visits for tumor assessments began at 8 weeks ± 1 week after randomization, then every 12 weeks ± 1 week up to 116 weeks (relative to the date of randomization), then every 16 weeks ± 1 week until 3 years after randomization, and then every 6 months until objective disease progression.

2.2 Simulation of the Impact of COVID-19-Related Deaths on OS/PFS

It was assumed that K patients at risk had COVID-19-related death within the pandemic window, where K was an arbitrary number based on evaluating the impact of COVID-19-related deaths from 1% to 5% of target events. For example, if the target number of events was 300, there would be 1 to 15 COVID-19-related deaths. For these K patients, the updated event calendar date was the minimum of calendar date from first step or COVID-19-related death date, whichever came first. The analysis date was the date when updated number of events within the analysis set reached the target number.

Two analysis populations were considered, i.e., the original intent-to-treat (ITT) population for the pandemic scenario, and a modified ITT (mITT) population, which excluded ITT population patients with COVID-19-related deaths from the analysis, for the pre-/post-pandemic scenario. Three additional analysis strategies, i.e., censoring COVID-19-related deaths and redefining data cut-off [CP]; censoring COVID-19-related deaths with current data cut-off [CS]; and competing risk [CR] were detailed in Table 1. For the approaches using the ITT and mITT populations, and the CP and CS analysis strategies, we used a univariate Cox model to estimate the HR and quantify potential bias in treatment benefit, and a log-rank test with Efron's tie handling approach to evaluate power and type I error rate. The Fine–Gray model (Fine and Gray, 1999) was used for the CR approach.

To simulate the impact of COVID-19-related deaths on time-to-event outcomes (i.e., pandemic scenario), time-to-event data without COVID-19 deaths (i.e., no pandemic scenario) was first simulated with the general study design assumptions. The pandemic window, in which patients at risk (ongoing on study without an event) had a chance of dying due to COVID-19, was then determined. Three scenarios were considered: 1) risk of COVID-19-related deaths was equal for patients at risk in both treatment arms; 2) risk of COVID-19-related deaths was mainly in the experimental arm; 3) risk of COVID-19-related deaths was mainly in the control arm. The pandemic start time was fixed at April 1, 2020 (assuming a global outbreak starting from Q2 2020), when evaluating the impact of COVID-19-related deaths on the primary analysis. The evaluation of the impact of COVID-19-related deaths was based on 10,000 simulations.

To quantify the impact on bias in HR estimate, type I error rate, and power within each of the three COVID-19-related deaths scenarios, we simulated sub-scenarios from 1 up to 15 COVID-19-related deaths, representing approximately 5% of target number events at FA for each trial. Short-term (3 months) and long-term (12 months) pandemic windows were also defined, assuming that COVID-19-related deaths were distributed uniformly within these windows. The

Table 1: Analysis approaches used in simulations of pandemic and pre-/post-pandemic scenarios.

Population (Scenario)	Characteristic	Questions/Estimand assessed
ITT population (pandemic scenario)	Includes all deaths due to any cause	What is the impact of the pandemic on survival & treatment benefit vs. control? What is the impact of treatment on COVID-19-related deaths?
mITT population (pre-/post-pandemic)	Excludes patients with COVID-19 -related death from ITT population	What is the treatment benefit vs. control in the absence of a pandemic?
CP approach (pre-/post-pandemic)	Patients are censored at the time of COVID-19-related death; the data cut-off is redefined	What is the treatment benefit vs. control in the absence of a pandemic, accounting for COVID-19-related deaths by modifying the follow-up period to mitigate for the loss of events?
CS approach (pre-/post-pandemic)	Patients are censored at the time of COVID-19-related death; the original data cut-off is used	What is the treatment benefit vs. control in the absence of a pandemic, accounting for COVID-19-related deaths without modifying the follow-up period?
CR approach (pre-/post-pandemic)	Analyzes the times to all deaths due to any cause	When do COVID-19-related deaths occur in the trial compared to disease related deaths, and how does it impact survival outcomes?

Abbreviations: COVID-19: coronavirus disease 2019; CP: censoring COVID-19-related deaths and redefining data cut-off; CR: competing risk; CS: censoring COVID-19-related deaths with current data cut-off; ITT: intent-to-treat; mITT: modified intent-to-treat.

impact of the timing of a fixed pandemic window of 3 months relative to the timing of the DCO for the FA was also assessed, with COVID-19-related deaths fixed at 15.

2.3 Simulation of the Impact of Time Off-Treatment on OS/PFS

To assess the impact of COVID-19 in broader settings, we assumed that the pandemic began at 35 or 53 months after FPR for PFS, and at 35, 53, or 68 months after FPR for OS. Pandemic duration was 3, 6, or 9 months. If the pandemic occurred 6 months before FA, then the pandemic duration was 3 or 6 months.

We assumed that 10% or 30% of patients came off-treatment during the pandemic (i.e., these patients did not get any treatment during the pandemic), and that there was an equal chance of coming off-treatment in both arms. We assumed a multiplicative factor of 1.0 or 1.1 for the hazard rate in the control arm and a multiplicative factor of 1.4 for the hazard rate in the experimental arm due to time off-treatment. This was to simulate that without receiving the experimental drug, the hazard rate would be similar to that of the control arm. The multiplicative

factor of 1.4 for the hazard rate in the experimental arm means that, if off-treatment, the HR for PFS is 0.97 (1.4×0.69) and the HR for OS is 1.0 (1.4×0.72) when assuming no increased or decreased hazard in the control arm due to the pandemic (multiplicative factor for the control arm is 1.0).

There are two possible consequences of coming off treatment. First, the missed visits may cause difficulty in the ascertain of cancer progression status. The operational impact of off-treatment due to missed visits was assessed by simulation of the missed visits in the next section. Second, time off-treatment may have results in different excess hazards for the patients in two arms. Patients in the experimental arm tend to be impacted more than those in the control arm. When both the probability of missed visits and impact/excess hazard of off-treatment occur, the impact on survival analysis is more complicated and hard to disentangle.

2.4 Simulation of the Impact of Missed Visits on PFS

The survival times could be censored due to incomplete follow-up or competing events (e.g., dropout). If a censoring time C occurred before the actual event time T^*, the actual observed event time $T = \min(C, T^*)$. To minimize the impact of missing visits, the patients who progressed or died after 2 or more consecutive missed visits may be censored at the last non-missing visit time; this is referred to as the 2-missed-visits rule (Denne et al., 2013). The 2-missed-visit censoring rule was defined as follows. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 assessment. However, if the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2-missed visits instead of using disease progression; the same applied if a COVID-19-related death was reported by the investigator (note: a non-evaluation visit was not considered a missed visit) (US Food and Drug Administration, 2020).

For the analysis of the impact of missed visits on PFS, two approaches were considered, where a 2-missed-visit censoring rule either was or was not applied. If the 2-missed-visit rule was not applied, censoring only occurred when the actual date of PFS or OS happened after the end of the study. The date of death or disease progression, whichever occurred first, was assumed to be known for these scenarios. The missing status for each visit was generated from Bernoulli distributions with missing probability P. Two types of missing mechanisms were considered. In the first scenario (patient-level missing), we assumed that a patient missed all scheduled visits during the pandemic, with a probability of P. In other words, $P \times 100\%$ patients missed all scheduled visits. In the second scenario (visit-level missing), we assumed that for each patient, the scheduled visits during the pandemic had a probability of P for being missed. We assumed that the missing probability $P = 25\%$ or 50%, representing moderate or high missing rates.

When the censoring is informative (not random), methods such as inverse probability of censoring weights (IPCW) may be used to restore the balance between treatment arms (Robins and Finkelstein, 2000; Lipkovich et al., 2016). In the current analysis, we examined the impact of COVID-19 on the Phase III clinical trials with registration purpose. In this situation, Cox model and the log-rank tests are the primary analysis methods accepted by the regulatory agencies, where only certain modifications e.g., definition of events and censoring or change of study duration are acceptable in protocol amendment. The IPCW and related methods can be used as sensitivity analysis, but are not considered as the primary analysis in this simulation.

3 Results

The simulation results are summarized below. Further details are available in the Supplementary Material.

3.1 Impact of COVID-19-Related Deaths on OS/PFS

3.1.1 Imbalance in COVID-19-Related Deaths

We only present the results of the simulation of the impact of the pandemic on OS. Simulations of the impact on PFS were also conducted but, as the results are similar, are not presented in this manuscript. The results presented here reflect the operating characteristics at IA and FA.

If the pandemic window was short with 3 months, under the null hypothesis of no treatment benefit, the impact of COVID-19-related deaths on HR estimates was negligible, with type I error maintained at nominal level, across all approaches when the risk of COVID-19-related deaths was equal for patients at risk in both arms (Table 2 and Supplementary Figure 2(a)). When the risk was mainly in either the experimental arm or the control arm, the ITT and CP approaches were associated with severe bias in HR estimates, with varying degrees of impact on type I error, whereas neither HR estimates nor type I error were severely affected with the approaches in which COVID-19-related deaths were either excluded (mITT approach: slight impact) or censored (censoring COVID-19-related deaths and redefining data cut-off (CP approach) and censoring COVID-19-related deaths with current data cut-off (CS approach): negligible impact) (Table 2 and Supplementary Figure 2(a)). Under the alternative hypothesis, under all three scenarios for occurrence of COVID-19-related deaths in different arms, both power and HR estimates were affected (severely when the risk was mainly in either the experimental arm or the control arm) with the ITT and CP approaches; approaches in which COVID-19-related deaths were either excluded or censored were not associated with severe impact on power and unbiased HR estimates, with the least impacted strategies being the censoring approaches, CP and CS (Table 2 and Supplementary Figure 2(b)).

In summary, COVID-19-related deaths led to power loss and biased treatment effect estimation, with the impact being more severe when there are more COVID-19-related deaths in the experimental arm. Censoring COVID-19-related deaths (CP and CS approaches) would minimize the impact on power and HR estimation. Power loss could be further minimized by extending DCO (CP approach), to mitigate for the loss of events due to censoring.

3.1.2 Three-Month Versus 12-Month Pandemic Duration

Similar trends were seen for power and HR estimates, when a long-term pandemic window of 12 months was applied under both the null hypothesis (no data presented) and the alternative hypothesis with the same number of COVID-19 related deaths (Supplementary Figure 3). This demonstrates that the length of the pandemic window has little impact on power and HR estimates.

The timing of the pandemic window relative to the timing of the case study is presented in Supplementary Figure 1. Simulations of the impact of the pandemic timing on OS were based on a 3-month pandemic window, assuming approximately 5% of all deaths were COVID-19-related (Tables 3, 4 for null and alternative hypotheses respectively and Supplementary Figure 4).

With a fixed number of COVID-19-related deaths and length of pandemic window, the approaches using the ITT and mITT populations were affected by the timing of the pandemic

Table 2: Impact of COVID-19-related deaths (estimated 15 deaths) on type I error, HR estimates, and power of OS with a short-term pandemic window under null and alternative hypotheses.

Null hypothesis										
Risk of COVID-19 related death	ITT population		mITT population		CP approach		CS approach		CR approach	
	size	HR	size	HR	size	HR	size	HR	size	HR
Equal risk for both arms	Maintained at nominal level (increase up to <0.1%)	Negligible bias (decrease up to <0.001)	Maintained at nominal level (increase up to <0.1%)	Negligible bias (decrease up to <0.001)	Maintained at nominal level (decrease up to <0.1%)	Negligible bias (0)	Maintained at nominal level (increase up to <0.1%)	Negligible bias (decrease up to <0.001)	Maintained at nominal level (increase up to 0.1%)	Negligible bias (decrease up to <0.001)
Mainly in treatment arm	Decrease (up to 2%)	Severe increase (up to 0.11)	Decrease (up to <0.5%)	Increase (up to 0.01)	Maintained at nominal level (increase up to <0.1%)	Negligible bias (0)	Maintained at nominal level (increase up to 0.1%)	Negligible bias (increase up to <0.001)	Severe increase (up to 5%)	Severe decrease (up to 0.07)
Mainly in control arm	Severe increase (up to 10%)	Severe decrease (up to 0.10)	Increase (up to 1%)	Decrease (up to 0.01)	Maintained at nominal level (decrease up to <0.1%)	Negligible bias (decrease up to <0.001)	Maintained at nominal level (decrease up to <0.1%)	Negligible bias (decrease up to <0.001)	Decrease (up to 2%)	Severe increase (up to 0.08)
Null hypothesis										
Risk of COVID-19 related death	ITT population		mITT population		CP approach		CS approach		CR approach	
	size	HR	size	HR	size	HR	size	HR	size	HR
Equal risk for both arms	Decrease (up to 4%)	Increase (up to 0.01)	Decrease (up to 2%)	Negligible bias (increase up to <0.001)	Maintained at nominal level (decrease to <0.5%)	Negligible bias (increase up to <0.001)	Decrease (up to 2%)	Negligible bias (up to 0)	Decrease (up to 3%)	Increase (up to <0.01)
Mainly in treatment arm	Severe decrease (up to 38%)	Severe increase (up to 0.09)	Decrease (up to 6%)	Increase (up to 0.01)	Maintained at nominal level (decrease up to <0.5%)	Negligible bias (increase up to <0.001)	Decrease (up to 3%)	Negligible bias (increase up to <0.001)	Increase (up to 11%)	Severe decrease (up to 0.05)
Mainly in control arm	Severe increase (up to 16%)	Severe decrease (up to 0.06)	Increase (up to 1%)	Decrease (up to 0.01)	Maintained at nominal level (decrease to 0.1%)	Negligible bias (increase up to <0.001)	Decrease (up to 2%)	Negligible bias (increase up to <0.001)	Severe decrease (up to 26%)	Severe increase (up to 0.06)

Abbreviations: COVID-19: coronavirus disease 2019; CP: censoring COVID-19-related deaths and redefining data cut-off; CR: competing risk; CS: censoring COVID-19-related deaths with current data cut-off; HR: hazard ratio; ITT: intent-to-treat; mITT: modified intent-to-treat; OS: overall survival. All analysis assumes up to 5% COVID-19-related deaths (15 events). Onset of the pandemic is fixed at approximately 13 months after first patient randomized.

relative to the progress of the trial. The earlier the timing of the pandemic window relative to final analysis, the greater the power loss when using the ITT population; when using the mITT population, the closer the timing of the pandemic window relative to final analysis, the greater the impact on power.

3.1.3 Mitigation Strategy of COVID-19-Related Deaths

In the evaluation of COVID-19 related deaths in randomized oncology trials, we assume the COVID-19 pandemic will end after certain time window, where COVID-19 pandemic will end eventually, or COVID-19 symptom become mild. With this assumption, the scientific question practitioners would like to address in the late phase randomized oncology trial is, what is the treatment benefit in terms of overall survival (or other time to event endpoint) of a new regimen compared to the standard therapy post pandemic, where COVID-19-related deaths are unlikely to occur in real-world clinical practice post pandemic.

Under the three hypothetical scenarios of COVID-19-related death discussed in the manuscript, i.e, 'equal risk for patient in both arms', 'mainly in the experimental arm' or 'mainly in the control arm', if we use the ITT approach and treat COVID-19-related death as event at the time, the cause-specific COVID-19-related HRs are 1, positive infinity, and 0, corresponding to the three scenarios. This would cause bias in estimating HR of interest, which is the treatment benefit of the experimental therapy compared to the SoC post pandemic.

Both the CP and CS approaches follow the ITT principle and the hypothetical strategy for handling intercurrent event (International Conference on Harmonization, 2019): All subjects randomized will be included in the analysis; a COVID-19-related death is censored at the time when event occurs. The difference between the CP and CS approaches is that the CP approach requires real-time monitoring COVID-19-related death and is an event-driven analysis based on updated data-cut-off for counting only non-COVID-19 related death. While the CS approach performs event-driven analysis based on deaths due to any causes.

Compared to the ITT approach that treats COVID-19-related death as an event at the time when it occurs, the CP and CS methods, on the other hand, will follow patients until the COVID-19-related events occur and censor them at the event times. The assumption is the patient censored due to COVID-19-related death has the same hazard of tumor progression or death due to disease progression as those not censored. Thus, it mitigates the risk of bias in estimating HR of the treatment benefit and also the risk of type 1 error issues under the null hypothesis (Supplementary Figure 2).

For all oncology trials during pandemic, it is critical to record COVID-19 related information for all patients who have discontinue due to COVID-19. From an analysis perspective, both CS and CP method are recommended options for time to event analysis for oncology trials with suspicious COVID-19-related death during pandemic.

For the CS approach, the efficacy analysis should be performed based on the target number of events including COVID-19 related deaths. Therefore, the original time line is still retained (comparing to the ITT approach and treat COVID-19-related death as event at the time when event occur). The CS approach may be ideal for the following scenarios where extended followup is not a good option: 1) it is very close to readout when COVID-19 evaluation just begins; 2) Event accumulation dramatically slows down by the end of the study and it might take a very long time to recover the event loss due to COVID-19-related deaths; 3) Extended follow-up is a concern for other reasons, like cross-over to new anti-cancer therapy.

The CP approach is preferred if extended follow-up is not a concern. Since for most oncology

Table 3: Impact of timing of the pandemic relative to the timing of the clinical trial on OS with a short-term pandemic window under null hypothesis.

Risk of COVID-19 related death	ITT population		mITT population		CP approach		CS approach		CR approach	
	size	HR	size	HR	size	HR	size	HR	size	HR
Equal risk for two arms										
30m before FA	Maintained at nominal level (increase <0.1%)	Negligible bias (increase up to <0.001)	Maintained at nominal level (increase 0.1%)	Negligible bias (0)	Maintained at nominal level (increase 0.1%)	Negligible bias (0)	Maintained at nominal level (increase 0.1%)	Negligible bias (decrease <0.001)	Maintained at nominal level (increase 0.1%)	Negligible bias (decrease up to <0.001)
3m before FA	Maintained at nominal level (decrease <0.1%)	Negligible bias (decrease up to <0.001)	Maintained at nominal level (increase 0.1%)	Negligible bias (decrease <0.001)	Maintained at nominal level (decrease <0.1%)	Negligible bias (0)	Maintained at nominal level (decrease 0.1%)	Negligible bias (decrease <0.001)	Maintained at nominal level (decrease 0.1%)	Negligible bias (decrease up to <0.001)
Higher risk in treatment arm during pandemic										
30m before FA	Decrease (2%)	Severe increase (0.11)	Decrease (1%)	Increase (0.03)	Maintained at nominal level (decrease <0.1%)	Negligible bias (0)	Maintained at nominal level (decrease 0.2%)	Negligible bias (increase <0.001)	Increase (3%)	Decrease (0.05)
3m before FA	Decrease (1%)	Increase (0.05)	Decrease (2%)	Severe increase (0.09)	Maintained at nominal level (0)	Negligible bias (decrease <0.001)	Maintained at nominal level (decrease <0.1%)	Negligible bias (0)	Maintained at nominal level (increase 0.2%)	Decrease (0.01)
Higher risk in control arm during pandemic										
30m before FA	Severe increase (10%)	Severe decrease (0.10)	Increase (2%)	Decrease (0.03)	Maintained at nominal level (increase <0.1%)	Negligible bias (increase <0.001)	Maintained at nominal level (decrease <0.1%)	Negligible bias (increase <0.001)	Decrease (2%)	Increase (0.05)
3m before FA	Increase (3%)	Decrease (0.05)	Increase (8%)	Severe decrease (0.08)	Maintained at nominal level (decrease <0.1%)	Negligible bias (increase <0.001)	Maintained at nominal level (0)	Negligible bias (0)	Maintained at nominal level (decrease 0.3%)	Increase (0.01)

Abbreviations: COVID-19: coronavirus disease 2019; CP: censoring COVID-19-related deaths and redefining data cut-off; CR: competing risk; CS: censoring COVID-19-related deaths with current data cut-off; FA: final analysis; HR: hazard ratio; ITT: intent-to-treat; mITT: modified intent-to-treat; OS: overall survival. All analysis assumes fixed 5% COVID-19-related deaths (15 deaths).

Table 4: Impact of timing of the pandemic relative to the timing of the clinical trial on OS with a short-term pandemic window under alternative hypotheses.

Risk of COVID-19 related death	ITT population		mITT population		CP approach		CS approach		CR approach	
	size	HR	size	HR	size	HR	size	HR	size	HR
Equal risk for both arms										
30m before FA	Loss (4%)	Increase (0.01)	Loss (3%)	Negligible bias (increase 0.001)	Maintained at nominal level (increase 0.2%)	Negligible bias (decrease <0.001)	Loss (2%)	Negligible bias (increase <0.001)	Loss (3%)	Negligible bias (increase 0.001)
3m before FA	Loss (2%)	Increase (<0.01)	Loss (3%)	Increase (<0.01)	Maintained at nominal level (decrease 0.2%)	Negligible bias (0)	Loss (1%)	Negligible bias (0)	Loss (1%)	Negligible bias (increase <0.001)
Higher risk in treatment arm during pandemic										
30m before FA	Severe loss (36%)	Severe increase (0.09)	Severe loss (15%)	Increase (0.03)	Maintained at nominal level (increase 0.3%)	Negligible bias (decrease; <0.001)	Loss (2%)	Negligible bias (0)	Increase (7%)	Decrease (0.03)
3m before FA	Severe loss (13%)	Increase (0.03)	Severe loss (25%)	Severe increase (0.06)	Maintained at nominal level (increase <0.1%)	Negligible bias (decrease <0.001)	Loss (1%)	Negligible bias (increase <0.001)	Maintained at nominal level (increase <0.1%)	Decrease (<0.01)
Higher risk in control arm during pandemic										
30m before FA	Severe increase (15%)	Severe decrease (0.06)	Increase (8%)	Decrease (0.03)	Maintained at nominal level (increase 0.2%)	Negligible bias (0)	Loss (2%)	Negligible bias (decrease <0.001)	Severe loss (15%)	Increase (0.03)
3m before FA	Increase (9%)	Decrease (0.03)	Severe increase (15%)	Severe decrease (0.06)	Maintained at nominal level (decrease <0.1%)	Negligible bias (increase <0.001)	Loss (1%)	Negligible bias (0)	Loss (3%)	Increase (<0.01)

COVID-19: coronavirus disease 2019; CP: censoring COVID-19-related deaths and redefining data cut-off; CR: competing risk; CS: censoring COVID-19-related deaths with current data cut-off; FA: final analysis; HR: hazard ratio; ITT: intent-to-treat; mITT: modified intent-to-treat; OS: overall survival. All analysis assumes fixed 5% COVID-19-related deaths (15 deaths).

studies, COVID-19-related deaths are rare (unlikely to be greater than 10 events), a reasonable extended followup time of no more than 2–3 months is enough (Supplementary Figure 5). In most cases, extended recruitment is not necessary since most randomized Phase III studies are adequately powered for registration potential. And through simulation, we show no power loss if the CP approach is applied and negligible power loss for the CS approach. For studies that are still at design stage, COVID-19-related discontinuation from recent studies should be accounted for when calculating the annual drop-out rate in the sample size calculation.

3.2 Impact of Time Off-Treatment Due to COVID-19 on OS/PFS

The impact of time-off-treatment on HR estimates and type I error rate under the null hypothesis for PFS is presented in Supplementary Table 1, and the impact on HR estimates and power of PFS under the alternative hypothesis in Supplementary Table 2.

In the scenario where patients in the experimental arm had excess hazards due to time-off-treatment resulting in an HR of 0.97 for PFS, simulations showed a moderate impact of time off-treatment on type I error rate, the power of PFS at FA and HR estimates.

Similar results were observed in the scenario where patients in both the control and experimental arms had excess hazards due to time off-treatment, resulting in a HR of 0.88 for PFS, with simulations showing a modest impact on type I error rate, power, HR estimates at final PFS analysis. Equally, similar results were observed for the simulations of the impact of time off-treatment on OS. Data are presented in Supplementary Tables 3 and 4.

3.3 Impact of Missed Visits Due to COVID-19 on OS/PFS

The number of patients impacted by the 2-missed-visit censoring rule during the COVID-19 pandemic is presented in Figure 2. The two vertical lines on the left are the starting and ending times of the COVID-19 pandemic. The top curve is the number of PFS events for the 530 patients and the middle curve shows the number of patients who have 2 missed visits due to pandemic; missed visits may occur after tumor progression. The bottom curve shows the number of patients with PFS events who are impacted by the 2-missed-visits censoring rule. Firstly, the following scenario was considered: the COVID-19 pandemic started 35 months after first-patient-randomized; the pandemic had a duration of 9 months; 54% (307/530) of patients had a PFS event; all more than 2 missed visits were due to the pandemic, with patients otherwise compliant; and the patient-level missing probability was 50% during the pandemic. This is shown as the top-left plot in Figure 2. In this scenario, the proportion of patients having at least 2 missed visits was 32% (170/530), and the proportion of patients with PFS events impacted by at least 2 missed visits was 11% (59/530).

With a patient-level missing probability of 25% during the pandemic, the proportion of patients having at least 2 missed visits and of patients with PFS events impacted by at least 2 missed visits was reduced, to 16% (86/530) and 6% (31/530), respectively. In a similar scenario with a 3-month duration of the pandemic duration, the proportion of patients having at least 2 missed visits and of patients with PFS events impacted by at least 2 missed visits was further reduced to 3% (15/530) and 1% (6/530), respectively. With a visit-level missing probability of 50% during the pandemic, these proportions were 24% (128/530) and 8% (42/530), respectively.

When considering the impact of missed visits on the power for PFS at IA, assuming a patient missing all visits during the pandemic with a probability of 50%, PFS analyses with a 2-missed-visits censoring rule resulted in a power reduction of approximately 5% from 67% at IA, if the

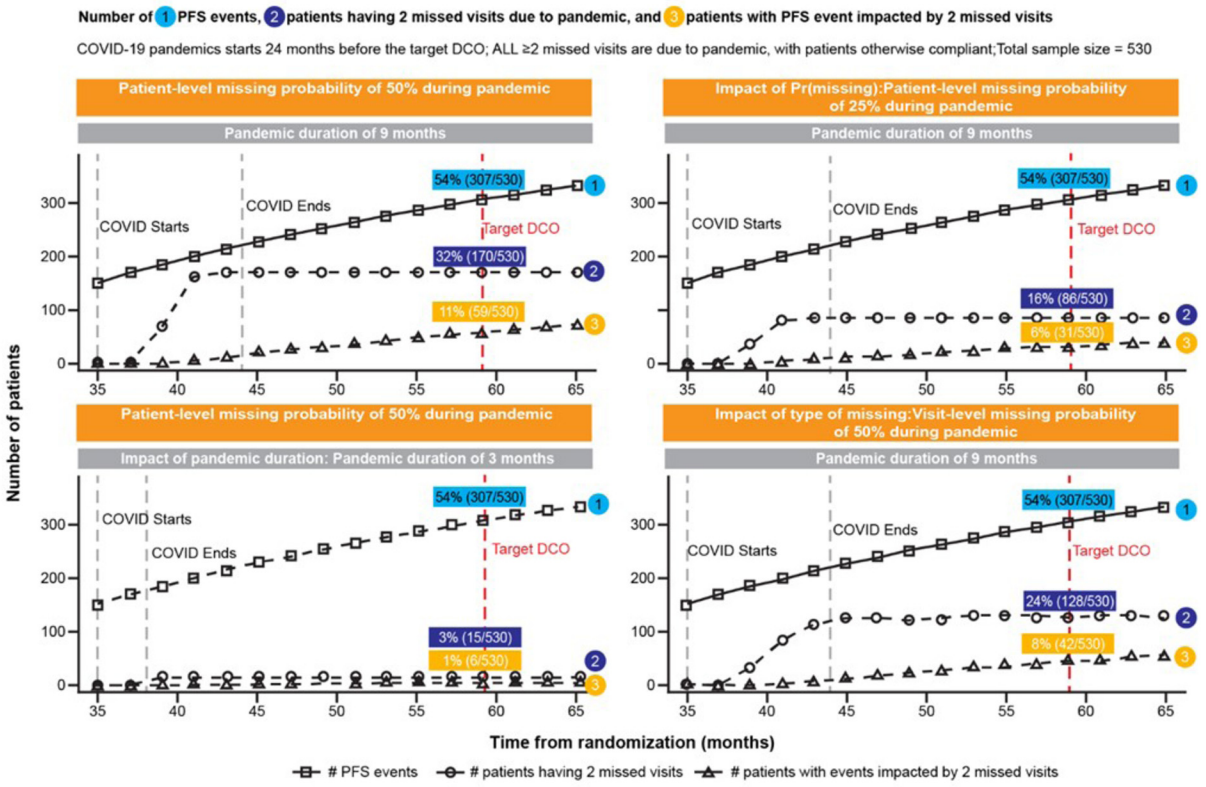

Figure 2: Number of patients being impacted by COVID-19 pandemic in the PFS analysis.

pandemic started 24 months before target DCO for FA and lasted longer (6 months). If the 2-missed-visits censoring rule was not applied, the impact on power was negligible (Supplementary Table 5).

In terms of impact on the power for PFS at FA (target power of 90%), with the same assumptions, PFS analyses with a 2-missed-visits censoring rule resulted in a reduction in the power of approximately 6.6% if the pandemic started 24 months before target DCO for FA and lasted longer (6–9 months). If the 2-missed-visits censoring rule was not applied, the impact on power was negligible (Supplementary Table 6).

With an expected type I error rate of 5%, the inflation of type I error rates was minimal if the 2-missed-visits censoring rule was not applied, with no apparent differences between probabilities of missing visits of 25% and 50% (Supplementary Table 7).

4 Discussion

Because ongoing oncology trials were initiated before the start of the COVID-19 pandemic, they were designed to assess the benefit of experimental drugs in a world without a pandemic, and survival endpoints were the outcomes of interest to determine benefit versus controls. In the context of the COVID-19 pandemic, it is reasonable to assume that some of the deaths recorded in oncology trials will result from complications due to COVID-19, with early evidence showing a disproportionately higher prevalence of COVID-19 in patients with cancer compared with the general population (Bakouny et al., 2020, 2022). Therefore, when assessing treatment benefit

with an experimental oncology drug, it is crucial to understand the impact of the COVID-19 pandemic on survival (time-to-event) outcomes. Simulations were conducted to provide a basis for understanding when modifications to trials, such as delaying DCO or enrolling additional patients to ensure adequate power, might be required.

The simulations performed in these analyses sought to assess the impact of the COVID-19 pandemic on phase III oncology trials, specifically assessing the impact of COVID-19-related deaths, time-off-treatment, and missed visits on survival outcomes, further examining the effects of varying both the timing of the pandemic onset relative to the progress of the trial and the duration of the pandemic. Simulations of the impact of COVID-19-related deaths on OS showed a more severe impact in terms of power loss (up to $> 35\%$) and introduction of bias in HR estimation when there was an imbalance in COVID-19-related deaths in the experimental arm. Simulations also indicated this could be addressed by censoring patients at the time of COVID-19-related death with an updated DCO (i.e., CP approach, with longer study duration), which would mitigate for power loss and potential impact on HR estimates. Censoring COVID-19-related deaths with the current DCO would be the preferred alternative if an updated DCO was not an option (due to high maturity or competing timeline), as it could minimize power loss and provide unbiased HRs.

It has been suggested that the Fine and Gray's competing risk regression modeling should not be used in the causal inference (Allison, 2018). With this approach, patients who die from COVID-19-related causes are considered in the at-risk set for non-COVID-19-related death, which explains the severe impact on type I error and bias in HR when COVID-19-related deaths are mainly in the experimental arm. Moreover, in our simulations, the pandemic was assumed to last only for part of the study duration (study initiation prior to pandemic starting time), with an assumed pandemic window shorter than the overall study duration. Therefore, interpreting treatment effect based on Fine and Gray's competing risk regression modeling may be misleading.

In our simulations around the timing of the pandemic relative to trial progress, with a fixed number of COVID-19-related deaths and length of pandemic window, the earlier the timing of the pandemic window, the greater the power loss. Censoring analysis strategies, particularly the CP strategy with an updated DCO, would not be affected by the pandemic time window, and would provide minimal power loss and unbiased HR estimates, regardless of which treatment arm was mainly impacted by the pandemic. The approaches using the ITT or mITT populations would make the analysis sensitive to the timing of the pandemic; a more severe impact would be observed with the approach using the ITT population when the pandemic occurs at the early stages of the trial, and with the approach using the mITT population when the pandemic occurs close to FA. Additionally, both approaches may inflate type I error when the COVID-19-related deaths occur mainly in the control arm. Importantly, although the simulations of the impact of COVID-19-related deaths on time-to-event outcomes presented here focus on the impact on OS, the results of simulations on the impact of COVID-19-related deaths on PFS provided similar results, indicating that these observations can also be applied to PFS.

The key learning from this first set of analyses for future trials is that if the risk of COVID-19-related deaths is equal for patients at risk in the study arms, there will be no change in HR, but there might still be an impact of the pandemic on treatment benefit. This is consistent with the argument made by Hernan (2010), since HR tends to be time-varying and does not reflect the distribution of events over the follow-up. In this analysis, we used HR as the primary measure of treatment effect because we considered a Phase III clinical trial with registration intent. When HR is time-varying, a single HR may not be the appropriate summary measure of treatment benefit. Cumulative survival, restricted mean survival time (RMST) and other

alternative measures may be supplemented.

If there is an imbalance in COVID-19-related deaths between study arms, COVID-19-related deaths would need to be monitored, and there might be an impact on survival outcomes depending on the relative proportion of such deaths. This would need to be addressed by either deciding to change the protocol upfront (i.e., blanket protocol changes, such as extended DCO and enrollment of additional patients, across hundreds of trials), or through a more targeted approach (i.e., implementing changes to the protocol only when the number of COVID-19-related deaths might have an impact on study outcomes). Because a blinded review would not allow for such potential imbalances to be identified, sponsors could set a pre-specified threshold of events (based on simulations) and propose a protocol amendment prior to database lock if the number of events crossed the threshold. Alternatively, sponsors could choose to do an unblinded review through an Independent Data Monitoring Committee.

As a pandemic may cause patients to miss on-study procedures or clinical visits (Serrano et al., 2020; Pinato et al., 2020; Seguí et al., 2020), we assessed the impact of time-off-treatment on HR estimates, type I error, and power. The simulations of the impact of time-off-treatment due to COVID-19 showed a modest impact on power for both PFS and OS, and a moderate impact on type I error and HR estimates. The simulations of the impact of missed visits on the power of PFS with the 2-missed visit censoring rule showed a more severe impact if the duration of the pandemic was 6–9 months, compared with 3 months. If the 2-missed visit censoring rule was not applied, the impact on power was negligible, independently of the duration of the pandemic.

Taken together, the results of our analyses are especially relevant for confirmatory trials, where a negative outcome for the primary analysis results in any additional analysis being considered exploratory in nature. Therefore, any approach that can mitigate the impact of COVID-19 on the primary analysis outcome should be considered, and identifying the primary outcome of interest before determining which analysis strategy to use, is crucial. An additional question is how regulatory agencies will respond at the time of submission. Two investigational products could have the same outcomes for a pandemic-adjusted population and an ITT population. If one study had undergone modifications to adjust for the pandemic, and the other had not, would regulatory agencies approve one drug and not the other? If the primary, unadjusted endpoint was negative and the adjusted endpoint was positive, would companies still be able to submit for regulatory approval? Consequently, it will be important to capture all necessary data related to COVID-19 (in particular, whether cause of death was related to COVID-19) in the electronic case report form, in order to perform the analyses described in this work. Additionally, the strategies proposed here to mitigate the impact of COVID-19-related deaths, time-off-treatment and missed visits could also be applied to other time-to-event outcomes (e.g., event-free survival and disease-free survival).

A limitation of this analysis is that, in practice, not all patients with a severe infection or fatality due to COVID-19 are getting tested. Therefore, it is possible that only a subgroup of the COVID-19-related deaths are captured in the database. As a result, censoring these events may introduce an inherent bias, due to the lack of uniform data reporting across all patients. Additionally, censoring may not be independent of outcome and therefore can itself generate biased estimates. Sponsors should collect all relevant information related to COVID-19 in the database, and collect data beyond those related to death (e.g., adverse events, severe adverse events, objective response rate, or patient-reported outcomes), and attempt to follow-up patients with COVID-19 infection in an effort to better understand its long-term sequelae.

5 Conclusion

The simulations conducted in this analysis provide a framework to help understand when modifications to clinical trials might be required, based on the critical question regulatory agencies want an answer for. The approach using the ITT population would answer the question "What is the treatment benefit of the experimental drug in the presence of the COVID-19 pandemic?", whereas censoring analysis strategies would help to answer the question "Will the experimental drug have treatment benefit post-pandemic?".

With the pandemic set to last for the foreseeable future, it is important to weigh the pros and cons of both options and identify the outcome of interest in oncology trials to determine which option might be most appropriate.

Conflicts of Interest

Binbing Yu, Helen Mann, David Wright, Cristian Massacesi, Serban Ghiorghiu, and Renee Bailey Iacona are all current employees of AstraZeneca. Antony Sabin, Jiabu Ye, Pralay Mukhopadhyay (P.M) and Zsolt Szijgyarto were employed by AstraZeneca at the time of this analysis. P.M. also reports ownership of stocks in AstraZeneca.

Supplementary Material

More comprehensive description of simulation procedure and results are presented in the supplementary material. We also include the codes for simulations. The data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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