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EDITORIAL ARTICLE

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Effects of COVID-19 pandemic on the conduct of clinical trials

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Introduction

The novel coronavirus (SARS-CoV-2) is a new strain of coronavirus that affected the whole world. On 11 March 2020, WHO announced COVID-19 as a pandemic (Organization, 2020). The COVID-19 pandemic has impacted all walks of life including the conduct of clinical trials of medical products globally. The pandemic-related restrictions resulted in difficulties in recruiting new patients or continuing the ongoing trials. ClinicalTrials.gov registered 1773 trials that were suspended between March 2020 and April 2021, the COVID-19 pandemic being the reason for this in the majority of trials (McDermott & Newman, 2021). At the same time, a large number of trials were initiated to test the safety and efficacy of COVID 19 vaccines around the globe (Kim et al., 2021). This article will focus on the effects of the COVID 19 pandemic on the non-vaccine trials. The challenges that were faced by the sponsors and investigators were mainly due to lockdowns, individual quarantines, conversion of trial sites into COVID treatment facilities thereby, forcing the temporary closure of sites, travel restrictions, disruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects became infected with COVID-19.

Healthcare systems in many parts of the world were burdened and, in some places, continue to be so medical personnel was deputed for COVID-19 related activities. These restrictions affected trial monitoring, data collection, and drug supply activities. Moreover, the participants were not willing to visit the trial sites (hospitals) or travel by public transport where they may come in contact with COVID -19 patients. On the other hand, they might have been unable to visit the site during the scheduled visits due to health issues related to COVID infection, for example, self-isolation, quarantine. or hospitalization. They might have taken medication for the treatment of COVID-19 symptoms which were not anticipated at the design stage of a given clinical trial. One more challenge was repeated sample collections required for COVID 19 infection confirmation before every hospital visit. For example in an anticancer drug trial protocol sometimes two swabs are mandated and only after the negative test results trial drug could be administered. If a patient tested positive for COVID-19, a swab test had to show negativity after the quarantine period, and its confirmation at times delayed schedule of the drug administration.

When faced with these challenges, it would have been difficult to adhere to procedures specified in the protocols that are essential for efficacy assessments and to perform diagnostic or laboratory tests. This would result in compromised trial data and problems in the interpretation of clinical trial results.

The impact of these challenges will depend on the severity and duration of each wave of the COVID 19 pandemic, the

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duration of the trial, the disease condition for which the trial is conducted, the type of subjects to be recruited or that were recruited for the trial and trial design elements such as number of visits, the investigation to be carried out during each visit, etc.

When faced with the risks and benefits of continuing clinical trials during the pandemic, the trial personnel had the following alternatives:

- To discontinue trials if no immediate benefits to the participants were observed. As we are aware, the benefits of therapeutic intervention in a randomized trial cannot be predicted until the trial is completed. Some of these trials might be very beneficial for millions of people with chronic, debilitating diseases in the post-pandemic era. The decision to discontinue an ongoing trial would result in a wastage of resources and the time and effort of participants who may have already completed the trial, and of trial personnel.
- If the disruption in subject recruitment or monitoring was substantial it might not have been feasible for the trial to be continued.
- Trials might have been continued, but the data collected during the pandemic period will be suspect, posing many methodological challenges (T. R. Fleming et al., 2020; McDermott & Newman, 2020; Meyer et al., 2020; Wolkewitz & Puljak, 2020). By "suspect" it means that the data might have been collected under different circumstances and in a different manner than specified in the protocol, and may be questionable in terms of its quality (Akacha et al., 2020).
- If the enrolment of the participants was complete before the pandemic, trials may have been continued unchanged if the participants could complete the protocol procedures safely.
- Once the vaccines were available and many enrolled patients had taken either the first or second dose of the vaccine, trial protocols had to be amended to include such vaccinated status of patients mentioned.
- Continued with the trial while replacing the in-person interactions with remote approaches such as using a courier or drop-off services to deliver devices or oral medication (Lenze et al., 2020; McDermott et al., 2021), and telephone or web-based interactions (Depner et al., 2020) to monitor the participants.
- It may be better to delay the initiation of enrolment of participants for trials that had not yet begun, or temporarily stop the enrolment in ongoing trials, based on the site-specific severity of COVID 19 (T. R. Fleming et al., 2020). Once the number of COVID cases comes down, the recruitment may be initiated again.

The U.S. Food and Drug Administration (Food & Administration, 2020), the European Medicines Agency (T. R. Fleming, 2011) (EMA 2020a), and CDSCO (2020) have come out with guidelines for sponsors on how they should manage the clinical trials and participants during the COVID-19 pandemic. The sponsors are required to collect the protocol deviations (PDs) and reasons for discontinuation of clinical trial elements for all ongoing trials. These PDs can be specified separately as COVID-related to differentiate them from other COVID unrelated PDs. EMA published second guidance (EMA 2020b) on actions that sponsors should take for ongoing clinical trials affected by the COVID-19 pandemic. It provides points to consider to reduce the risk of compromising the integrity and interpretability of ongoing trials due to COVID-19 while safeguarding the safety of trial participants as a priority while maintaining compliance with good clinical practice (GCP).

Data integrity is defined as the extent to which all trial data are complete, consistent, accurate, trustworthy, and reliable throughout the data lifecycle (WHO 2019). During the pandemic period, it is essential to adopt methods of data collection that will increase the validity of assessments of safety and efficacy (T. R. Fleming, 2011). Similar to data integrity, trial integrity is another broader trial conduct-related concept, which encompasses data integrity and which refers to the ability of a trial to produce results that are reliable and valid (McDermott & Newman, 2021). It specifically implies that results are not affected by (unknown) biases. For example, unblinding during an ongoing trial can result in a loss of trial integrity (Akacha et al., 2020).

The data collected and the conclusions drawn from a clinical trial are directly affected by data and trial integrity. To avoid loss of data integrity, sponsors should consider other approaches for data collection such as electronic data capture by patients at home, telecommunication, or telemedicine (McDermott & Newman, 2020). Centralized data monitoring, home visits by the site staff, or use of local instead of central laboratories are some of the other options available for the continuation of data collection during the pandemic. Home delivery of the trial medication could be done through courier or personal visit by the site staff, ensuring the stability of the medication and the confidentiality of the participants. Similarly, if the participants are reluctant to visit the hospitals for the trial-related procedure for the fear of traveling by public transport, investigators could arrange for private transport facilities.

Adverse event reporting

Any SAE that is both unexpected and for which there is a reasonable possibility that the investigational product caused the SAE, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event, must be reported to the CDSCO and ethics committee by the sponsor. There is a possibility that the participant who gets

infected with COVID 19 during the trial may develop SAEs that are associated with the disease and not due to the investigational product or the participant may have become more susceptible to developing SAE due to COVID 19 infection. Whether the SAE is causally related or unrelated to the investigational product may be decided only after analysis of the unblinded data and is the responsibility of the Data Monitoring Committee (DMC). Under the pandemic situation, CDSCO is accepting e-mail submissions of SAE reports with electronic signatures. This has helped in the timely submission of safety reports (Davis & Pai, 2020)

Challenges due to intercurrent events, estimands, and missing data

The COVID 19 pandemic affected the clinical trial sites and subjects in terms of conducting the trial as per the protocol, data integrity, and data analysis (Akacha et al., 2020). These challenges could be categorized into two broad categories: those related to administrative and/or operational procedures and those that are related to the impact of the pandemic on the participants.

Table 1: Challenges due to intercurrent events, estimands, and missing data

Sr. No.	Challenges related to administrative or operational procedures	Challenges due to the impact of COVID-19 / the pandemic on the participants
1	Treatment discontinued due to disruption or delay in drug supply	Trial treatment was discontinued due to COVID-19 symptoms
2	Treatment discontinued due to participant's concerns	Intake of additional medications to treat COVID-19 symptoms
3	Failure to carryout procedures such as, laboratory/diagnostic tests or biopsies.	Inability to attend scheduled visits due to COVID-19 infection in participants
4	Missed visits due to personal safety concerns, lockdowns, or quarantines	Exacerbation of chronic conditions such as asthma, hypertension, or diabetes due to inability to visit hospitals
5	Visits outside of the designated time window	Newly occurring symptoms due to pandemic such as depression, altered quality of life
6	Modified visits due to overburdened hospital personnel such as telecommunication with sites, different doctors, etc.	Death due to COVID-19 infection

None of these challenges were anticipated during the designing of the ongoing trials. In the randomized, blinded trials, the effect of this may be expected to be equally distributed in both treatment arms but this may not happen with open-labeled trials. If the clinical trials being carried out are for immunomodulators or immunosuppressants and anticancer drugs affecting the immune status, the treatment arm may show increased complications and subsequent discontinuation of the treatment if the subjects get infected with COVID 19 virus. The severity of the pandemic also varied from country to country and sites may have been affected to a variable degree. Similarly, trials with elderly subjects and those with co-morbidities such as diabetes and hypertension, chronic kidney or respiratory diseases, were more likely to be affected by the COVID 19 and might have been affected by the challenges mentioned in **Table 1**. (Brown et al., 2020; Cawthon et al., 2020).

The pediatric clinical trials too were disturbed by the pandemic. Despite children being less severely affected by COVID-19 in the first and second wave, the pause in trials affected some important studies cross all pediatric domains including many that had taken years to establish (P. F. Fleming et al., 2021). There was an indirect financial loss when this pause resulted in delayed sharing of results that had potential cost-saving implications for the larger patient population (Marshall et al., 2020; Rubio-San-Simón et al., 2020).

ICH E9(R1), introduced the estimand framework to precisely describe the treatment effect of interest in a randomized clinical trial. An estimand is defined in the guidance as *"...the target of estimation to address the scientific question of interest posed by the trial objective"* and has five attributes – population, treatment, variable (endpoint), intercurrent events (defined as events that can occur post-randomization and preclude or affect the interpretation of the variable) and the summary measure (ICH, 2019). An example of an intercurrent event in a clinical trial context could be the discontinuation of treatment. Many of the intercurrent events might have been addressed during the designing stage of the study but the COVID 19 related intercurrent events would not have been. Hence it is important to differentiate between COVID-related and unrelated intercurrent events. In such a situation there is a need to modify the research question to address the unanticipated intercurrent events due to pandemic. The unforeseen intercurrent events due to COVID-19 introduce an element of uncertainty to the original research question that needs to be taken into consideration while analyzing the data (Akacha et al., 2017).

The next challenge faced was the missing data. As per the definition of missing data according to the ICH E9 addendum (ICH 2019): "*Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.*". Missing data results in loss of information and may introduce selection bias. Many of the administrative or operational challenges indicated in Table 1 may lead to missing data such as missed diagnostic tests or missed scheduled visits to the site. If such missing data are not related to the treatment or the health status of the subject, may be that valid inference can be derived based on the available data only, that is, there is no need to model the missingness process (Molenberghs & Kenward, 2007). But if the missing data is due to the health status of the subjects because of the impact of COVID 19 (Column 2 of **Table 1**), then the missing data needs to be accounted for using sensitivity analysis. If such missing data is of significant magnitude, the protocols and statistical analysis plans will have to be reorganized, taking the approval of regulatory authorities, and ethical committees (Akacha et al., 2020).

Collection of Data related to complications due to COVID 19

Data related to a trial participant suffering from confirmed or suspected COVID-19 infection, concomitant medication, and associated outcomes can be captured as adverse events that are mandated to be documented during any clinical trial. Other complications that need to be captured are owing to various other reasons such as:

- Withdrawal of consent or stopping of the drug before the date
- Missed or postponed visits beyond protocol permitted time window
- Alteration in the assessment, for example, done at home or done at local laboratories.

While documenting the complications, it would be prudent to mention the detailed account of the complications as discussed in the above para instead of mentioning 'due to COVID 19". This information will be extremely useful during the handling of missing data and primary and secondary data analyses. Moreover, this will help in understanding the impact of the pandemic on the conclusions drawn from the trial. These can be either captured along the protocol-associated PDs or captured separately.

Finally, it is in the hands of the trialists to decide whether to continue the trial based on the local conditions, possibility, and value of continuing or the burden of discontinuing the trial. Accordingly, changes in the protocols and analysis can be planned and informed to all concerned stakeholders. We still are in the process of learning about the ultimate impact of COVID 19 infection in terms of manifestations due to emerging variants, treatments, and extent of distribution of the disease. Data Monitoring Committees (DMCs) will have a significant role to ensure trial integrity and patient safety (EMA, 2020b).

Moving forward in "New-Normal"

While designing new clinical trials, the lessons learned during the pandemic might be taken into account while designing the protocols.

- The trials conducted in the past have strict requirements for data collection, diagnostic tests/procedures, and assessments. The time windows provided for these may be difficult to keep up for both patients and the trial site, resulting in more PDs, as discussed above. It would be worthwhile to evaluate the effects of these PDs on the trial integrity and data interpretation. Based on these findings the new trial protocols could have more flexible periods and fewer in-person visits and data collection requirements that are related to primary endpoints, without affecting the data and trial integrity (Davis & Pai, 2020). Instead of in-person visits, tele-visits could be considered, keeping the site visits for essential procedures or tests (McDermott et al., 2021); McDermott & Newman, 2021).
- For recruiting the new participants, the investigator will have to follow all COVID-related behaviors (CRB) as mandated by the state and central Government policies. Patient safety, comfort, and protection need to be the main priority while recruiting new patients.
- Investigators and CRAs need to be tech-savvy so that they are prepared for remote monitoring and remote approaches if this becomes an accepted norm in the future. Patient compliance could be improved for remote monitoring by explaining the importance of it and including it in the ICF. Training program for team personnel to handle such situations or SOPs to be framed
- Sponsors could consider risk-based monitoring or central monitoring or remote monitoring to minimize the risk to the monitoring and the site team (Davis & Pai, 2020).
- Sponsors could think about increasing monetary compensation for both the participants and the investigators considering the risk involved in conducting trials during the pandemic.
- Budget provisions should be made to manage unforeseen situations such as home visits by site personnel, door delivery of investigational products, etc.
- In case of injectable trial medication, either the patient or the caregiver may be trained to give subcutaneous injections, or a local nurse after wearing personal protection equipment may be recruited to administer the drug.

- Responsibility and importance of maintaining the investigational product in a safe and secured place, not accessible to other family members including children, have to be intimated to the participants.
- If the trial medication has to be injected at the trial site, administration of injections at clinical facilities capable of achieving adequate social distancing should be considered.
- In case the investigational product is temperature-controlled ambient or cold (−2°C–8°C), stability requirements need to be further evaluated. Door delivery should be undertaken only if the stability can be maintained for the estimated transit duration from the site to the patient's residence (Davis & Pai, 2020)

It would be helpful if the sponsors, investigators, and institutional ethics committees develop Pandemic-associated protocols based on their experience of conducting trials during the COVID 19 pandemic. This would come in handy in case we face any other long-term natural disasters or if the COVID 19 continues to affect our lives.

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Conflict of Interest

None.

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