Review Article

COVID-19 diagnostics and early phase clinical trials: challenges and risk mitigation in the Omicron variants era

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Abstract: The evolution of the coronavirus disease 2019 (COVID-19) pandemic and widespread community of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants continues to present new challenges for early phase clinical trials and COVID-19 diagnostic strategies. Many regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) continue to provide updated guidance on the operations of clinical trials during the pandemic. However, guidance is limited with respect to medical and scientific specific issues, such as COVID-19 diagnostics. Here we discuss, the challenges for early phase studies associated with COVID-19 diagnostics in the Omicron era and potential risk mitigation strategies in the face of continued widespread community transmission. We note how careful consideration and planning can help mitigating the risk of COVID-19 impacting the medical and scientific validity and patient safety in clinical trials. Clinical study design should consider mitigation strategies at the patient, investigator, and clinical research organization (CRO)/Sponsor level following evaluation of the overall for their specific study/investigational product and patient overall wellbeing. Specific language regarding COVID-19-related policies and procedures should be included in the study protocol. Special considerations should be taken for novel immunotherapeutics which may require interruption in the event of a subject developing COVID-19 or for investigative products that may have hazardous interactions with commonly prescribed anti-COVID-19 therapies. Moving forward, its essential for trials to remain adaptable to evolving nature of the pandemic.

Keywords: Coronavirus disease 2019 diagnostics (COVID-19 diagnostics); molecular testing; antigen testing; clinical trials; oncology

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Introduction

The unrelenting and progressive evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to place immense and unpredictable burdens on healthcare systems all around the world. The emergence of the Omicron lineages, characterized by unprecedented infectivity and transmissibility, along with immune escape capacity sufficient to cause symptomatic infection in those vaccinated against coronavirus disease 2019 (COVID-19) (1), has led to widespread community transmission, and further mutation of this lineage, with Omicron sublineage BA.5 now dominant in the United States and in many other countries (2). While this latest variant has been associated with milder illness in most (3), nonetheless Omicron continues to impact the global economy, with supply chain issues and labor shortages impacting nearly every industry, including healthcare and the life sciences, while still causing significant mortality, with ~400–450 deaths reported on average per day in the US in the current BA.5 wave (2).

The ongoing and evolving pandemic has led to significant challenges for clinical research (4), especially early phase trials, whose results are critical for maintaining the pipeline of drug development and the hope for millions around the world, especially those diagnosed with lethal diseases, such as cancer, or other rare diseases, where limited treatments are available. For oncologic patients, early phase trials often represent a last chance after failure with several lines of current standard of care therapy, whilst these studies represent a vital opportunity for industry to obtain the data needed to enable funding and regulatory support for further clinical trials needed to bring a new drug to market. Indeed, we and many others have demonstrated the significant impact on routine cancer screenings caused by the pandemic (4,5). In the United States, there were ~10 million missed cancer screenings between January 2020 to July 2020 (6). This impaired screening, expectedly, led to an increase in severity of cancer at diagnosis, with an 11% increases in patients diagnosed at inoperable or metastatic stage between March-December 2020 as compared to March-December 2019. Similarly, past and ongoing delays in cancer treatment due to the pandemic, will likely further compound this issue. Given this data, it is likely that demand for participation in early phase trials will likely increase in the coming years (7). With the deep and far ranging impact of COVID-19 on cancer research, maintaining drug development and initiation of new clinical trials is critical despite the continued evolution of the pandemic.

Clinical trials have faced challenges in both initiation of new clinical investigations and operations of ongoing studies (8). Many regulatory agencies, including the US Food and Drug Administration (FDA) (9) and the European Medicines Agency (EMA) (10) continue to provide updated guidance on the operations of clinical trials during the pandemic. However, guidance is limited with respect to medical and scientific specific issues, such as COVID-19 diagnostics and test-to-treat public health programs, which may significantly impact the validity of early phase clinical studies. Here we discuss, the challenges for early phase studies associated with COVID-19 diagnostics in the SARS-CoV-2 Omicron era and potential risk mitigation strategies in the face of continued widespread community transmission.

Challenges

Continued widespread community transmission in the Omicron era presents numerous challenges to clinical trials that must mitigate risks associated with COVID-19. This is compounded by a general change in person and societal attitudes regarding the virus and the pandemic (11). Moreover, in the context of widespread transmission, patients may assume a COVID-19 diagnosis without confirmatory test given symptom status, and not report the diagnosis or seek treatment or guidance from their physician. This is also exacerbated by general concerns over the accuracy of diagnostic testing throughout the Omicron era (12-14), as well as by the wish (often by the need) to avoid long periods of mandatory isolation after testing positive in some countries. This has inherently led to widespread use of self-testing using "At-Home" rapid SARS-CoV-2 antigen immunoassays (rapid diagnostic tests; RDTs), whose positive results would then escape official notification, thus contributing to consistently lowering the "real" number of COVID-19 cases around the world.

The lack of recording of a confirmed SARS-CoV-2 infection, even in asymptomatic or mild COVID-19, can confound multiple variables in a clinical trial, with early phase studies at higher risk due to their intrinsic properties, including smaller sample sizes and reliance on biomarker-based endpoints. Undiagnosed or unrecorded COVID-19 can bias interpretation of adverse events, especially with some Omicron sublineages being characterized by more general symptoms (fatigue, myalgia, etc.) and less by pathognomonic symptoms like smell and tase loss (15). Of particular importance to phase 1 studies, the evolving symptomatology of COVID-19, in which an atypical or constitutional Omicron symptom may result in triggering an adverse event (AE) that meets the criteria of a dose limiting toxicity, without other pathognomonic symptoms (fever, cough, etc.). Undetected SARS-CoV-2 during the screening period can lead to inaccurate baseline assessments (or in some cases lead to inaccurate eligibility assessment) and lead to triggering (or lack thereof) of appropriate safety signals during the trial, which may not accurately reflect the medical status of patients.

It should be noted, even mild COVID-19 can lead to substantial derangement of multiple systems resulting in numerous laboratory abnormalities, such as lymphopenia, increase of inflammatory biomarkers and low immunoglobulins, that can persist for several months post-infection (16-18). Moreover, with up to 50% of people experiencing at least 1 post-COVID symptom at 6 months after infection (19), so called "long COVD" can further dilute study observations.

Table 1 Summary of risk mitigation strategies at the patient, investigator/site, and CRO/sponsor level

Patient level	Investigator/site level	CRO/sponsor level
❖ Study ID cards or wristbands ❖ Fact sheets with COVID-19 and vaccine related study procedures described ❖ At-home COVID-19 testing of self and household contacts	❖ Patient education on COVID-19-related study procedures ❖ Access to readily available and accurate COVID-19 testing ❖ Proper recording of COVID-19 tests results ❖ Routine screening of COVID-19 medical history at each study visit and recording results in eCRF	❖ Continual assessment/re-assessment of COVID-19 related trial risks ❖ Site education on COVID-19-related study procedures ❖ Establishment of reporting procedures for COVID-19 test results ❖ Re-screening policies for COVID-19 ❖ Protocol language to address COVID vaccination before and on study

CRO, clinical research organization; COVID-19, coronavirus disease 2019; eCRF, electronic case report form.

A factor particularly important to any trial testing an immunomodulatory investigational product (IP), is the potential impact of SARS-CoV-2 on the immune system, both acutely and long-term. COVID-19 can, even in mild disease, trigger multiple aberrations in immunologic biomarkers, including cell indices and cytokine profiles (16,20). Moreover, research has indicated that immunological dysfunction may persist for up to 8 months after mild or moderate COVID-19, which is characterized by highly activated innate immune cells, a lack of naive T and B cells and elevated expression of interferons (21). As such, immune dysfunction may not only effect measurements of study biomarker endpoints, but may impact as well the efficacy of the IP, thus highlighting the importance of accurate monitoring and recording of SARS-CoV-2 diagnoses throughout the study period.

Finally, while the development of new SARS-CoV-2 therapies has helped improve outcomes and reduce the overall burden on healthcare, it also presents new challenges for some clinical trials. Paxlovid™ , which was granted emergency use authorization in December 2021 by the FDA, is a combination of nirmatrelvir and ritonavir, and is now widely used in the US (22). Ritonavir is a a strong inhibitor (i.e. causes at least a five-fold increase in the plasma area under the curve (AUC) values or more than 80% decrease in clearance) of both cytochrome P450 enzymes CYP2D6 and CYP3A4 (22), leading to strong potential for hazardous drug interactions as CYP3A4 accounts for a substantial proportion of the metabolism of many prescribed and experimental drugs (23). More concerning for clinical trials, is the fact that in the US, Paxlovid™ is available via test-to-treat initiatives, enabling patients to receive the treatment directly from a pharmacist following a positive COVID-19 test without seeing their doctor in many US states (24). It can be expected that some patients may understandably be more concerned about their active COVID-19 and forget to provide details related to their participation in a clinical trial, and thus at risk of potentially hazardous drug interactions.

Risk mitigation strategies

A summary of risk mitigation strategies at the patient, investigator/site, and clinical research organization (CRO)/sponsor level, are provided in *Table 1*. The overall strategies exploited to mitigate COVID-19 risks should be based on an individual study's assessment of risk, inclusive of considerations to the study design, nature of the IP, and the impact of COVID-19 on patient safety and scientific validity. Such assessments should be performed by the Sponsor medical team routinely as the virus evolves, disease severity dynamics change, new anti-COVID medications/vaccinations become available, and community transmission fluctuates.

Key to the study ensuring the reliability of early phase trials and safety of participants is having a planned reporting procedure of patient COVID-19 positivity during screening, before enrollment, and on study. Both patient-level (phone, email, app based, etc.) and investigator-level (i.e. routine COVID-19 history and testing during each screening/study visits with results recorded in the case report form (CRF)) processes should be considered. Inclusion of a re-screening option/window and procedure in the event of a positive COVID-19 result prior to study enrollment should be considered to ensure both patient safety and patient/site compliance with COVID-19 procedures.

Both patients and site/investigators should be educated on procedures related to COVID-19 during the study trial. Patient education is of particular importance if the IP must be stopped in the event of a COVID-19 diagnosis

or with initiation of treatment with an available SARS-CoV-2 therapy (i.e. due to hazardous drug interactions). To this end, with the readily available access to COVID-19 therapies via test-to-treat programs without a visit to the patient's physician, the issuance of study wrist bands or ID cards should be considered as additional preventative measure to ensure subject study. Patients being treated with Paxlovid™ should be re-tested for COVID-19 prior to resumption of study IP, due to high risk of rebound COVID-19 associated with the drug (25). Guidance should be provided to both patients and investigators/sites with respect to any interactions between COVID-19 therapies and study drug, as well as procedures for stopping IP if required for safe administration of a given COVID-19 therapeutics.

When possible, sites should be encouraged to ensure easy access to COVID-19 testing through either the site itself or partnerships with clinical laboratories, where results can be shared with their treating study physician to ensure proper recording in the CRF and appropriate protocols are followed to ensure timely treatment of a patient's COVID-19.

Language specific to COVID-19 procedures should be included in a study protocol and amended as needed as both the study pandemic and evolves to ensure patient safety. In studies that may be a high-risk of COVID-19 related complications (i.e. IP interacts with study therapy or IP may be impacted by COVID-19 immune related dysfunction), routine or as needed (symptoms, high-risk exposure) COVID-19 testing procedures via at home (antigen RDTs, self-based) tests, but ideally lab-based molecular tests, should be considered. Some recent evidence suggests that mRNA vaccinated persons may be at increased risk of false negative anti-SARS-CoV-2 nucleocapsid testing (At-Home antigen RDTs) (26), while the FDA has now recommended a 3-test policy for At-Home tests following a high-risk exposure but absent symptoms (27). That said, providing patients (self) At-Home tests to use throughout the study for both the patient and close contacts (immediate household) remain a sound policy if used within the context of proper guidelines, encompassing accurate instruction on how the sample shall be collected, the test performed, and the results interpreted, as well as if/when to repeat testing or seek further medical guidance. However, only a lab-based molecular test should be utilized during patient screening to rule-out SARS-CoV-2 infection at baseline, due to the significantly higher sensitivity of these assays as compared to the antigen RDTs. Overall, an integrated study COVID-19 testing plan may be appropriate dependent on the overall risk of a particular trial.

Finally, studies should address COVID-19 vaccination within the protocol, during both screening and on study periods. This is particularly important with new updated Omicron-specific (chimeric or dimeric) boosters expected to become available in the next few months, which highly susceptible patients may be eager to obtain. Consideration should be given to differentiating between IP-related and vaccine-related adverse events in such situations and potential confounding of any immunologic endpoints weighed against risk of COVID-19 related outcomes in the current environment (level of community transmission, immune escape of circulating variants, severity of circulating variants, etc.) to ensure patient safety. Protocols amendments with respect to vaccination should be used as needed to ensure patient wellbeing during the evolving pandemic. Similarly, though outside the scope to this article, studies should begin to at least contemplate policies on monekypox vaccination and individual patient disease risk in a specific therapeutic area (i.e. immunocompromised patients may be at increased risk), in order to be prepared *a priori* as this outbreak progresses and we move towards more widespread vaccination, as well as easier access to monkeypox interventional therapies which could interact with study IP (28).

Conclusions

The evolution of the COVID-19 pandemic and widespread community of SARS-CoV-2 Omicron lineages continues to present new challenges for early phase clinical trials and COVID-19 diagnostic strategies. That said, careful consideration and planning can help mitigating the risk of COVID-19 impacting the medical and scientific validity and patient safety in clinical trials. Clinical study design and protocol development should consider mitigation strategies at the patient, investigator, and CRO/Sponsor level following evaluation of the overall for their specific study/IP and patient overall wellbeing, and remain adaptable to evolving nature of the pandemic.

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Footnote

Conflicts of Interest: Both authors have completed the

ICMJE uniform disclosure form (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-60/coif). GL serves as the Editor-in-Chief of Journal of Laboratory and Precision Medicine. BMH serves as an unpaid editorial board member of Journal of Laboratory and Precision Medicine from January 2021 to January 2023. BMH is an employee of Cmed Research Inc. and the Cincinnati Children's Hospital Medical Center, and serves as Chairman of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) SARS-CoV-2 Working Group and a member of the IFCC COVID-19 Task Force. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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