Ensuring Patient Safety and Cardiovascular Clinical Trial Integrity during a Global Pandemic

The susceptibility to and the outcomes of COVID-19 are strongly associated with presence of CV risk factors and with established CV disease[1,2,3]. CV risk factors, including hypertension and diabetes, are associated with high mortality in patients with COVID-19. Further, COVID-19 has been reported to cause cardiovascular disorders, such as myocardial injury, arrhythmias, acute coronary syndrome and thromboembolism[4]. As a result, those conducting CV clinical trials have had to restructure those trials in response to the need for protecting vulnerable patient populations amid rapidly evolving pandemic-related restrictions.

Clinical trials investigating new CV interventions often recruit participants in hospitals and emergency departments, or during outpatient interventions or assessments. Populations with CV disease, or underlying conditions, may experience heightened anxiety and greater hesitancy to visit healthcare facilities and study centres due to higher risk of COVID-19 infection and complications. What's more, COVID-19 social distancing and quarantine guidelines have only made patients even more reluctant to travel to clinics. Consequently, many healthcare systems and clinics have chosen to delay non-emergency procedures in an effort to protect vulnerable patients during the COVID-19 pandemic. These factors, combined, have posed increased challenges to recruitment, adherence and retention in CV trials.

Regulatory authorities around the globe have recognised these challenges and issued guidance to assist sponsors in assuring the safety of participants, while maintaining compliance with good clinical practice and trial integrity. To overcome operational challenges, sponsors should consider deploying an integrated solution that can be tailored to meet the needs of each individual study. Here we highlight strategies to implement in ongoing CV trials.

Links between Cardiovascular Disease and COVID-19

People with co-morbidities such as hypertension, coronary heart disease, diabetes and obesity have been shown to be more susceptible to infection with SARS-CoV-2[5]. Further, this population also is more likely to have worse outcomes from COVID-19, according to reports from China, the USA and Italy[4,3]. This includes a high case-fatality rate from COVID-19. For example, hypertension was reported in 40 percent of patients who died in an analysis of more than 40,000 confirmed COVID-19 patients in China[6]. This study also showed that established CV disease was associated with a five-fold increase in risk of death from COVID-19[6].

In addition to CV patients at high risk for SARS-CoV2, the virus has been shown to cause acute or delayed myocardial injury, arrhythmias and acute coronary syndromes. In fact, myocardial injury is found in more than 25 percent of critical cases of COVID-19[4].

Reduced access to medical services due to the COVID-19 pandemic restriction can also increase the prevalence and severity of cardiovascular disease because of poorer recognition and control of cardiovascular risk factors and established disease[5]. Increasing recognition of these links between cardiovascular risk, disease and severity of COVID-19 offer opportunities to improve outcomes of COVID-19 in patients participating in clinical research.

Routinely Conduct Country- and Site-level Risk Assessments

Routinely tracking the impact of COVID-19 on country and individual site levels in real time can provide invaluable data for use in mitigating delays in site activation and screening, and in redeploying study resources, where appropriate. These risk assessments are critical for studies actively enrolling patients to monitor the constantly evolving global situation and to ensure adequate follow-up for patients under study.

When restarting enrolment at sites where COVID-19 issues have caused a temporary suspension, sponsors must consider site-specific solutions. For example, to assess site readiness, sponsors can utilise a questionnaire to assess principal investigator and staff availability for study visits, data entry and safety reporting requirements, as well as research pharmacy capabilities and internal review board (IRB) readiness to address protocol modifications.

Additionally, as patients in CV trials are at high risk for COVID-19, protocols should not cause delays in vaccine administration. The administration of vaccines for COVID-19 should be well documented in the case report form (CRF). Study site staff must also be aware of information on participant vaccines when assessing potential adverse events.

Utilise Home Health Services to Improve Study Adherence

Typically, study visits for CV trials are performed in outpatient private or academic clinics. And when involving a medical device, they often require hospitalisation or the use of hospital-based treatment facilities. However, local travel restrictions and limited access to hospitals and research sites due to shifting medical priorities caused by the pandemic – coupled with participant concerns for potential exposure to the virus in these settings – have increased the possibility of missed study visits and/or procedures, which could ultimately contribute to missing data and patient dropout.

To keep trials moving forward and prevent delays, sponsors should consider conducting a thorough review of the visit schedule to identify which visits must be conducted in person and which can be conducted using alternative means, including over the phone or via telemedicine.

In addition, many clinical trials have adopted home health services to ensure patient safety, compliance and retention. Using these services reduces or eliminates the need for subjects to travel to the research centre by having nurses or phlebotomists conduct visits at the patient's location, decreasing the risk of contracting COVID-19. In several ongoing CV trials, home health services have been used to collect blood samples, record ECGs and measure vital signs. Concierge services also can be deployed to arrange transportation to sites or institutions where study procedures must be performed.

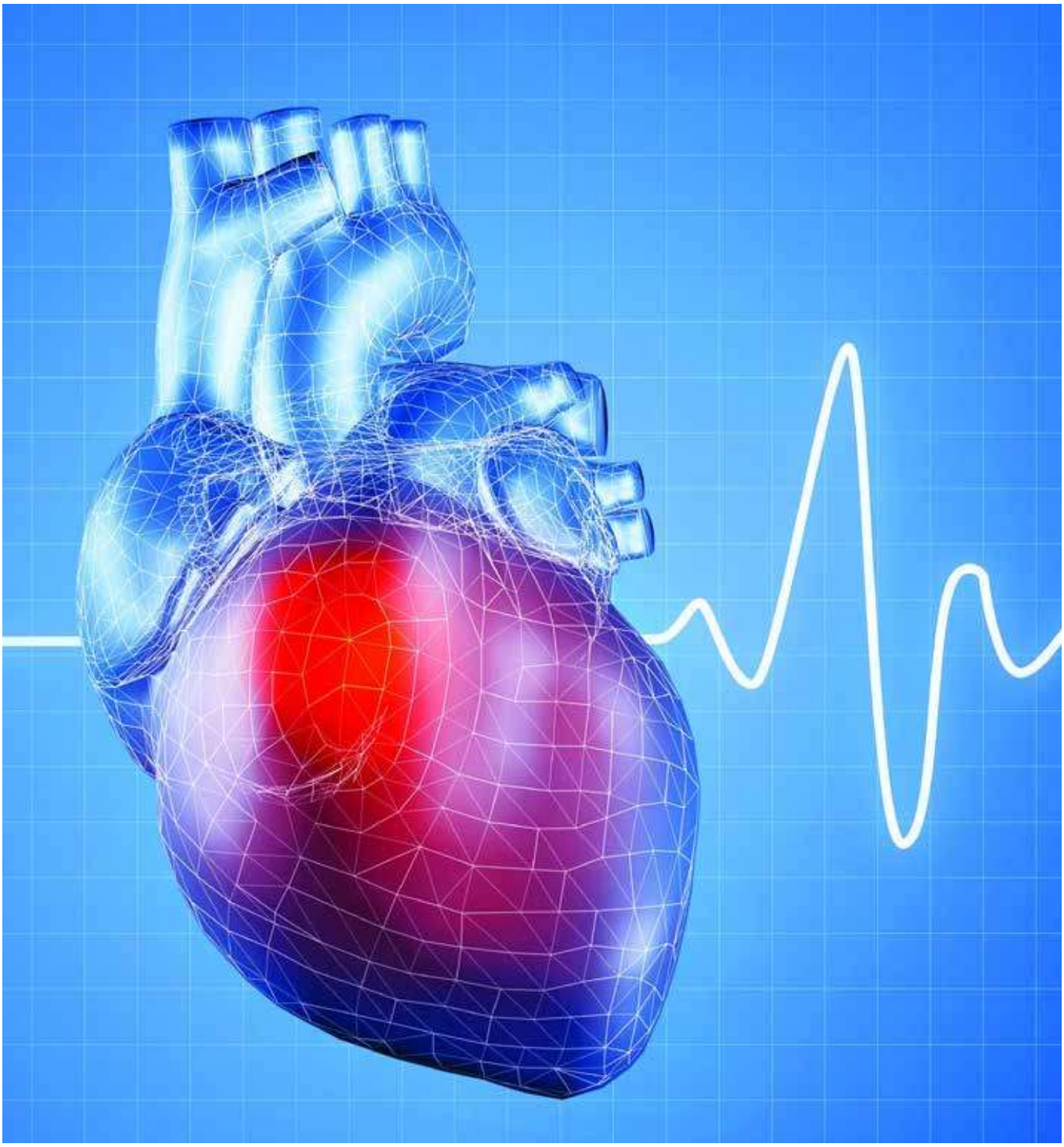
Implement Remote Monitoring

Ensuring that protocol compliance, in addition to accurate and timely data collection, is being performed, even during pandemic disruptions, is integral for clinical trial site management. Remote source data verification, remote source data review and remote/central monitoring can be employed where on-site monitoring is no longer feasible. Moreover, investigator meetings and study-specific training can be conducted remotely to ensure sites are professionally trained, updated and engaged. They also can help sponsors stay connected with sites and minimise operational disruption.

Deploy Digital Health Technologies to Capture Data and Monitor Safety

Digital health solutions can help to minimise COVID-19-related disruptions to CV clinical trials and will continue to have a more prominent role in future studies. If, for example, a patient is unable or unwilling to go to a centre for an ECG, sponsors can use emergency authorised portable ECG devices for safety surveillance during the pandemic. Additionally, there are existing and emerging digital health devices that can be used to remotely measure other parameters of interest, including blood pressure, pulse oximetry, activity levels and heart sounds.

Recently, there have been a number of "point of care" echocardiography platforms intended for expanded access to imaging services. Some are designed to allow remote guidance from experienced sonographers to non-sonographers to guide imaging acquisition. Despite these devices not having the image



resolution of high-end platforms, depending on the specific study requirements, they may provide an effective solution. When required, consideration can be given to having a trained sonographer perform studies with high-end echocardiographic platforms in the patient's home or at another location closer to home.

Develop Effective Remote Drug Delivery Protocols

To proactively mitigate potential disruptions in dispensing investigational products (IPs), sponsors can track upcoming study visits which require medication dispensation. When sites are unable to directly dispense study medication to a participant, advanced arrangements should be made for secure direct-to-subject shipping using a dedicated vendor experienced in handling the IP. Other options include using home healthcare nurses and local clinics to ensure continued distributions of IP.

Maintain Regular Site Communications and Document Compliance

Lastly, maintaining regular contact with study sites and participants to communicate protocol changes and to facilitate compliance and study retention is key to managing CV clinical trials during disruption. When needed, operational changes in study conduct must be promptly communicated to research staff, participants and local IRBs before protocol amendments are implemented and before re-consenting trial participants.

For example, establishing a dedicated COVID-19 email address can facilitate communications between site personnel and the study operational team to coordinate timely and consistent responses to COVID-19 and to address specific patient management questions. Using a dedicated digital mailbox makes possible rapid proactive sharing of effective site-level solutions with other institutions destined to face similar challenges.

In addition to dedicated, transparent communications, COVID-19-related protocol modifications and deviations must be well documented. Sponsors will need to implement ways to capture this information in ongoing CV trials. One solution to consider is adding a dropdown menu to the case report form for COVID-19-related events, which captures missing visits or assessments and the specific causative circumstances, including reasons for failing to obtain efficacy endpoint data. Processes such as these have the potential to avoid many site questions related to appropriate documentation.

Conclusion

Sponsors who adopt the aforementioned strategies specifically designed to meet the needs of individual clinical studies will be well positioned to confront the operational challenges of the evolving COVID-19 pandemic, therefore ensuring patient safety, while reducing disruptions to trial timelines and maintaining protocol compliance.

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