Adapting to a Pandemic — Conducting Oncology Trials during the SARS-CoV-2 Pandemic

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ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has necessitated changes in cancer care delivery as resources are reallocated. Clinical trials and other research activities are inevitably impacted. Start-up activities for new trials may be deferred and recruitment suspended. For patients already enrolled however, there are challenges in continuing treatment on trial. Regulatory bodies have issued guidance on managing clinical trials during the pandemic, including contingency measures for remote study visits, delivery of investigational product, and site monitoring visits. New cancer clinical trial practices during the SARS-CoV-2 pandemic include new risk assessment strategies, decentralized and remote trial coordination, data collection, and delegation of specific therapeutic activities. This experience could provide evidence of more feasible and cost-effective methods for future clinical trial conduct.

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has spread to over 200 countries as of April 2020 (1). The ongoing pandemic has resulted in increasing pressure on hospitals and healthcare systems in general, as resources are diverted or reallocated. Cancer centers around the world are preparing and adapting their delivery of care to patients with cancer (2). Travel restrictions, a more vulnerable population of immunosuppressed patients, and potential drug supply chain interruptions, all further complicate the ability to administer even standard therapies. There have been harrowing first-hand accounts (3), and numerous guidelines and experiences on the impact of general cancer care during the pandemic (4, 5).

Clinical trials in oncology represent a fundamental component of modern practice, providing the crucial evidence to evaluate the efficacy of new therapies. However, with limited resources, the SARS-CoV-2 pandemic is inevitably impacting on research activities and conduct. Commonly, start-up activities for new trials may be deferred and recruitment to existing trials suspended (6). Resources may then be focused on continuing care for patients already enrolled on trials, especially if they are benefiting from treatment, which in itself poses numerous additional challenges. As a consequence, many regulatory bodies have issued guidance on managing trials during the pandemic. This includes the FDA (7), the European Medicines Agency (8), the United Kingdom Medicines and Healthcare products Regulatory Agency (9), as well as Singapore's Health Sciences Authority (10). These guidelines detail potential difficulties in adhering to protocol-defined study requirements and appropriate contingency measures with a view to maintaining patient safety and trial integrity. Nevertheless, each trial and patient should be considered on a case-by-case basis, accounting for differences in individual circumstances, with regards to the appropriateness of implementing these measures. Furthermore, close and regular consultation between investigators, sponsors, and institutional review boards is critical to ensure patient safety. Herein, we discuss several important aspects in adapting the conduct of clinical trials during the COVID-19 pandemic, and how it may potentially shape the future direction for trials in oncology.

Remote Study Visits

Travel bans, quarantines, and stay at home notices have been implemented to varying degrees, both domestically and internationally throughout many regions of the world. Naturally, this introduces limitations on patient visits for scheduled study assessments and procedures. Clinical trials also tend to be conducted at large tertiary referral centers, meaning patients often travel from long distances for trials. Conducting remote study visits with telemedicine or video calls (11) and using patient's local facilities for laboratory investigations and imaging are alternative approaches for regular study assessments. Careful attention to the appropriate accreditation of local laboratories and differences in reference ranges is critical. Close communication with patients, ensuring procedures are performed promptly and as completely as possible is similarly important. Results must be reviewed and acted upon where necessary. Subsequent transfer of source of documents must be done within established timelines. Comprehensive telemedicine consultations to review adverse events and concomitant medications for patient safety should be conducted.

Delivery of Investigational Product

Where patients are unable to attend trial sites to receive investigational product (IP) supply, delivery directly to patient can be considered. Pharmacovigilance remains paramount, ensuring the security, accountability, traceability, and compliance to IP storage requirements. To maintain patient privacy and data confidentiality, delivery of IP direct from trial site to patient's homes may be necessary, and not from drug distributors or central depots. Clearly, only oral therapies may be suitable for direct delivery of IP and steps should be taken to ensure blinded therapies are not compromised. Other important considerations include complete traceability of IP throughout the supply chain, appropriate storage requirements both en route and at patient's homes, and documentation of all communication and instruction.

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Translational Relevance

Cancer clinical trials are increasingly complex with novel toxicities and molecular subsets adding to challenges with trial conduct and recruitment. The impact of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic on cancer clinical trials' operations and conduct has been wide reaching. Compounding barriers to speedy drug development is ever-increasing regulatory complexity that burdens drug development. Furthermore, this burden has been the risk-averse position of stakeholders at all levels in the drug development process, except perhaps in those patients with lethal conditions. Some degree of risk is inherent in any research. The central questions are whether that risk is reasonable under the circumstances, and whether the participant or surrogate has been adequately informed of the risk and deems it to be acceptable. The experience of conducting clinical trials during the SARS-CoV-2 pandemic where equipoise in the risk and benefit may be altered may stimulate the development of more efficient and streamlined methods of trial conduct and data collection in the future.

Site Monitoring Visits

Limitations for sponsors in attending sites for monitoring visits is another aspect which may require adjustment. Centralized monitoring or remote monitoring is an option which may be implemented. In cases of remote monitoring, using virtual technologies, patient privacy and data confidentiality must be maintained. Data may be reverified during later on-site visits. Although protocol noncompliance during COVID-19 may increase substantially, reporting requirements remain, and serious breaches must be actioned appropriately.

Local Experiences in Singapore and the United States

In Singapore, imported COVID-19 cases were initially detected in late January (12). Travel restrictions were implemented initially for visitors from China and later followed by visitors from all other countries (13). The National Cancer Centre Singapore is a leading global cancer center, with over 200 ongoing clinical trials, including one of the largest early-phase trials' units in Asia. As a regional hub, many patients on trials come from around the region, including South East Asian countries such as Malaysia, Indonesia, the Philippines and Vietnam, as well as from China. Many patients have been affected by travel restrictions, unable to make visits and travel to Singapore. Telemedicine consultations and patient's local laboratories and facilities for safety and efficacy assessments have been used successfully. Particularly for delivery of IP, there has been increased complexity in navigating local regulatory requirements of different countries; however, a majority has been able to continue on oral therapies.

The Duke University Hospital in Durham, NC, similarly conducts a large number of early- and late-phase clinical trials. The pandemic has resulted in widespread changes to workflows and resource allocation, as with many large academic institutions in the United States. Provisions have been made for telemedicine, as video and telephone encounters have been introduced, and are now eligible for reimbursement by payers. Some of the clinical assessments necessary for clinical trial patient can be performed via telemedicine. However, most clinical trials assessments require face to face encounters. Some studies have been considered nonessential and are thus on hold until further notice, but patients, their caregivers, and clinicians are still keen to pursue therapeutic clinical trials. Many of these patients need to travel from areas considered high risk or "hot zones" and the decision to accept referrals for clinical trials has become more complex than usual.

As the COVID-19 pandemic evolves, and varying levels of travel restrictions may need to be in place for the foreseeable future, the need to adapt to changing circumstances may continue. Close communication between trial sites, sponsors, and regulatory bodies is crucial.

Future Directions – Decentralized Clinical Trials

Undoubtedly, COVID-19 will have negative consequences on the development of many novel therapeutics with significant delays in trial recruitment and completion. More broadly, the economic impact of the pandemic may hamper the clinical trial ecosystem as a whole, including stakeholders such as contract research organizations (CRO). However, could this provide a roadmap for more efficient and streamlined conduct of clinical trials in the future?

With the increasing role for precision oncology and biomarker-enriched trials in rare molecular subsets, and the rapid development of other novel individualized therapies such as cell therapies, there is a definite need for greater flexibility in the conduct of clinical trials (14). Moreover, regulatory approval of novel molecularly targeted drugs based on early-phase clinical trial data is increasing. Patients often live far from specialized centers, creating extra burden on patients and caregivers and impacting trial recruitment (15). Furthermore, the burgeoning costs associated with conducting large randomized trials shows no signs of slowing down (16). A move toward a more decentralized clinical trial model (**Fig. 1**) or satellite sites (**Fig. 2**) could improve the adaptability of trials. Indeed, there have been ongoing efforts in this space (17).

Decentralized clinical trials represent a concept that data can be collected at remote locations, and the method of data collection may also be virtual (18). This is in contrast to traditional clinical trials, where data must be collected at the designated research facility and via

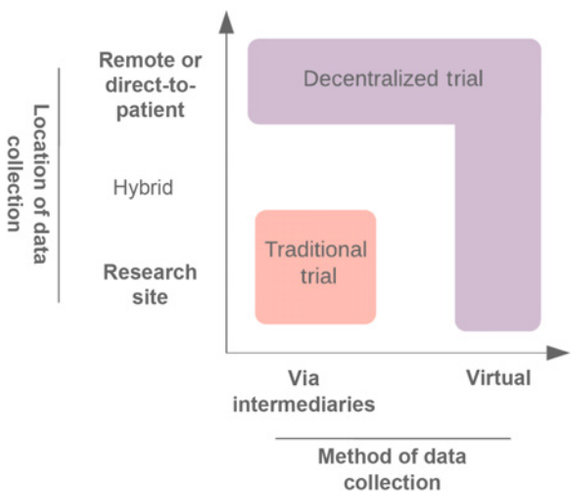

Figure 1.
Decentralized versus traditional clinical trial models. Adapted from Khozin and colleagues (21).

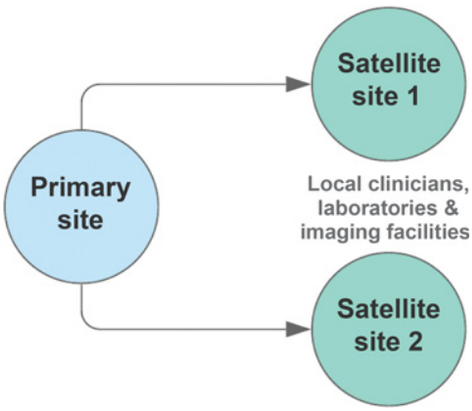

Figure 2.
Primary and satellite clinical trial sites. Adapted from Sabesan and colleagues (17).

intermediaries such as CROs. Importantly, decentralized trials do not compromise on study design or statistical consideration. It refers predominantly to the locality and method of data collection. Accordingly, protocol-specified procedures compliant with regulatory requirements may still be conducted. The FDA's increasing focus on real-world evidence (RWE), to generate evidence and data outside the tools and methods of traditional trial settings, is recognition of the unharnessed potential to capture multiple data sources (19). RWE is not restricted to retrospective collection of data from routine delivery of care, but also includes pragmatic clinical trials, which can be conducted in the real world. Additional benefits may be to improve the generalizability or external validity of the evidence obtained from clinical trials, without significant sacrifices in internal validity. The use of remote completion of study procedures and visits may improve patient recruitment, retention, and engagement. Finally, other virtual digital health tools may also be incorporated, including mobile applications, wearable technologies, and digital biomarkers, to facilitate the decentralized model (20).

There are of course, barriers and challenges to decentralized clinical trial models. There is potentially greater reliance on data security and increased complexity in supply chain logistics (21). Additional training, insurance and indemnity considerations, and management of adverse events and serious adverse events must be considered (22). Oral therapies are more suited, compared with parenteral therapies. For trials in unselected populations of common tumor types in which patient recruitment is less difficult, it may not prove cost-effective. Similarly, early-phase studies with intense and specialized pharmacokinetic and pharmacodynamic sample collection requirements may not be well suited. However, hybrid models incorporating decentralized components may still improve efficiency. For rare cancers or rare molecular subsets, current trial models may not be practical in the long term. Ultimately, key to decentralized clinical trials is maintaining the quality and integrity of data, which can be collected remotely, away from the primary study site.

Conclusion

During the SARS-CoV-2 pandemic, controversy surrounding the drug development path for potential antivirals has taken center stage in the mainstream media with fundamental questions arising about appropriate checks and balances. We have previously argued that drug development strategies and the availability of new agents for rare cancers are at risk of stalling owing to the ever-increasing complexity and costs of clinical trials and that finding solutions to these problems is imperative to the future of cancer care (23). A greater degree of risk sharing is needed than is currently accepted to enable the use of new methods with confidence, and to keep pace with scientific advancement. Perhaps, due to the SARS-CoV-2 pandemic, the public's new focus on such issues may accelerate such reform. The SARS-CoV-2 pandemic has necessitated adaptation in conducting oncology clinical trials, which may need to continue for a while to come. A potential silver lining to the SARS-CoV-2 pandemic could be demonstrating the feasibility of more efficient and cost-effective methods of conducting clinical trials, without compromising ethical conduct, safety, and data integrity.

Disclosure of Potential Conflicts of Interest

D.M. Ashley is an employee/paid consultant for Istari Oncology, Oblato, and Diverse Biopharma, and holds ownership interest (including patents) in Istari. M. Khasraw reports receiving other commercial research support from Bristol-Myers Squibb and AbbVie. No potential conflicts of interest were disclosed by the other author.

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Development of methodology: M. Khasraw
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.C. Tan, D.M. Ashley
Writing, review, and/or revision of the manuscript: A.C. Tan, D.M. Ashley, M. Khasraw
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