CLINICAL TRIALS

Reimagining Global Oncology Clinical Trials for the Postpandemic Era: A Call to Arms

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INTRODUCTION

The process of developing new anticancer therapeutics has been considered by some to be expensive,[1] time consuming,[2] bureaucratic,[3] and, to some extent, inefficient.[4] The coronavirus disease 2019 (COVID-19) pandemic has significantly affected clinical oncology studies[5,6] and underlined the need to embrace and accelerate long-pending and awaited reforms to cancer clinical trial methodology.[7-9]

This article highlights the need for optimal use of technology, reduced paperwork and bureaucracy, speedier trial setup, and greater patient centricity in the design and conduct of future clinical and translational cancer studies around the world.

INCREASED USE OF TECHNOLOGY

The basic technology to enable secure and reliable telephone/video contact between clinicians, study coordinators, and patients to facilitate remote medical consultation has been available for a number of years; however, its adoption has been limited for a variety of reasons, including lack of access to such technologies in some developing countries and concerns surrounding privacy, safety, financial reimbursement, and legal and regulatory issues. Changes to reimbursement rules and regulations have been recently announced to encourage the use of telemedicine during the COVID-19 lockdown.[10,11] These and other such pandemic-era reforms should be adopted not only for the current situation but should also be considered for permanent adoption.[12-14]

Electronic consent and telemedicine consultation could replace some protocol-mandated clinic visits, especially those for which medical imaging, biosample collection, or physical examination are not required.[15] Reduced exposure to the hospital environment could enhance patient safety, comfort, and quality of life while also perhaps lowering the number of protocol deviations in clinical trials and the overall burden of trial participation.[16] It may also help reduce inequalities in access to clinical trials resulting from transportation challenges because of geographic, financial, or physical issues, and would also reduce the burden on patient caregivers. Virtual formats could replace in-person investigator meetings, steering committee meetings, etc, thereby reducing physical, financial, and environmental burden while increasing speed and flexibility. Using social media as an easily accessible communication tool could also help to optimize the care of patients enrolled in cancer clinical trials.[17] Measures that can be self-reported by patients are increasingly being used in clinical practice and trials, and these data can be collected remotely as electronic patient-reported outcomes (ePROs).

During the ongoing pandemic, patients, clinicians, and hospitals have become increasingly comfortable using telemedicine, and many stakeholders agree that the resulting improved access, lower cost, reduced risk of infection, and time saved should make telemedicine an integral part of our standard practice in cancer care and research moving forward, at least for predefined activities.[18,19] Adopting digital pathology and radiomics platforms to enable images to be seamlessly analyzed at a remote and/or central facility could increase efficiency in cancer trials.[20,21]

Use of artificial intelligence could help efficiently match the unique clinical and molecular pathology characteristics of a given patient to relevant clinical trials within their region of the country,[22,23] thereby providing access to potentially life-enhancing trials for a broader and more diverse population.[24]

Physical activity trackers, smart watches and other wearable devices, and smartphones with health applications allow for the real-time remote collection of health parameters, such as physical activity, ECG, temperature, blood glucose level,[25] oxygen saturation,[26] and ePROs.[27] Validated, secure, and approved wearable devices could autopopulate trial databases with robust longitudinal data, reducing the need for manual data entry and providing more efficient and improved data quality and integrity.[28] Use of clinical decision support algorithms to detect early signs and symptoms of concern (eg, fever and tachycardia suggestive of infection) and to alert the

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treating clinical team should be explored in cancer clinical trials where feasible.[29] Such algorithms can also be customized to support specific clinical trial protocols, which may help to improve protocol adherence and care consistency across investigators in decentralized sites so that clinical trials can be opened in additional community sites and be more accessible for more patients closer to their homes.

Remote monitoring by contract research organization staff, other auditors, and even by regulatory inspectors could also be enabled by secure technologic solutions.[30,31]

We should acknowledge, however, that there are challenges to the increased use of such technologies in clinical trials, especially related to cybersecurity. It is also important to ensure that the increased use of technology does not have the unintended consequence of excluding individuals who are unable or unwilling to access that technology, such as the elderly and disadvantaged. Moreover, the increased use of technology may be both an opportunity and a threat to increasing clinical trial participation by people in low- and middle-income countries where access to mobile devices may be relatively good but other infrastructure less so.

Cutting the Clutter

Eliminating unnecessary complexity and bureaucracy from clinical trials could help reduce the cost and time required to answer research questions.[32,33]

Reducing the verbosity and complexity of the informed consent form is long overdue.[34,35] In case patients who are enrolled in ongoing studies need to have their consent reobtained, the updated informed consent forms should not repeat information already presented in the initial consent documents, and the application of eConsent technologies provides an efficient source of this revised information and an effective audit of review and signature.

Each data item that is collected in clinical trials generates burden and cost (data entry, multiple levels of checks, source data verification, and query generation and resolution). Despite this, a significant proportion of the data collected during cancer trials may never be used; for example, a Canadian study found that only 18% of data elements collected during clinical trials were reported in future publications,[36] although a part of such unpublished data may still have been used effectively.

Whereas the collection of research biopsies may enable useful future correlative science, their immediate utility often remains uncertain.[37] A strong scientific rationale for collecting tissue should be defined and ethical issues should be carefully considered before making them mandatory in cancer trials.[38] Alternate specimen types, such as liquid biopsies, for enrollment or monitoring purposes should be considered when and where appropriate. The process of submitting diagnostic blocks and other biosamples should be streamlined and standardized,[39] and we should aim to collect only the essential data and samples required to answer the predefined objectives of the ongoing study, allowing the option to collect more data and samples from interested patients/sites for subsequent translational research.

Published and reusable standards, rather than just templates, of trial charters, biospecimen collection protocols, and toxicity management guidelines could help reduce paperwork and duplication of effort. Attempts at the standardization of trial methodology should be encouraged and adopted.[40] A greater ease of administration for ethical review across institutions, which would allow for a single ethics board to be designated lead for multiple centers within a region, country, or even continent, should become standard.

Regulators, such as the US Food and Drug Administration[41]; health systems, like the United Kingdom National Health Service[42]; professional oncology societies, such as the European Society of Medical Oncology and the American Society of Clinical Oncology[30,43]; academicians; and industry should continue to make efforts to streamline clinical research and reduce the burden of paperwork.[44] It is a challenge for principal investigators to sign off and act as guarantor for electronic case record forms and multiple serious adverse event reports; it is important that investigator oversight is not diluted by collecting ever-increasing volumes of data for which they are not easily equipped to vouch and certify.

Speedier Approvals and Permissions to Launch Clinical Trials

Regulators and stakeholders involved with planning and executing cancer studies should carefully analyze and adopt best practices where possible from some large COVID-19 trials, like RECOVERY (EudraCT 2020-001113-21), DisCoVeRy (ClinicalTrials.gov identifier: NCT04315948), and SOLIDARITY (ClinicalTrials.gov identifier: NCT04330690), which were designed quickly and built to greatly reduce the bureaucratic burden on participating sites, with rapid startup, simplified requirements for recording consent, collection of only essential data, and ease and flexibility in methods of data entry, which enabled a remarkably early first readout of efficacy.[45]

Patient Centricity

With numerous societal changes underway, this is also an opportunity for a step change in patient involvement in clinical trials. Much progress has been made with patient and public involvement in clinical trials, grant applications, and trial oversight groups. Still, there is scope for deeper engagement with patient and public involvement groups to set the global oncology research agenda. Such a relationship must be transparent and integral to study design and conduct and not merely superficial. Many COVID-19 trials

had broad entry criteria, and there is now an opportunity similarly to broaden eligibility criteria[46,47] and to recruit an ethnically diverse population in cancer trials.[48]

The COVID-19 pandemic has given a boost to the emerging concept of the virtual or decentralized trial, which is a siteless study in which patient recruitment is done via Web-based methods that involve social media, patient portal and telemedicine applications, informed consent via remote electronic document access, review and signature, some trial activities done via video conference, physical examination done via remote visit or in-home nurse visit, laboratory specimen collection done by local clinics or in-home phlebotomist visit or patient service draw centers, data collection via digital health devices or ePROs, shipping of drugs to the patient's home, and outcomes collected by remote methods using digital tools.[49] A fully virtual trial is not feasible for most cancer studies, given the need for detailed and often delicate discussions, especially at the time of informed consent[50]; intravenous drug administrations; medical imaging; and toxicity surveillance. However, decentralizing some elements when appropriate could make conventional trials more efficient, potentially reducing patient burden and consequential clinical trial dropout and optimizing health care resource utilization. These hybrid trials would be located on a spectrum, with interventional clinical trials at one end and pragmatic or real-world studies at the other.[51] A careful review of the number of mandatory visits to the hospital should be performed and, where possible, reduced.[8] Social media platforms should be used to share results of clinical trials in innovative and patient-centered ways, including lay-language summaries and intuitive data visualization.

Future Perspectives

The coming era of more patient-friendly clinical trials will require changes to the way cancer services are currently organized and delivered, with the aim of reducing the number of times the patient and contract research organization staff need to visit the site. Home visits by specialized nurses and phlebotomists, delivery of certain medications to patients' homes, and precise and timely communication with family physicians or local clinics to perform laboratory testing will likely improve the patient experience. It will, however, require careful coordination by the sites, which could be challenging in areas with limited capacity or resources. We must also be careful to ensure that any changes we adopt should not result in the systematic exclusion of potential patient pools based on geographic location, rural versus urban settings, access to digital technology, educational level, ethnicity, ability, or age.[52,53]

In conclusion, the pandemic has revealed certain limitations in the current models of cancer care and the traditional conservative approach to cancer research.[54-56] Consequently, the move toward patient centricity has accelerated, with increasing use of easily accessible and comprehensible technology, such as video, mobile phones, apps, telemedicine, and wearable devices. It has also created an opportune moment to reflect on past practices and fine tune the technologies, policies, and methodologies that we adopt in future cancer studies to enable us to develop better medicines for our patients in a faster and more efficient manner.

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