The impact of COVID-19 on cancer care and oncology clinical research: an experts’ perspective

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The coronavirus disease-19 (COVID-19) pandemic promises to have lasting impacts on cancer clinical trials that could lead to faster patient access to new treatments. In this article, an international panel of oncology experts discusses the lasting impacts of the pandemic on oncology clinical trials and proposes solutions for clinical trial stakeholders, with the support of recent data on worldwide clinical trials collected by IQVIA. These lasting impacts and proposed solutions encompass three topic areas. Firstly, acceleration and implementation of new operational approaches to oncology trials with patient-centric, fully decentralized virtual approaches that include remote assessments via telemedicine and remote devices. Geographical differences in the uptake of remote technology, including telemedicine, are discussed in the article, focusing on the impact of the local adoption of new operational approaches. Secondly, innovative clinical trials. The pandemic has highlighted the need for new trial designs that accelerate research and limit risks and burden for patients while driving optimization of clinical trial objectives and endpoints, while testing is being minimized. Areas of considerations for clinical trial stakeholders are discussed in detail. In addition, the COVID-19 pandemic has exposed the underrepresentation of minority groups in clinical trials; the approach for oncology clinical trials to improve generalizability of efficacy and outcomes data is discussed. Thirdly, a new problem-focused collaborative framework between oncology trial stakeholders, including decision makers, to leverage and further accelerate the innovative approaches in clinical research developed during the COVID-19 pandemic. This could shorten timelines for patient access to new treatments by addressing the cultural and technological barriers to adopting new operational approaches and innovative clinical trials. The role of the different stakeholders is described, with the aim of making COVID-19 a catalyst for positive change in oncology clinical research and eventually in cancer care.

Key words: cancer care, clinical research, real-world evidence, collaborative framework, COVID-19

The coronavirus disease-19 (COVID-19) pandemic promises to have lasting impacts on cancer clinical trials, from accelerating the implementation of new operational approaches and innovative clinical trials to a tighter collaboration among all clinical trial stakeholders that could lead to faster patient access to new treatments.

The pandemic has had various impacts on the treatment of cancer patients and oncology clinical trials in different regions and countries (Figure 1). The high mortality associated with certain cancers has certainly motivated patients and physicians to continue ongoing treatment. However, patients with non-emergent medical issues were not allowed into some health care facilities. There has been a reduction in new cancer diagnoses as people postponed screening procedures; this is likely to cause an increase in advanced-stage diagnoses in the near future (Figure 2).

Data from surveys of key opinion leaders around the world and from internal databases indicate that in oncology trials the accrual of new patients decreased during the COVID-19 pandemic, but to a lesser extent than in non-oncology trials. For example, between April 2020 and March 2021, 386 oncology trials were halted, with 274 subsequently reactivated and 74 remaining stopped.
Oncology study starts* were disrupted throughout 2020 but increased through the year and into 2021

Oncology interventional industry-sponsored clinical trials “study starts”: change over prior year

![Graph showing oncology study starts over time with data points for 2019, 2020, and 2021 with specific weeks and percentage changes]

*Clinical Trial starts: first posting dates into CT.gov
Source: ClinicalTrials.gov, accessed April 19th, 2021

There have been geographical variations depending on COVID-19 outbreaks and case rates, government policies and implementation of measures to assure the quality of the primary efficacy data and the safety of patients. A minority of oncology trials were terminated or withdrawn, most of which were early-phase studies. The most frequent responses to COVID-19 were amending protocols (involving 43% of participants), switching patients to virtual visits (40%), extending patient visit windows (33%) and shipping investigational drugs to patients (27%). Planning has become more difficult due to the reduced availability of health care personnel, who are in high demand due to the pandemic in some regions and to the COVID-19 fluctuations. Overall, during the pandemic, there has been a shift in the way clinical trials are executed toward decentralized models. Once an extensive vaccination has been carried out, the current scenario is forecast to improve rapidly; however, the successful new approaches to remote management of patients and studies have paved the way for new ways to practice oncology and conduct clinical trials. This is encouraging investigators, sponsors, regulatory authorities and others to discuss ways to optimize the conduct of clinical trials.

This article reports the results of discussions among an international panel of oncology experts on the lasting impact of the pandemic on oncology clinical trials and proposes solutions for clinical trial stakeholders, with the support of recent data on worldwide clinical trials collected by IQVIA.

NEW OPERATIONAL APPROACHES TO ONCOLOGY TRIALS

Oncology trials can be very demanding for patients and their families in terms of time, travel, costs and stress, which made the decision to participate complicated even before concerns about COVID-19. During the pandemic, institutions aimed to limit the time patients spent on their premises by minimizing and streamlining procedures in the sense of unit flow optimization and replacing in-person visits by remote options. While intended to reduce the risk of COVID infection, these procedures effectively also reduced the burden of care and of clinical trials for patients. Optimizing both the trial design and study conduct from an operational perspective, with more streamlined clinical visits and some visits and treatments occurring in patients’ homes, may make participation in clinical trials less burdensome, while expanding the reach of the trial to a broader population (Table 1).

Patient-centric, fully decentralized virtual approaches, where all study components are completed outside of the site, or hybrid formats, where a portion of site-based visits remain while other components are coordinated with patients from their homes, were already being proposed before the pandemic. However, uptake was scarce. Since the pandemic, decentralized trials have been adopted by several clinical programs. Virtual approaches include remote assessments via telemedicine and remote devices, supported by structured data collection, decentralized data collection with use of laboratories and imaging facilities located close to where patients live. They also include...
adoption of connected devices, home nursing visits and direct-to-patient drug shipment. Similarly, remote monitoring, with or without centralized monitoring and a risk-based approach, has been promoted and implemented to replace onsite monitoring, again with variations among regulatory agencies related to type of trial and duration.

Innovation could be advanced by collaboration among clinical trial stakeholders focusing on validation and acceptance of the following components of virtual and hybrid trials:

Types of oncology studies that could benefit from new operational approaches

In IQVIA’s experience, most oncology clinical trials could benefit from a hybrid approach rather than a fully virtual solution. The latter is more appropriate for non-interventional investigations such as long-term follow-up studies. While most clinical trials might benefit from new approaches, it is important to assess each study based on factors such as the phase of the study (e.g. early versus late phase), the mode of action of the drug or intervention being tested, the route of administration (e.g. oral versus intravenous), the safety and tolerability profile, the patient population and the study objectives and endpoints.

Geographical and cultural differences in telemedicine uptake

A recent paper in The Lancet notes that many of the changes made to clinical trials during the pandemic could have been made long ago. The paper quotes Kevin Sheth, chief of neurocritical care and emergency neurology at Yale University, Connecticut, as saying, “Telemedicine technology has been around for 10, 15, 20 years. In many cases, the barriers to incorporating telemedicine more widely into clinical practice really have been in large part administrative and bureaucratic, having to do with cost and reimbursement—not because of some conceptual or technological limitation. The same is true in the clinical research world”. Geographical differences in the uptake of remote technology, including telemedicine, are impacting the local adoption of new operational approaches and may jeopardize site participation in decentralized trials.

In Italy, telemedicine between physicians and patients currently involves primarily phone calls and emails, while physician-to-physician consultation includes the sharing of radiologic images such as computed tomography scans, as well as laboratory results. A local oncology or ‘oncologia territoriale’ project is in advanced development to enable a
network of family physicians to connect with oncologists about the oncologists’ existing patients. The aim is to avoid the need for these patients to travel to oncology centers for every checkup, and instead to consult with their family physician. However, there are reservations among Italian oncologists about the use of telemedicine directly with patients, due to a belief that successful oncology treatments require development of a personal relationship between physician and patient, which may be hard to create remotely; and those patients might not feel as free to ask questions in a telemedicine setting as in person. Telemedicine is supported by Italian oncologists only for communicating laboratory results.

In Asian countries, telemedicine is primarily being used outside of clinical trials at present and is increasing in popularity. Cultural or other barriers, including age, do not appear to be jeopardizing patient acceptance of telemedicine in Asia. Patients typically appreciate the option of communicating with the doctor by phone or video and the reduced need for travel. Local oncologists suggest that telemedicine should only be paid for if new medical information—for example, from blood tests or imaging—is communicated, which requires a medical consultation.

In the United States, medical licenses are granted on a state-by-state basis, thus limiting the ability to provide telemedicine across state borders within the country. This limits patient access to physicians and trials that they might otherwise reach out to.

The responses from a European patient community (Melanoma Patient Network Europe) to telemedicine have been mixed. Some patients missed the real-world interaction with their treating oncologists, in particular, in the event of bad news. Others in the same situation found it beneficial being able to have a family member beside them, rather than receiving bad news alone due to COVID restrictions on family members at clinic visits. Patients further commented on the dramatically reduced impact on their lives, thanks to reduced travel and out-of-pocket expenses such as parking fees. Interestingly, patients also commented on the fact that telecommunication leveled the interaction between them and their oncologist and that they appreciated the scheduled interaction, rather than over-running consultations or broad call-back windows (B Ryll, personal communication).

**Geographical differences in uptake of remote monitoring**

Remote monitoring relies on availability of appropriate technologies and authorization for private patient data to be used. Local and regional differences can have a strong influence on trial participation for investigators and sites. Regional differences in addressing confidentiality and data safety may create a wide variety of rules for sponsors and monitors to follow, increasing complexity and cost.

In Switzerland, remote monitoring is not currently available due to data protection concerns, and the fact that hospitals do not allow access to patients’ medical records from outside their firewalls. In addition, access would be all-or-nothing, with no option to provide access only to defined elements of the chart.

The Swiss Group for Clinical Cancer Research (SAKK) reports that the national regulatory body, Swissmedic, is allowing minimal changes to clinical trials during the pandemic. This is based on guidance issued by both Swissmedic and Swiss Association of Research Ethics Committees (Swissethics) in December 2020 and updated in January 2021. The Swissmedic website notes that, “Remote source data verification of aspects critical for patient safety and data integrity is permitted under certain conditions within the framework of clinical trials with medicinal products in times of the pandemic. Adjustments have also been made to the submission process for reporting/applications due to the current situation”.

The SAKK perspective is that from an administrative and financial point of view, it is better to remain adherent to approved good clinical practices, since any changes would require extensive human and structural resources (P Durrer, Head of Quality Assurance, Regulatory Affairs & Pharmacovigilance at SAKK, personal communication).

In Italy, very few institutions (an estimated 2 out of 65 Italian clinical sites) currently allow remote monitoring or provide access to electronic health records (EHRs). This is due to concerns about patient privacy, less extensive site
availability of EHRs than in other countries and lack of available technology to enable selective sharing of elements of the EHR that are pertinent to a given clinical trial. National efforts are underway to create an oncology EHR network, such as the one led by the Periplo Foundation.

In Spain, the regulatory authorities have granted permission for remote monitoring for COVID-19-related trials and for oncology trials. The implementation rate varies between institutions and among pharmaceutical companies and clinical research organizations (CROs). In Vall d’Hebron Institute of Oncology, remote monitoring has been implemented for ~30% of clinical trials.

In the United States, remote monitoring was available at some institutions pre-COVID, but many institutions did not allow it, due to concerns including the need for offsite access to patient data. During the pandemic, this mindset changed, and remote monitoring rapidly became the norm at many sites. However, some sites found this approach more difficult to utilize than others, due to rigid contracts that needed to be signed to minimize potential for breaches of patient confidentiality. As many sites are still using remote monitoring due to continued COVID cases and people still working offsite, a hybrid model will likely be developed post-pandemic, where various elements of monitoring are carried out remotely and others, onsite.

**INNOVATIVE CLINICAL TRIALS**

The COVID-19 pandemic has driven real-world evidence (RWE) uptake in clinical trials in several ways (Table 2).

There is a need for new trial designs that accelerate research and limit risks and burden for patients, especially for randomized trials versus placebo or versus an ineffective standard of care. At the same time, the pandemic is driving optimization of clinical trial objectives and endpoints, which are being re-assessed, while testing is being minimized. This approach is aimed at making trials more closely aligned to clinical practice in oncology. Eligibility criteria are being relaxed to facilitate recruitment of patients with unmet need and to enable enrollment completion. COVID-19 has disproportionately affected minority ethnic populations as shown in observational studies in the United States, UK and Brazil. Minority groups have so far been underrepresented in all COVID-19 clinical trials in which race and ethnicity categories have been reported, including the most recent ones for vaccinations. COVID-19 studies should prioritize and promote the participation of at-risk populations, while reporting on participation of these populations would improve the generalizability of the efficacy and outcomes data. A similar approach should be used for oncology clinical trials. More frequent protocol deviations, due to pandemic-related logistical issues and most with little or no impact on patient safety, have increased the workload involved. This raises the possibility of making trials more streamlined and efficient by capturing only significant deviations.

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**The role of real-world and clinical practice data**

The application of real-world data (RWD) to support drug approvals is not a novel concept, and is accepted by the European Medicines Agency (EMA), US Food and Drug Administration (FDA) and other regulatory agencies. However, RWD has been applied on a limited basis in past years, mostly for rare diseases.

In a recent article, Eichler et al. explain why the future will not see randomized clinical trials (RCTs) versus RWE, -
but rather both RCTs and RWE, further stimulating the long-standing debate recently fueled by Collins et al.29

Areas of consideration for clinical trial stakeholders should include consideration and validation of:

A NEW PROBLEM-FOCUSED COLLABORATIVE FRAMEWORK

A new collaborative framework between oncology trial stakeholders, including decision makers, could leverage and further accelerate the innovation in clinical research seen during the pandemic. This could shorten timelines for patient access to new treatments by addressing the cultural and technology barriers to adopting new operational approaches and innovative clinical trials.

Pharmaceutical companies, ideally with the support of medical societies, investigators, CROs, payers, providers and patients, should consider working with political, administrative and health authorities to build on the positive impacts of COVID-19 on oncology clinical trials.

The pandemic has driven improved collaboration among clinical trial stakeholders, e.g. leading to faster approval of protocols by institutional review boards (IRBs) and regulators and even to faster regulatory approvals (e.g. for vaccines), by simplifying and optimizing processes to facilitate innovative research.

Plans to minimize bureaucracy for trial approval and expedite amendments should be further developed. Since a streamlined global approach is needed, an ideal goal of a single IRB across sites and countries could be pursued through an agreement between regulatory authorities to minimize complexities due to regional requirements.

Since trials need to be designed with the patient as the center of attention, the new collaborative framework could address the barriers to the adoption of decentralized clinical trials with patient-centric virtual home-based components. This could reduce the burden of unnecessary examinations, tests and travel, making clinical trials closer to clinical practice, and also offering a way to engage more minority patient populations in clinical trials. A more universal medical licensing process could facilitate virtual patient access to physicians and clinical trials.

Furthermore, oncology trial stakeholders should be engaged to support development of guidance and policies related to aspects of virtual trials, in particular the protection of patient privacy and data confidentiality, and the evaluation of remotely collected data. Recommendations and guidelines on the skills and tools required for remote monitoring and their financial implications will have to be assessed and defined.

Clarifications of the acceptable differences in drug delivery and local handling of drugs from the current standards in clinical trials are also needed. Innovative trials leveraging RWD and clinical practice, including simplified eligibility criteria, should be subject to further development through a joint effort of all stakeholders.

Amended regulations are required from the EMA and FDA to further advance the adoption of virtual components in oncology trials and to update regulatory standards for drug approval, including the acceptance of RWE in the context of innovative clinical trials for regulatory decision making. This has been especially important since the start of the COVID-19 pandemic, as sponsors and CROs are concerned that virtual approaches, incomplete trials and missing data may pose a challenge in regulatory filings. Pragmatic and harmonized actions were needed to ensure flexibility and procedural simplification, maintaining trial integrity and protecting participant and site staff safety; updated regulations were issued first in 2020 by both EMA and FDA.30

Communication issues due to the pandemic restrictions have been reported between oncologists and patients and/or caregivers, on topics such as tumor status, response to treatment, future care options and opportunities for clinical trial participation. As a result, a critical assessment of a proactive and patient-centric approach to trials and related communications and specific guidance are needed.

Timely engagement with patients to incorporate their insights should guide the actions of a new collaborative framework between trial stakeholders, including decision makers, to leverage and further accelerate the innovative approaches in clinical research developed during the COVID-19 pandemic. These should include an evaluation of acceptable trade-offs on treatment endpoints, comparators and tolerability, preferences and feedback at every stage of clinical trials and the overall re-thinking of clinical trials by minimizing the overall burden on patients, caregivers and other stakeholders.33

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