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EDITORIAL

# Beyond the lessons learned from the COVID-19 pandemic: opportunities to optimize clinical trial implementation in oncology

## INTRODUCTION

Since the beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic has progressively affected millions of people worldwide and has brought many uncertainties for patients, health professionals, and policymakers. According to the World Health Organization (WHO), as of 3 June 2021, there were 171 222 477 confirmed cases of COVID-19, including 3 686 142 deaths.[1]

Published evidence consistently shows that cancer patients are at a higher risk of death from COVID-19.[2-4] In the first months of the pandemic, all levels of care (screening, diagnosis, treatment, and follow-up) were disrupted.[5-7] Moreover, cancer centers started prioritizing care services, cancelling nonurgent appointments, adapting treatment protocols, and shifting to home-based remote care relying on telemedicine consultations.[5,7] The deferral of screening programs and cancer-directed interventions generates concerns for an increase in the number of patients diagnosed with advanced disease stage and poor outcomes.[6-12]

In these unprecedented circumstances, health care institutions, researchers, and policymakers adapted quickly with variably coordinated responses worldwide. Along with vaccine development and research for COVID-19 therapies, international collaborative registries such as the ESMO-CoCARE[13] or CCC19[14] initiatives were set up in record time with the aim to gather evidence from patients with cancer infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition, many societies such as the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) published recommendations to provide guidance for cancer institutions, oncologists, and patients.[15-17] However, this crisis also highlighted the need to optimize the delivery of care and the use of resources in clinical research. In this paper, we aim to capitalize on the lessons learnt from the impact of the COVID-19 pandemic on clinical trials and use them as a catalyst to launch a discussion over a framework of broader adaptations needed in the design and implementation of oncology clinical trials.

## THE EARLY IMPACT OF THE COVID-19 PANDEMIC ON CLINICAL TRIAL PERFORMANCE

Even before the COVID-19 pandemic important barriers impacted on the conduct of clinical trials.[18-20] Different research groups have been proposing a number of solutions in order to remedy the complex, and at times dysfunctional reality of clinical cancer research.[19-22] To add to this background, clinical research activities were seriously impaired at the beginning of the SARS-CoV-2 pandemic, resulting in many sites struggling to maintain their trial activity and to start new studies.[18,23-25] Recruitment of new patients and follow-up visits were reduced with the advent of lockdown measures in most places,[26,27] while the pandemic and quarantine policies significantly affected research staff availability and performance. In a survey conducted by the ESMO Resilience Task Force in oncology professionals ($n$ = 1520), 67% of responders reported a change in professional duties since COVID-19, 66% were not able to perform their job compared with the pre-COVID-19 period, and 38% experienced burnout symptoms.[28]

As a consequence, the launch of new clinical trials, screening, and enrollment of new patients, clinical visits, updates of case report forms were affected.[23,25,26,29] The pandemic also hindered patient empowerment (decision-making process) due to the distancing between investigators, caregivers, patients, and families. In fact, several background problems for clinical trial research became even more difficult to manage during the COVID-19 pandemic (Table 1).

The need for adjustments in clinical trial procedures prompted the European Medicines Agency (EMA) and American Food and Drug Administration (FDA) to publish guidance during the COVID-19 pandemic.[29,30] At the same time, trial sponsors adapted protocols with a series of amendments, including the need to 'reconsent for trial enrollment during COVID-19'. Sponsors, investigators, and patients improvised with adaptation strategies while experts and scientific societies highlighted the need and opportunity to rethink how clinical trials are run.[18,31-34] In Table 2 we recapitulate the educative lessons to be considered for the future of clinical research post-COVID-19 (Table 2).

## BEYOND THE PANDEMIC: OPPORTUNITIES TO OPTIMIZE CLINICAL TRIAL IMPLEMENTATION

### *Reduce administrative load and optimize performance of clinical trials*

In a recent survey by the ESMO Clinical Research Observatory (ECRO), clinical investigators ($n$ = 940) strongly agreed on the excessive burden of administrative tasks that reflect negatively on the quality of clinical research.[19] While adherence to international guidelines such as the Helsinki

**Table 1. Obstacles in clinical research and their changes during the pandemic**

| Obstacles in clinical trial research before the SARS-CoV-2 pandemic | Deterioration during the SARS-CoV-2 pandemic |
|---|---|
| Excessive burden of administrative tasks | More difficult to accommodate with restrictions in clinical and research activities |
| Organizational, resource, and staff limitations to accommodate a growing number of novel-design clinical trials | Pandemic and quarantine policies significantly affected research staff availability and their burnout levels; significant reduction in clinical trial performance; inability to rapidly adapt to new research and clinical conditions |
| Excessive time in research meetings (local visits, audits, and data monitoring events) | Extremely difficult to accommodate with lockdown policies and reduced staff available |
| Length and complexity of informed consent | Patient empowerment reduced due to the distancing between investigators, patients, and caregivers; more reconsents needed |
| Patient difficulties to access research centers (living far, elderly, comorbidities, economic conditions) | Aggravated following lockdown measures and quarantine policies |
| Disproportionate/unnecessary number of time-demanding clinical trial appointments for patients | More difficult to maintain following lockdown measures and changes in hospital-care and research pathways |
| Restrictive eligibility criteria and under-representation of real-world population | Increased difficulty to keep enrollment goals with many patients reducing their hospital visits; low representativeness of patients at a higher risk of death from COVID-19 (e.g. elderly; patients with cancer or heart dysfunction) in vaccine pivotal trials. |
| Weak correlation between some surrogate endpoints and clinical meaningful outcomes | Unprecedent short landmarks in time for (COVID-19) vaccines efficacy considering the global urgency. |
| Significant dropout rates from clinical trials due to excessive administrative load, visits, or uncertainties with treatment efficacy and toxicity | Patients refraining from visiting cancer centers for treatments or follow-ups |

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2. Pathways for optimizing oncology clinical trial implementation based on the coronavirus disease 2019 (COVID-19) pandemic experience as a catalyst**

| Pathways |
|---|
| Reduce administrative load, optimize performance of clinical trials |
| • Reduce redundant documentation or procedures in strict compliance with good research practices<br>• Revisit burdensome internal procedures of research sponsors<br>• Reduce on-site and increase remote visits for research staff meetings, audits, and monitoring<br>• Increase the use of validated artificial intelligence tools and text-mining technologies for data collection and monitoring<br>• Develop organizational flexibility for novel research methodologies and technologies<br>• Optimize research cooperation with national and international networks expanding clinical trial access to more centers and patients<br>• Develop shared databases of resources and operational information related to investigators and logistics of trial implementation |
| Improve informed consent |
| • Simplify informed consent (IC) and reconsent documents using readability methodologies<br>• Promote use of remote electronic consent (eConsent), by either videoconference (oral) or procedures for e-signatures. Facilitate face-to-face meetings when easy to schedule or requested by patients<br>• Develop specific eConsent guidelines to ensure patient empowerment<br>• Engage patient representatives in the development of IC and eConsent documents<br>• Increase patient literacy in clinical trial research, improving sources of e-information and web-based networking |
| Promote telemedicine and decentralize point of care |
| • Expand use of telemedicine in oncology clinical trials<br>• Provide research, training, and validate guidelines for telemedicine and remote procedures in clinical trials<br>• Develop and use validated electronic patient reported outcomes and tools (quality of life scales; wearable devices; phone apps; online reports) with continuous data collection from patients, particularly in the adjuvant and curative trial settings<br>• Involve regional centers close to patient residency as co-research institutions, allocating proper training and incentives<br>• Allow examinations (clinical; laboratory; radiology) to be performed close to patient home with easy assessment by the main research institution<br>• Deliver oral medicines to patient homes, with accountability, monitoring, compliance and follow-up procedures in place |
| Optimize clinical trial impact: trial population, endpoints, and validation |
| • Use broader inclusion criteria in trials in select clinical circumstances, simulating real-world settings<br>• Further develop novel trial designs, based on molecular enrichment, master protocols, and pragmatic control arms<br>• Promote generation of real-world evidence from well-designed, high-quality complementary RWD studies<br>• When surrogate endpoints are used in trials in areas of unmet need, validate any benefit from new drugs with the impact on clinically meaningful patient-centered endpoints in trials supplemented by RWD, preferably on overall survival and/or quality of life<br>• Build consensus on significant methodology and quality requirements of RWD, along with development and validation of artificial intelligence tools linked to clinical evaluation of therapeutics and biomarkers |

RWD, real-world data.

Declaration and good clinical practice regulations are *sine qua non*, their overinterpretation may undermine the efficiency in all clinical research processes. For instance, the General Data Protection Regulation 2016/679 (GDPR) of the European Union (EU), which came into force on 25 May 2018, raised concerns in the oncology community, due to the misinterpretation of the measures required by various clinical research stakeholders.[22] Pharmaceutical industry sponsors and contract research organizations commonly demand more rigid, burdensome administrative and recording procedures than those stipulated in international recommendations, with many of those extra tasks being extremely time and resource demanding. These factors decrease investigator motivation, hinder drug development, and patient's access to innovative treatments.[19,21,35] This background problem became more complex to manage as

the pandemic started affecting health institutions, forcing research sponsors to revisit their internal procedures to facilitate implementation of clinical trials.

Well-conducted studies require resources, trained investigators, and dedicated teams. Lack of preparedness and mechanisms for flexible adaptation of these elements affected several research centers and contributed to the significant reduction in clinical trial activity.[25,36] Organizations should develop a clear resilience plan to be implemented during challenging conditions (such as the pandemic), bringing together investigators, administrators, and patients for its development in a base-to-apex approach. Digital technologies and remote data collection/review approaches are integrative in such contingency plans.

Data monitoring events, local meetings, and audits are very demanding activities for sponsors and researchers[19-21] and although necessary, they can be trimmed and be performed remotely, without compromising the integrity and quality of clinical research. This was successfully tested during the pandemic and could be continued in the future.[36-39] Remote meetings, data verification, and monitoring (phone calls, video visits, emails) of data collected from each clinical trial site may be permitted in appropriately defined settings, after validated standard operating procedures are set in place. In addition, artificial intelligence tools and text-mining technologies for data collection, review, and monitoring, when properly validated, could be used to reduce the burden of work needed by a human hospital operator.[40-42]

Cancer clinical trials, especially early phase, are often run in centers in a 'cocoon' environment limited to the center. A functional web-based portal with a trial database and trial-specific contact points could promote awareness, diffuse information, and coordinate patient screening and accrual procedures across a vast network of centers. Moreover, although clinical trials are similar in their implementation conditions, commonly each local investigator team and each trial sponsor need to develop the administrative resource package from zero, resulting in loss of time and resources. Centralized, shared, updatable databases collecting all relevant data from trained investigators and sites (good clinical practice training records, financial disclosures, feasibility conditions, standardized Curriculum Vitaes) can lead to more efficient, fast implementation of clinical trials. Such a strategy could be managed by regulators overseeing clinical research.

### *Improve informed consent*

The informed consent (IC) is a cornerstone trial feature empowering patients and relatives with the most relevant information for their own decisions. With current practices it is often too complex, long, having excessive medical jargon, and time demanding for both patients and investigators.[43,44] Besides, IC amendments are frequently required, and both patients and researchers need to go through a time-consuming process of reconsent. As the pandemic surged worldwide, sponsors rapidly adapted their trials with amendments, resulting in more in-person visits for reconsents.

Over time, remote consents, which were not common before the pandemic, became progressively permitted either by videoconference (oral consent) or via electronic records and signatures. With modern technology and electronic security mechanisms in place, a remote consent (or reconsent) could be maintained after the pandemic, particularly for patients having difficulties to access the research center. However, provisions for face-to-face meetings and authorizations should be made possible, specifically if requested by the patient. The trend for more remote consents raises the need to develop specific eConsent guidelines and validation studies with close monitoring to ensure patient empowerment, efficiency, and data security.[45] An implementation process is needed to provide information on how to determine whether eConsent is a feasible approach, which multimedia components are a reasonably good fit for a specific study, and the external and internal data security/audit processes to consider when implementing.

In order to improve patient and relatives' literacy in clinical research, dedicated sources of information should be developed. Web-based networks and compassionate communities can foster dialogue between patients and promote the exchange of information as well as literacy, participation, and compliance with clinical trials.[46-48] Finally, new opportunities to improve and simplify ICs, such as applying readability methodologies,[49] shortening documents, and engaging patient's advocates in IC development, will optimize patient empowerment.

### *Promote telemedicine and decentralize point of care*

Different studies have reported significant dropout rates of cancer patients in clinical trials.[50-52] The extensive paperwork, number of visits, examinations might demotivate many patients and investigators from complying with intensive research protocols. These obstacles increased during the pandemic[53] with many patients self-isolating and dropping out from trials.[26,27]

The average number of hospital visits for patients enrolled in clinical trials can be time consuming as the number of activities, such as toxicity assessment, physical examination, vital sign measurements, patient-reported outcome monitoring, blood tests, treatment administration contribute to long hours in the cancer center. Some of these tasks could be reduced, or assessed at home or in a nearest institution. Local health centers could be engaged in trials for clinical assessment or diagnostic examinations, where research teams should receive proper training, incentives, and be considered co-investigators, under the supervision of the main research team. These measures can bring several advantages: (i) patient comfort, (ii) access to research and financial incentives to local/regional centers, (iii) increase of recruitment of patients, and (iv) decrease of the workload pressure at the main institution center.

The EMA guidance for clinical trials during the pandemic accepted, exceptionally, laboratory examinations, imaging, or other diagnostic tests to be performed locally, outside the research center.[29] There are good reasons to keep this practice beyond pandemic times, including the lack of evidence supporting the superiority of central over local testing, at least for routine procedures. Nowadays, many diagnostic examinations can be performed under the same conditions in different institutions with proper certifications without undermining the quality of data. This patient-friendly policy may reduce disparities in access to clinical trials for patients living remotely.

For all these clinical and laboratory pathways, there must be an agreement between patients, research centers, and the sponsor, with scientific and financial incentives provided for local and regional centers by the latter. For laboratory examinations, it should be formally certified that the same methodologies and units are used, and data are easily interoperable, accessed, or sent to the main research center. Imaging modalities may also be decentralized, provided a standardized protocol is used for image acquisition, all examinations are digitized, stored securely, anonymized, and easily accessed by the main research center. Only essential study procedures, such as biomarker assessments or tumor biopsies, should be validated centrally for good scientific reasons.[54] In addition, in many countries and hospitals the delivery of cancer medication to patient's home expanded to more patients, clinical conditions, and drugs as a response to the pandemic. While not yet generalized in clinical trials, this could be considered in future for some oral treatments, after setting up proper protocols for drug delivery, accountability, and compliance monitoring.

Current clinical trial protocols are strict with face-to-face visits and do not consider remote appointments, despite provisional permission of telemedicine use during the pandemic. Reducing the number of appointments and converting some physical visits into telephone or video consultations (e.g. for safety reporting; clinical assessment) was a positive experience during the COVID-19 era,[18,36,39,55] with high satisfaction rates reported from both clinical trial participants and investigators.[56,57] Telemedicine could be contemplated in future clinical trial protocols, to ensure that only strictly necessary visits are performed at sites. However, specific guidelines and procedures should be very well defined in the protocol[58] and patients with lower technological skills should not be excluded or discriminated. Monitoring toxicity could be performed from distance only in low-grade cases, while upon suspicion of a significant adverse event or disease progression, the patient should have a face-to-face appointment as soon as possible in the primary or collaborating trial hospital. It must be noted that telemedicine requires dedicated time and conditions for all staff, proper technology infrastructure, training, and research into the adequate patient—doctor relationship adjustments. Moreover, it should be considered a regular clinical activity from all perspectives.

Novel electronic patient reported outcome strategies could be used to collect patient-level reliable data, while reducing the number of physical appointments. These may include quality of life scales and use of wearable devices, phone apps, or online reports.[59,60] The use of these remote monitoring tools can enable symptom management to be performed either remotely or locally at the patient's home. However, more research is needed before all these tools are properly validated to be considered in clinical trials, and this avenue should be pursued.[61] To date, evidence of benefits of digital symptom monitoring has been largely focused on patients receiving treatment for metastatic cancer. There has been scant evaluation of impact on patients with curable disease receiving time-delimited adjuvant therapy who have minimal disease burden and symptoms.

### *Optimize clinical trial impact: trial population, endpoints, and validation*

The scientific community has been identifying several challenges and opportunities to improve cancer clinical research.[20,62-64] Before the pandemic, the restrictive eligibility criteria and under-representation of real-world population were already considered potential deficits in clinical trials.[51,65] Elderly patients and those with severe comorbidities, abnormal laboratory profiles, or moderate performance status are commonly excluded from pivotal research, although they represent a significant proportion of the real-world cancer population.[65-69]

Another important challenge for cancer research has been the definition of endpoints capturing relevant outcomes in each research setting as timely as possible, in order to provide the patient with rapid access to innovative therapeutics. Ideally, surrogate endpoints with strong correlation with clinically meaningful outcomes should serve this purpose, but few comply to this definition.[70-72] As an example, after granting accelerated approval for several immune checkpoint inhibitors, the FDA announced that four indications were voluntarily withdrawn, and six others were under review, as reported results from confirmatory trials have not verified clinical benefit.[73] Consequently, surrogate endpoints, as important as they are to rapidly bring innovative treatments to patients with cancer, need to be validated in each context for their correlation with clinically meaningful outcomes, such as improvement of overall survival and/or quality of life, in the setting of clinical trials. Real-world data may be extremely important to validate such correlations in contexts in which trials are unethical (unmet need, no effective therapy) or not feasible (rare tumors).

In an analogous experience, the pandemic emergency led to the launch of several clinical research projects, vaccines were developed and approved in record time, and many real-world evidence studies were published. Shorter-term endpoints were used in COVID-19 trials, resulting in marketing authorization of several effective vaccines. However, relevant endpoints such as the long-term vaccine protection, interruption of virus transmission, and rare events were not considered, while some population groups (cancer, immunosuppression, adolescents) were not included, resulting in knowledge gaps.[74] To partly remedy this, close

monitoring with trials and real-world studies further confirmed vaccine effectiveness[75,76] while safety signs were captured in time by pharmacovigilance systems.[77,78] Nevertheless, there were also contradictory evidence from different real-world studies assessing some treatments against COVID-19, such as with chloroquine or remdesivir, due to variations in local management, data quality, and granularity.

The SARS-CoV-2 vaccine trial experience, and overall the challenges encountered in clinical trial activities due to the stress imposed by a viral pandemic, should become the catalyst for initiating a multistakeholder discussion on broader reforms in the design, organization, and implementation of clinical research in oncology. Inefficiencies highlighted by the pandemic can become opportunities to elicit carefully designed adaptations aiming to improve (i) representativeness of trial populations, (ii) balanced use of accelerated drug approvals based on surrogate endpoints, and (iii) validation of benefits from new drugs captured by surrogate endpoints in clinically relevant outcomes in trials and real-world data.[79,80] Both before and certainly after the pandemic, we advocate for trials with relevant, patient-centered, and clinically meaningful endpoints in representative populations as similar as possible to real-world settings, while acknowledging the need for fast-track patient access to promising novel therapeutics. When proof of remarkable benefit is provided by a novel treatment in an area of unmet need in the setting of a clinical trial using surrogate endpoints, fast conditional approval can be justified, coupled to future validation in confirmatory studies (clinical trials supplemented with real-word data) assessing mature, clinically meaningful, 'hard' endpoints. In this setting, the role of real-world data as a synergistic and complementary research methodology to traditional randomized trials should be further assessed after building consensus on significant methodology and quality requirements.[63]

The pandemic impact sorely stressed the need to study optimal paths for delivering these goals. Mechanisms such as the PRIME scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need could be expanded, with periodic reassessment.[81] The development of artificial intelligence tools offers promise for the empowerment of real-world data in the assessment of therapeutics and biomarkers; however, they should be rigorously validated before general use.

## Conclusion

The COVID-19 pandemic affected millions of people globally, and its effects on society, patients, health institutions, and governments may persist. Clinical trials are our best tool to improve cancer treatment for patients through testing the clinical value of a new treatment or intervention; however, they were particularly affected by the COVID pandemic, despite frantic adjustments. Still, the challenges imposed by the pandemic on daily running of clinical trials in oncology highlighted pre-existing inefficiencies. The pandemic and its impact should be revisited as an opportunity and catalyst to ignite a discussion among all stakeholders on pragmatic reforms that will transcend through and expand beyond pandemic lessons, ultimately aiming to improve cancer clinical research in all contexts. The clinical trial administrative load could be significantly reduced, without affecting the quality of research and ethics principles. Cancer centers should adapt their structure faster to molecular oncology and novel trial designs. Importantly, the number of physical visits to research institutions could be reduced with telemedicine and routine examinations should be performed in local institutions (co-research centers), maintaining adherence to good clinical and research practices. Clinical trials should adopt broader inclusion criteria and better outcome definitions and be more focused on real-world population needs, while fast-track drug approvals based on surrogate endpoints should be linked to strict validation requirements. The COVID-19 pandemic is a dramatic and negative experience, however lessons learnt could be further developed in order to facilitate equitable access to clinical trials of real-world populations in a pragmatic, simplified, and methodologically robust modus operandi for the benefit of all our patients.

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