



Virtual oncology research—different models and lessons learned

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Purpose of review

The COVID-19 pandemic posed several challenges to cancer research including halting of trials, reduced recruitment and protocol violations related to inflexible processes followed in clinical trials. Researchers adopted innovative measures to mitigate these problems and continue studies without compromising their quality. This review collates these adaptations that could well continue after the pandemic.

Recent findings

The COVID-19 pandemic forced researchers globally to adopt innovative measures to overcome the challenges of the pandemic. These included protocol amendments to adjust to the pandemic and travel restrictions, and increased use of digital technologies. 'Virtual' clinical trials were conducted increasingly with adaptations in ethics and regulatory approvals, patient recruitment and consenting, study interventions and delivery of study medications, trial assessments, and monitoring. Many of these adaptations are safe and feasible, without compromising study quality and data integrity. Although these may not be universally applicable in all types of research, they bring many benefits including more diverse patient participation, less burden on patients for study procedures and reduced resources to conduct trials.

Summary

The COVID-19 pandemic has affected cancer research adversely; however, learnings from the pandemic and adaptations from researchers are likely to improve the efficiency of clinical research beyond the pandemic.

Keywords

cancer research, COVID-19, pandemic, virtual clinical trials

INTRODUCTION

The COVID-19 pandemic has had a widespread impact on health and healthcare in many ways. In addition to the morbidity and mortality of the infection itself, the focus on COVID-19 has diverted attention and resources from other illnesses, especially noncommunicable diseases. Cancer care has undoubtedly been affected adversely; however, a less recognised effect has been the impact on cancer research. Recruitment into trials and maintaining due process during the conduct of studies was particularly challenging. However, the pandemic resulted in an exponential use of digital technology to replace various in-person processes, and this extended to the conduct of clinical research as well. Even prior to the pandemic, several clinical trials had some components that were conducted remotely; the restrictions during the pandemic have led to increasing acknowledgement of the utility of digital technology in the conduct of clinical trials – the so called 'virtual' clinical trials.

Virtual clinical trials (also known as remote, decentralised, digital, siteless or direct-to-participant trials) refer to digitally empowered clinical trials that utilise technology at every stage of the trial process to bring trials closer to the participant. In this review, we look at the components of virtual clinical trials, and their benefits and disadvantages. To identify relevant articles on this topic, we searched PubMed using a combination of the terms 'virtual' AND 'oncology' OR 'cancer' AND 'clinical trial' OR 'research'. We did not restrict the search to a particular time period or language

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KEY POINTS

- Clinical research in general including cancer research has the potential to be far more efficient than it is currently
- Several aspects of clinical research can be conducted virtually using digital and other tools that can diversify patient participation, improve study efficiency, and make research patient-centric rather than site-centric.
- These learnings and adaptations from the pandemic could well be extended to normal times without compromising study quality or data integrity.

THE IMPACT OF COVID-19 ON CANCER RESEARCH

The COVID-19 pandemic affected cancer research in several ways [1,2]. Travel restrictions during the pandemic and the fear of acquiring COVID-19 resulted in decreased hospital visits with slow recruitment on trials and protocol violations related to study interventions and assessments. Oncology research protocols were adapted or modified to minimise immunosuppression which could increase the risk of acquiring COVID-19, or to reduce the frequency of assessment and follow-up. Disruptions of pharmaceutical supply chains resulted in nonavailability of investigational products. There were staff shortages due to deployment to clinical areas or due to infection or quarantine. Laboratories were burdened with the need for testing for COVID-19, putting research investigations on the backburner. Funding was diverted from research to essential areas. The overall impact of these measures was a substantial decrease in new oncology trials, decreased patient accrual on existing trials, and temporary or permanent cessation of several trials, leading to delays in the development of therapies in oncology [2].

Based on data from clinicaltrials.gov, Upadhyay and colleagues reported considerable decreases in patient enrolment in oncology clinical trials during the early part of the pandemic [3]. Out of 36 oncology researchers in the USA and Europe, less than 20% were continuing to enrol patients on trials. In a follow-up study [4], they found that overall, between March 2020 and April 2021, 386 oncology trials were halted. The peak stoppage occurred in June 2020 followed by a slow recovery. Even a year after this (mid-2021), almost 30% of these trials were still on hold or had been withdrawn or terminated. Data from 64 National Cancer Institute (NCI) designated cancer centres, showed a precipitous fall in enrollment in the early stages of the pandemic

which had not recovered to pre-pandemic levels even in mid-2021 [5]. There was a 60% decrease in the number of launches of oncology clinical trials of drugs and biological therapies on a commercial clinical trial platform during the pandemic [6]. Similarly, many other centres have reported declines in research activities due to COVID-19 [7–11].

Several oncology societies and organisations such as the US-FDA, NCI, European Medicines Agency (EMA), and the United Kingdom Medicines and Healthcare products Regulatory Agency issued guidelines to navigate the challenges of conducting oncology research during the pandemic [12–16]. These guidelines focus on a digitally enhanced, decentralised and participant-centric approach.

CLINICAL TRIALS IN ONCOLOGY

Conventional clinical trials in oncology are extremely resource-intensive. They are site-centric i.e., centred around medical facilities like the hospital or clinic, which are usually academic centres in urban settings and are not easily accessible to patients from remote areas, or those who have difficulty in travelling to the site. Oncology protocols also tend to be complex, necessitating frequent visits by participants for initial screening, delivery of study interventions, and safety and outcome assessments. For most trials, monitoring to ensure data integrity and participant safety involves multiple site visits by monitoring staff. All of these require investment in terms of infrastructure, human resource and funding.

THE 'VIRTUAL' CLINICAL TRIAL

In any clinical trial, all or some aspects may be carried out remotely - defined as 'virtual' or 'hybrid' clinical trials. It is now clear that the advantages offered by the virtual or hybrid approach will be useful even in the postpandemic period. Several authors have described the key features of virtual clinical trials [17^{**},18^{**},19^{**},20^{**}–22^{**},23^{**},24^{*}].

ETHICS AND REGULATORY APPROVALS

The pandemic resulted in several ethics committees adopting procedures for electronic submission of documents by researchers, and virtual meetings to approve projects. Regulatory agencies also switched to acceptance of electronic submissions. Many countries laid out guidelines for the expedited approval of research projects especially those related to the diagnosis and management of COVID-19. Some centres initiated the process of single committee approval for multicentric projects, hastening the trial approval process [25,26]. Aided by developing

technology, these processes could continue well beyond the pandemic to non-COVID-19 research as well.

PARTICIPANT RECRUITMENT

Patient recruitment is a major hurdle in clinical research and it has been estimated that less than 10% of patients with cancer are part of a clinical research study even in normal times [18²²,27]. The use of digital technology can help to improve recruitment rates [23²³]. For example, the use of artificial intelligence tools can help to match patients to appropriate ongoing clinical trials and to identify rare groups of patients with uncommon cancers [18²²,28]. Screening tests are carried out prior to patient enrollment to determine if participants meet the eligibility criteria and can safely receive the study interventions. The screening of patients for eligibility for participation could be carried out virtually by reviewing essential clinical parameters and investigations through digital techniques [21²¹]. For this, it is preferable to restrict screening tests to those which are absolutely essential to ensure participant safety and study validity.

PARTICIPANT ENROLLMENT

Technology can also be used to streamline the enrollment process, including participant counseling and consenting. The process of informed consent for participation in a trial usually includes several site visits involving dissemination of information to the participant, counselling and clarification of queries and finally the signature process. In a remote consenting technique, blank consent forms are mailed to participants, followed by a virtual discussion and forms are signed electronically. A reduction in the number of visits needed for enrollment will allow inclusion of populations that are traditionally under-represented in clinical trials e.g., those living in remote areas or those with mobility issues [18²²].

STUDY INTERVENTIONS

Trial participants make several site visits to receive study interventions. In a virtual clinical trial, various modalities could be used to deliver study medications to the participant [19¹⁹,23²³]. These include personal delivery of study drugs to participants by research staff, use of medical delivery services, medication pick-up from specified sites or shipping of study medications through the mail. For medications which need to be delivered parenterally, tie-ups with local providers or home-based care

providers may be needed. During these processes, it is essential to ensure that there is accountability for the investigational product, that storage and delivery requirements are adhered to, and that blinding is maintained [22²²].

CARE OF RESEARCH PARTICIPANTS

Continued medical care of participants during the trial is important to monitor compliance to trial interventions, ensure the safety of participants and allow early identification of adverse events. In conventional clinical trials, this involves repeated site visits for the assessment of safety and efficacy outcomes. In a virtual clinical trial, the care of trial participants could be transferred to local providers to decrease travel requirements. Digital technology using telemedicine or video calls can also be used to allow investigators to conduct remote consultations with participants.

STUDY ASSESSMENTS

In a virtual clinical trial, it is essential to choose appropriate study outcomes. Since collection of samples may be difficult, researchers should also consider converting outcomes to those that can be measured at home. Various approaches have been described to allow remote study assessments [20²⁰]. Participants could use home-based non-invasive devices (e.g., pulse oximeter, glucometer, fitness bands) to provide data on parameters such as vital signs, physical activity, or sleep patterns. In addition to providing real-time data, these methods allow early identification of adverse events compared to interval-based assessments [18²²]. Participants could also report symptoms using self-administered, telephonic or web-based questionnaires. If clinical examination is needed, coordination with local healthcare providers can allow in-person assessments, and researchers could access electronic health records to obtain the relevant information.

Study assessments requiring laboratory tests or imaging techniques may pose a problem. Again, local facilities may be used for these assessments. Alternatively, participants could be instructed to perform simple home tests (e.g., finger-prick method or urine samples) or home visits by laboratory personnel could be arranged. Depending on the complexity of the test required and the resources available locally, samples could either be analysed at local labs or shipped to a central laboratory for testing. For imaging modalities, digital images could be shared to a central facility for review by a radiologist.

Table 1. Components of a clinical trial and modifications for a virtual format.

Ethics and regulatory approval	<ul style="list-style-type: none"> • Electronic submission of documents • Virtual meetings of Ethics Committees • Centralised Ethics Committee approval for multicentric studies
Patient recruitment	<ul style="list-style-type: none"> • Include peripheral sites • Use artificial intelligence and machine learning tools to match patients to trials
Patient screening	<ul style="list-style-type: none"> • Use digital methods to review eligibility and investigations
Consenting	<ul style="list-style-type: none"> • Establish virtual communication to counsel potential participants • Enable electronic methods for consenting
Delivery of study medications	<ul style="list-style-type: none"> • Home delivery via courier or postal services • Pick-up at prespecified local facilities • Delivery by home health services
Study interventions	<ul style="list-style-type: none"> • Self-administered - e.g., oral medications, subcutaneous injections, behavioural therapies, exercise strategies • Via home health services • Refer participants to local healthcare providers
Study assessments	<ul style="list-style-type: none"> • Use outcomes that can be self measured • Data collection from wearable devices - either transmitted directly or uploaded by the participant • Self tests using home kits • Virtual assessment by the research team • Assessment via home visits • Assessment by local healthcare providers • Use local labs or imaging centres • Self collection of samples - courier samples to central lab • Data collection via electronic health records • Self-administered or virtually administered questionnaires (telephonic or video)
Safety monitoring	<ul style="list-style-type: none"> • Real-time data from wearable devices • Assessments by local healthcare providers • Virtual assessments by the research team • Patient-reported adverse events
Study monitoring	<ul style="list-style-type: none"> • Remote monitoring • Risk-based monitoring

MONITORING OF CLINICAL TRIALS

Periodic monitoring of ongoing clinical trials helps to protect participant safety and data integrity, and ensures that the trial is conducted in keeping with the study protocol. Typically, in-person study monitoring is conducted at each trial site by a monitoring team. In virtual trials, monitoring can be conducted remotely using digital tools to access trial-related documents. This can be done in many ways: e.g., sharing scanned copies of trial documents via e-mail, sharing computer screen via a video-conferencing application or providing remote access to electronic medical records. A large part of trial costs is attributed to on-site monitoring, which for some large global clinical trials could be up to 60% of all trial costs [29]. However, there is no evidence to support this approach, and none of the randomised trials comparing intensive with less intensive monitoring have shown clinically relevant treatment outcomes [29]. We strongly advocate an approach of remote monitoring and risk-based monitoring even after the pandemic.

Table 1 lists the components of a clinical trial and the modifications that can be made to suit the virtual format.

EXAMPLES OF VIRTUAL TRIALS

The TOPAZ trial was a home-based trial evaluating the efficacy of zoledronic acid in preventing fractures in elderly patients with Parkinson’s disease [30]. The virtual format of this trial with recruitment via support groups and websites, online consenting, diagnosis through telemedicine, administration of home-based therapy via research nurses, and assessment of endpoints by surveying electronic health records or follow-up via mail, e-mail or phone every 6 months made the trial feasible in a population which might otherwise have not been able to participate in a site-centric trial due to mobility issues.

Oxman studied the effect of Valerian for insomnia in a web-based randomised trial [31]. Participants were recruited through a weekly nationally televised health program and enrollment and data collection was carried out via the internet. Study

medications were mailed to participants and outcomes were assessed via a self-recorded diary.

ADVANTAGES OF VIRTUAL CLINICAL TRIALS

Virtual clinical trials offer several benefits for oncology (and other biomedical) research. They expand the pool of patients who can participate in a trial and enhance participant enrolment [18¹⁸]. Since trial processes are carried out at or near the participants' location, the burden on participants is reduced, leading to fewer drop-outs and better retention. This also ensures better compliance with the protocol, with fewer violations and improved data quality. Virtual trials consume less resources in terms of staffing, infrastructure and funding [32]. Real-time monitoring of outcomes may allow the earlier detection of adverse events [18¹⁸]. The inclusion of a diverse pool of participants, along with patient-centred study processes provides real-world data on the efficacy of an intervention compared to the results of a site-centric clinical trial with its tightly controlled operations [33].

CAVEATS WITH VIRTUAL CLINICAL TRIALS

However, virtual trials also pose several challenges. These trials may not be suitable in all settings [22²²]. For example, early phase trials that need pharmacokinetic monitoring or studies involving complex interventions which may be performed only at specialised centres need to be carried out at specific sites. Similarly, these trial formats may work better with oral rather than parenteral medications and for interventions whose safety has already been established but are now being considered for a new indication. Participants with acute health conditions like trauma, stroke or myocardial infarction, or those with cognitive impairment may not be able to comply with the requirements of a virtual trial. Virtual trials are heavily technology-dependent; the digital divide means that certain populations who have poor access to, or are unable to use the required technology may still be under-represented in such trials. Regulatory requirements related to research are constantly evolving and while many countries have eased up research regulations during the pandemic, these vary between countries and may not apply to the post-pandemic situation. Electronic consent, data capture and data sharing require specialised encrypted secure web applications. There are concerns about the privacy of participants and the security and confidentiality of data. The delivery of study drugs to the participant without site visits increases the complexity of supply chain logistics.

Standards of drug storage, handling and administration may be variable leading to inconsistent drug delivery and effect. Quality control and acceptable limits for differences in drug delivery need to be specified. For some interventions such as cognitive therapy or behavioural interventions, remote delivery may not be as impactful as when carried out in person [20²⁰]. In addition, some interventions may be risky when carried out remotely by unsupervised participants e.g., walk tests in elderly patients. For laboratory and imaging assessments carried out at local facilities, reference values may be different [22²²]. Care should be taken to include only accredited facilities with the incorporation of quality control measures at regular intervals. If adverse events occur, they need to be managed at the local level. Though remote monitoring has been accepted by many regulatory authorities, some of them mandate re-verification of documents in a subsequent in-person visit. Switching to the virtual format requires additional training of all stakeholders in the research process. Finally, there may be specific insurance and indemnity requirements that need to be accounted for.

CONCLUSION

Virtual clinical trials are an excellent and feasible alternative to conventional clinical trials in certain situations. They are patient rather than site-centric and allow decentralisation of trial-related processes. They decrease the complexity of trials, consume less resources, reduce costs, shorten timelines and can potentially improve participant engagement, recruitment and retention. However, they may not be suitable in all settings and need to be considered for specific types of research questions, study designs and patient populations.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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