**INTRODUCTION**

The COVID-19 pandemic has had considerable consequences for the delivery of cancer care and for clinical trials. Patients with cancer are at an increased risk of death from COVID-19 (1). It has been predicted that a delay of six months to cancer surgeries would result in a drop from 18.1 to 15.9 life-years gained (2), and cancer services have been under pressure to maintain capacity. This has resulted in the restructuring of cancer services due the redeployment of resources to COVID-19 care and the effect of social distancing measures and lockdown policies designed to minimize the risk of viral transmission.

Cancer trials are an aspect of cancer care that has endured significant disruption during the pandemic. Medidata’s analysis of 4,667 studies and 186,807 study sites indicates that globally there was a 74% decrease in the number of patients entering clinical trials in May 2020, compared with the same time period last year (3). This was similar to the decrease seen in April (79%) and March (65%). The FDA has issued guidance on the conduct of clinical trials of medical products during the pandemic (4). This includes recruitment suspension, changes to patient monitoring, emergency deviations to the study protocol, and changes to the distribution of the investigational product, with the overall goal of ensuring the safety of trial participants. The guidance also outlines a number of measures that need to be taken, such as detailing contingency steps to ensure patient safety, the identification of trial participants, detailing the impact of these measures on each participant, and an analysis of the effect of these contingency steps on trial results. Depending on the trial, different steps have been taken to ensure the safety of trial participants. Though by definition disruptive, this has also provided a unique opportunity to improve the way trials are conducted.

The COVID-19 pandemic has caused widespread disruption of cancer clinical trials due to the restrictions on nonessential services and the reallocation of resources, and at the same time the urgent global effort toward discovering therapies that treat or prevent COVID-19 infection has led to shortening of traditional regulatory timelines. This experience should stimulate similar urgency in the way future cancer research is conducted.

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**THE EFFECT OF COVID-19 ON CLINICAL TRIALS**

The reallocation of resources and cessation of nonessential services have disrupted cancer clinical trial practices (7). During the pandemic, routine clinical research activities have been suspended and laboratories and universities have been closed with restrictions on nonessential travel. Suspension of nonessential clinical activities has affected trial recruitment, protocol-mandated clinic visits, routine scans, biopsies, and blood tests that will subsequently affect trial endpoints. Among other things, the closure of labs and universities has affected sample handling, processing, and data analysis, with travel restrictions affecting site inspections, appointments, and staff training by contract research organizations (CRO). In the United States, cancer trial recruitment in April 2020 fell 83% compared with April 2019 (3). Such disruption affects patient safety and delays drug development. Nevertheless, these problems can be mitigated with adaptations such as remote working practices.

The number and speed with which COVID-19 clinical trials have been registered over the last six months is exceptional even in normal circumstances (Table 1). This is typified by the WHO-led SOLIDARITY trial, an international clinical trial involving 400 hospitals from 35 countries. The design and conduct of this trial has taken 80% less time than a typical trial of this magnitude (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

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**Summary:** The COVID-19 pandemic has caused widespread disruption of cancer clinical trials due to the restrictions on nonessential services and the reallocation of resources, and at the same time the urgent global effort toward discovering therapies that treat or prevent COVID-19 infection has led to shortening of traditional regulatory timelines. This experience should stimulate similar urgency in the way future cancer research is conducted.

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The Global Research & Development Vaccine effort is unparalleled compared with any other period in clinical history: According to the WHO, as of June 29, 2020, 132 COVID-19 vaccine candidates were in preclinical development, with 17 candidate vaccines in clinical evaluation (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). International cooperation has been strong, and barriers between funders, regulators, public health bodies, academics, and industry developers have been made more porous to facilitate this development. Larger trials are often crucial to establishing a significant effect size in drug development, and this can be done quickly and successfully with the level of multidisciplinary cooperation seen here.

The rapid normalization of remote working practices that has developed during the SARS-CoV-2 pandemic has significantly affected a variety of professions. These working habits may provide key lessons for the cancer clinical trials community to learn from, delivering permanent change to the field in the future. Globally, in 2018, there were approximately 9.6 million deaths from cancer (8). By way of comparison, there were 500,000 deaths from COVID-19 in the first 6 months of 2020. Carrying forward this working impetus into clinical cancer research, once this pandemic is over, could reinvigorate the pace of drug development and progress.

**CANCER CLINICAL TRIAL RECRUITMENT**

One problem that cancer trials have faced is quickly recruiting sufficient numbers of patients to generate a large matched cohort with a treatment and a control arm. This is a problem common among clinical trials testing drug safety as well as drug efficacy in defined populations.

Patients are often recruited and reviewed at a specific center, which presents a barrier to participation for patients who live far away. The time commitment required to make frequent visits to the center can therefore be significant, and this contributes to the financial disincentives that hinder clinical trial participation.

The need to travel might exacerbate the profound difficulty in compiling representative samples that include a broad range of ethnic minority groups, as well as patients from more disadvantaged socioeconomic backgrounds or rural areas. Incorporation of remote working practices, such as the adoption of telemedicine, community visits, and the decentralization of trial centers to remote sites, will help mitigate these issues by improving accessibility to patients and reducing the need to travel.

**REMOTE WORKING PRACTICES TO REDUCE INEFFICIENCY**

Remote monitoring through effective use of video conferencing technology can present important opportunities to change clinical trials and address these issues. During the COVID-19 pandemic, there has been a strong emphasis on minimizing hospital-based patient contact, and telemedicine has been utilized as a way of assessing and interacting with patients. This trend could help cancer trials to decentralize from large study hubs and improve efficiency. Although important clinical assessments must be performed in person, many trials require frequent visits for low-risk patient monitoring; where feasible and safe, it might be appropriate and expedient that these be carried out through decentralized and remote sites. These sites could remove the burden of travel for patients with cancer and facilitate certain functions such as obtaining informed consent, physical examination, baseline investigations, structured interviews, and blood tests through a combination of telemedicine and mobile healthcare providers. During the pandemic, nurses have performed blood tests on patients in their homes or local health hubs to minimize infection risk, while electronic methods of consenting have been recommended for patients in isolation (4). Cancer trials could follow this example.

Previous clinical trials have noted difficulty in ensuring proper administration of oral investigational products (IP) without hospital visits: patients may frequently miss doses or take two doses of the IPs at once. Mailing IPs to patients’ homes and supervising IP administration using

<table>
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<th>Jan</th>
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videoconferencing technology might help to overcome the need for hospital visits in such situations.

USING TECHNOLOGY TO GALVANIZE RECRUITMENT

Remote working can be extended to improve efficiencies in study launch, site setup, and training. In March 2020, the American Society of Clinical Oncology launched a survey among its Cancer Research Committee and Research Community Forum Steering Groups to identify both challenges and opportunities to transform clinical trials after the pandemic (9). One of the key opportunities highlighted was the incorporation of remote industry sponsor and CRO visits. Enhanced electronic institutional review board (IRB) communications, the standard practice of e-signatures, and remote training were also considered. Incorporation of these key concepts will improve the efficiency of trial setup and recruitment.

During the COVID-19 pandemic, we have seen significant engagement from patients and effective online recruitment strategies for clinical trials. Adapted properly, technology has the potential to transform awareness of and access to cancer clinical trials. Remote interfaces and apps could be employed to help recruit matched participants and help inform patients with cancer about their eligibility for different studies as well as monitor symptoms and drug side effects. This may also help improve engagement in drug safety trials for well participants.

FLEXIBILITY OF PROTOCOL DEVIATIONS AND TRIAL DESIGN

Many trials that have defined strict time points for data collection, including clinical examination, blood tests, and imaging, have had to deviate from protocol in 2020 due to the pandemic. The impact on results and conclusions is presently unclear; however, this can inform future trial design: factoring in the effect of protocol deviation on time-dependent data collection points may enable the design of more dynamic trials.

The COVID-19 RECOVERY trial has highlighted what is possible in terms of design flexibility, allowing the addition of arms as evidence shifts. For example, in April 2020, one month after the trial launch, approval was granted for eligible patients to be randomized a second time to a tocilizumab arm (10).

TRIAL APPROVAL

Over the last two decades, randomized trials have been increasingly time-consuming and costly to conduct, due in part to the increasing complexity of the approval process and other bureaucratic challenges. The push to undertake crucial research is being suppressed by this level of regulation. The administrative burden is extensive, with the mandated collection of data less relevant to trial endpoints contributing to excessive costs of trial conduct (6). This inevitably results in a reduction in trial recruitment and in some cases prevents trials from being registered at all. Consequently, research is stifled and patient access to new treatments is curtailed.

The COVID-19 pandemic has shown that it is possible to significantly reduce the time, regulatory, and administrative costs involved in coordinating, registering, and conducting trials. This is typified by the rapid and efficient setup of large trials such as RECOVERY and the SOLIDARITY trial. For example, Medicines and Healthcare Products Regulatory Agency approval for the RECOVERY trial was given four days after initial application (https://www.recoverytrial.net/forsite-staff/site-set-up-1), and enrollment of the first patient took place nine days after the protocol was finalized (10). According to ClinicalTrials.gov, there have been 688 COVID-19 interventional trials with a study start date (first enrollment) between January 1 and June 1, 2020. By comparison, 174 lung cancer, 210 breast cancer, and 95 colorectal cancer trials were started during the same period in 2019. Moreover, the global vaccine development effort has been exceptional in its levels of cooperation between different international regulatory bodies, industry, and academia.

PUBLISHING DATA

Work during the pandemic has been disseminated quickly, with many researchers using the medrxiv and bioRxiv preprint servers to publish their work. There have been remarkable collaborative efforts such as the Johns Hopkins University COVID-19 Data Repository by the Center for Systems Science and Engineering, which has become an invaluable resource for tracking the pandemic in real time (11), and the GISAID platform, which hosts a repository for hCoV-19 genomes (12). According to the LitCovid literature hub, there have been 19,251 publications on COVID-19 in the last six months (13), with journals drastically reducing turnaround times during the pandemic. Nevertheless, the impetus to publish pivotal work quickly has come at a cost. On June 5, 2020, three authors retracted a Lancet and New England Journal of Medicine paper on the results of a multinational registry analysis on the use of hydroxychloroquine in COVID-19 outcomes, on the basis that they were unable to complete an independent audit of the data (14). Standards must be maintained while facilitating this speed of dissemination; this includes transparency in data sources and analytic methods (including code), reproducibility, and robust peer review.

CONCLUSION

Globally, in the first six months of 2020 there have been an estimated 500,000 deaths from COVID-19 and more than 4.5 million cancer-related deaths. This pandemic has enforced innovation and given fresh momentum to clinical trial development in a way that has not happened in cancer research. Cancer research has been disrupted, yet the innovative approaches in adapting to the restrictive environment must be taken forward. These include adopting remote practices to facilitate recruitment, patient contact, site visits, training, and IRB communications. Enforced protocol deviations may lead to increased flexibility in the design of new trials. Furthermore, the extraordinary speed and scale of COVID-19 trials has shown that unnecessary administrative barriers to trial approval and setup can be broken. There have been stellar
examples of collaboration, and publication turnaround time has significantly reduced during the pandemic; however, it is essential that quality is sustained while speed is facilitated. We must capitalize on our experience during this time to accelerate cancer clinical research progress. This can only serve to benefit our patients.

Disclosure of Potential Conflicts of Interest

C. Swanton reports grants from Pfizer, grants from Boehringer-Ingelheim, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from AstraZeneca, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Roche-Ventana, personal fees from Novartis, personal fees from MSD, personal fees from Illumina, personal fees from Celgene, personal fees from GSK, personal fees from Genentech, personal fees from Sarah Cannon Research Institute, personal fees from Medixcell, grants from Archer Dx Inc., personal fees and stock options from GRAL, stock options from Epic Biosciences, stock options from Apogen Biotech, personal fees from and is co-founder of Achilles Therapeutics, outside the submitted work. In addition, C. Swanton has a patent in Immune checkpoint intervention in cancer (PCT/EP2016/071471) issued, a patent in Methods for lung cancer detection (PCT/US2017/028013) issued, a patent in Method of detecting tumor recurrence (PCT/GB2017/053289) issued, a patent in Method for treating cancer (PCT/EP2016/059401) issued, a patent in Method of treating cancer by targeting insertion/deletion mutations (PCT/GB2018/051893) issued, a patent in Method of identifying insertion/deletion mutation targets (PCT/GB2018/051892) issued, a patent in Method of predicting survival rates for cancer patients (PCT/GB2020/052211) issued, a patent in Method for determining whether an HLA allele is lost in a tumor (PCT/GB2018/052004) issued, and a patent in Method for identifying responders to cancer treatment (PCT/GB2018/051912) issued. No potential conflicts of interest were disclosed by the other authors.

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