

Cancer Research: The lessons to learn from COVID-19

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Abstract

The COVID-19 pandemic has caused widespread disruption of cancer clinical trials due to the restrictions on non-essential services and the re-allocation of resources, and at the same time the urgent global effort towards 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.

Conflicts of Interest

C.S. receives grant support from Pfizer, AstraZeneca, BMS, Roche-Ventana, Boehringer-Ingelheim, and Ono. C.S. has consulted for Pfizer, Novartis, GlaxoSmithKline, MSD, BMS, Celgene, AstraZeneca, Illumina, Genentech, Roche-Ventana, GRAIL, Medicxi, and the Sarah Cannon Research Institute. C.S. is a shareholder of Apogen Biotechnologies, Epic Bioscience, GRAIL, and has stock options in and is co-founder of Achilles Therapeutics. C.B. and J.M. declare no conflicts of interest.

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 3 months to cancer surgeries would result in a drop of 18.1 to 15.9 life-years gained (LYG)(2), and cancer services have been under pressure to maintain capacity. This has resulted in the restructuring of cancer services due to the redeployment of resources to COVID-19 care and the effect of social distancing measures and lockdown policies designed to minimise 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 to the same time period last year(3). This was similar to the decrease seen in April (79%) and March (65%). The US Food and Drug Administration 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. These include detailing the contingency steps taken to ensure patient safety, the identification of trial participants, 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. While by definition disruptive, this has also provided a unique opportunity to improve the way trials are conducted.

The pandemic has highlighted what is possible when pressure demands; according to the COVID-19 clinical trials registry (www.covid19-trials.com) collated by Thorlund et al. over 1,000 clinical trials were registered internationally between January and May 2020(5). This is exceptional. Prior to the pandemic, regulation and bureaucracy acted as significant barriers to clinical trial research(6). The cancer community must capitalise on lessons

learned to stimulate a profound change of behaviour in the way clinical cancer research is conducted in the future and address the problem that current regulatory and trial approval timelines are too slow to meet patient need. In this commentary, we explore the pandemic's effect on the clinical trials landscape in both COVID-19 and cancer, and highlight some of the innovation that can be taken forward.

The effect of COVID-19 on clinical trials

The reallocation of resources and cessation of non-essential services have disrupted cancer clinical trial practices(7). During peak pandemic period, routine clinical research activities have been suspended, laboratories and universities have been closed with restrictions on non-essential travel. Suspension of non-essential clinical activities has affected trial recruitment, protocol mandated clinic visits, routine scans, biopsies and blood tests that will subsequently affect trial endpoints. Amongst 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 Organisations. In the United States, cancer trial recruitment in April 2020 fell by 83% from 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 6 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>). The global Research & Development vaccine effort is unparalleled compared with any other period in clinical history: According to the WHO, as of 29 June 2020, 132 COVID-19 vaccine candidates were in pre-clinical 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 in drug development, and this can only be done quickly and successfully with the level of multi-disciplinary cooperation seen here.

The rapid normalisation of remote working practices that has developed during the SARS-CoV-2 pandemic has significantly impacted 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 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 centre, which presents a barrier to participation for patients who live far away. The time commitment required to attend the centre for frequent visits is therefore 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 the adoption of telemedicine, community visits and the decentralisation of trial centres 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 usage 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 minimising 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 decentralise from large study hubs, improving efficiency as well as helping to mitigate centre, time or cohort-related biases. Whilst 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 decentralised, remote sites. These remote sites could remove the burden of travel for cancer patients 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 minimise infection risk, whilst 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 *per oral* investigational products (IP) without hospital visits: patients may frequently miss doses or take two doses of the IP at once. Mailing IP to patients' homes, and supervising IP administration using videoconferencing technology might help to overcome the need for hospital visits in such situations.

Using technology to galvanise recruitment

Remote working can be extended to improve efficiencies in study launch, site setup and training. In March 2020, ASCO launched a survey amongst 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 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 set-up 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 cancer patients 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. 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 addition of arms as evidence shifts. For example, in April, one month after the trial launch, approval was granted for eligible patients to be randomised a second time to a tocilizumab arm(10).

Trial approval

Over the last two decades, randomised 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, the 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 set up of large trials such as RECOVERY and the SOLIDARITY trial. For example, MHRA approval for the RECOVERY trial was given four days after initial application (<https://www.recoverytrial.net/for-site-staff/site-set-up-1>), and enrolment of the first patient took place nine days after the protocol was finalised(10). According to ClinicalTrials.gov, there have been 688 COVID-19 interventional trials with a study start date (first enrolment) between 1st January and 1st June 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 pre-print 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 (CSSE), 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 6 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 5th June 2020, three authors retracted a Lancet and New England Journal of Medicine (NEJM) 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 complete transparency in data sources and analytical methods (including code), full reproducibility and robust peer review.

Conclusion

Globally, in the first 6 months of 2020 there have been an estimated 500,000 deaths from COVID-19 and over 4.5 million cancer 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 set up 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 capitalise from our experience during this time to accelerate cancer clinical research progress. This can only serve to benefit our patients.

Acknowledgements

We thank Nicky McGranahan, Emlyn Samuel, Sarah Woolnough, Emma Greenwood, Oliver Buckley-Mellor and Ian Walker for their editorial contributions. C.S. is Royal Society Napier Research Professor. This work was supported by the Francis Crick Institute that receives its core funding from Cancer Research UK (FC001169,FC001202), the UK Medical Research Council (FC001169, FC001202), and the Wellcome Trust (FC001169, FC001202). C.S. is funded by Cancer Research UK (TRACERx, PEACE and CRUK Cancer Immunotherapy Catalyst Network), the CRUK Lung Cancer Centre of Excellence, the Rosetrees Trust, NovoNordisk Foundation (ID16584) and the Breast Cancer Research Foundation (BCRF). This research is supported by a Stand Up To Cancer-LUNGeivity-American Lung Association Lung Cancer Interception Dream Team Translational Research Grant (Grant Number: SU2C-AACR-DT23-17). Stand Up To Cancer is a program of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research, the Scientific Partner of SU2C. CS receives funding from the European Research Council (ERC) under the European Union's Seventh Framework Programme (FP7/2007-2013) Consolidator Grant (FP7-THESEUS-617844), European Commission ITN (FP7-PloidyNet 607722), an ERC

Advanced Grant (PROTEUS) from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 835297), and Chromavision from the European Union's Horizon 2020 research and innovation programme (grant agreement 665233).

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Table 1. Total number of COVID-19 trials by selected country and month of registration
 (source: covid-trials.org)(5)

| | 2020 | | | | | | Total |
|-----------------------|------|-----|-----|-----|-----|-----|-------------|
| | Jan | Feb | Mar | Apr | May | Jun | |
| China | 8 | 193 | 102 | 35 | 14 | 4 | 356 |
| France | 1 | 0 | 16 | 70 | 14 | 2 | 105 |
| Germany | 0 | 1 | 10 | 23 | 5 | 0 | 40 |
| India | 4 | 1 | 3 | 27 | 10 | 2 | 47 |
| Iran | 0 | 0 | 27 | 104 | 52 | 0 | 184 |
| Italy | 0 | 1 | 17 | 20 | 16 | 0 | 55 |
| Spain | 0 | 1 | 12 | 72 | 29 | 1 | 116 |
| United Kingdom | 0 | 1 | 8 | 31 | 17 | 0 | 57 |
| United States | 0 | 3 | 25 | 157 | 82 | 0 | 288 |
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CANCER DISCOVERY

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Cancer Discov Published OnlineFirst July 15, 2020.

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