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Rethinking cancer clinical trial conduct induced by COVID-19: An academic center, industry, government and regulatory agency perspective

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Abstract

The COVID-19 pandemic brought about major changes in cancer clinical trials. In its aftermath, the community has an opportunity to incorporate some of these changes as part of the future of trial conduct to put patients further at the center

Introduction

Conducting clinical trials following the highest standards has resulted in the development of multiple new therapies that have significantly improved the outcomes of patients with cancer. The standard practices in clinical trial conduct developed over the past decades provide reliable data to assess the effects of new treatments and correctly evaluate their

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benefits. Therefore, the field of oncology clinical trials has accumulated a series of rules and regulations, many of them self-imposed, that have gone unchallenged for a long time. However, the advent of the COVID-19 pandemic forced a re-evaluation of all these procedures and adaptation of them to the emergent situation. In the spring of 2020, clinical trial conduct halted and then restarted focusing on the bare minimum procedures that first allowed patients continued access to their experimental therapies, and then allowed clinical trial sites and sponsors to collect information on the effects of the therapies. The COVID-19-induced changes to clinical trials were a big challenge, probably the largest change in clinical trial conduct since the start of modern oncology clinical testing. But it also represents an opportunity to rethink the key aspects of clinical trial conduct that are strictly necessary to reach the goal of testing the effectiveness of cancer therapies, and which others are dispensable or only provide minor additional contributions. In this article, we describe the impact of these changes and how to incorporate them into the future conduct of clinical trials from the perspective of four key constituents of the clinical trials enterprise: academic centers, industry sponsors, government-sponsored clinical trials, and regulatory agency oversight.

Streamlining Clinical Trial Procedures

Required study procedures and data elements captured in the conduct of oncology trials has markedly increased over recent years. This is mostly due to the intent to glean as much information regarding efficacy and safety as possible from each study participant. Efficacy evaluations have expanded to include multiple clinical and surrogate biomarker analyses to increase the sensitivity of signal detection. With regard to safety, high-resolution data collection throughout the course of clinical development ensures that the size of a safety database will not be rate-limiting for regulatory approval once preliminary evidence of efficacy has been demonstrated. Ensuring that data integrity is of sufficient quality to satisfy regulatory standards for all patients who have received an investigational product further multiplies the work of clinical research staff and sponsor monitoring. In other words, the goal of increasing the overall efficiency of investigation for a novel approach and minimizing the number of patients needed to achieve regulatory approval has increased the burden on individual clinical trial participants and clinical research staff.

In the midst of the COVID-19 pandemic, the question arose as to what clinical trial protocol elements were essential for both efficacy and safety assessment. In Table 1 we detail clinical trial procedures for which the United States Food and Drug Administration (FDA) and the National Cancer Institute (NCI) issued guidance to adapt during the early phase of the COVID-19 pandemic, followed by how they could be incorporated to the new standards for clinical trials, and in Box 1 we add other issues that can be reconsidered in the setting of additional changes to make clinical trial conduct more patient-centered and incorporating technical advances that could facilitate collecting the adequate information to evaluate the effects of a new therapy in patients with cancer.

Impact at Academic Centers

Historically, the clinical trial site has been at the center of clinical trial conduct, providing the direct interaction between the experimental therapy and the patient volunteers (Figure 1A). Patients were expected to travel to the site for consenting, screening, laboratory work, imaging scans, experimental therapy administration, with frequent requirements for visits in-between therapies for pharmacokinetic and pharmacodynamic studies. COVID-19 imposed an initial freeze on visits to clinics, public policy measures and general guidelines restricted travel, and healthcare personnel considered non-essential, such as clinical trial staff, had to redeploy their efforts. But patients needed to be offered continuation on therapies that could provide benefit despite the clinical trial site not being able to perform at the same level as before. Therefore, the clinical trial site could no longer be the center of the clinical trial conduct. Strategies were needed that would minimize physical interaction between clinical trial participants, their physicians, and research staff. For oncology clinics embedded within multidisciplinary hospitals, ambulatory care resources often had to be redirected toward health system-wide COVID-19 management (Figure 1B).

The clinical trial issues outlined in Table 1 and Box 1 all impact patient interactions with the providers and staff to some degree. Digital tools for the purposes of educating patients regarding clinical trial participation and investigational product risk, and documenting informed consent have been developed and slowly adopted over the past several years. The pandemic underscored the importance of rapidly accelerating adoption of these platforms. Historically, symptom and toxicity data have been obtained by direct patient interview in between clinic visits and serially by research and clinical staff during clinic visits. Shifting these interactions to remote reporting via software platforms or phone or video conference interview became an immediate need. The reliance on outside laboratories and radiology facilities increased substantially for required safety monitoring with the consequent challenge of needing to obtain credentials and normal values for those laboratories. The distribution of oral investigational products to patients, with assurance of chain of custody was similarly an immediate change in trial conduct (Figure 1B). This left the infusion of intravenous therapies and the cell therapies, which are largely the domain of the oncology clinics and inpatient services, respectively.

Impact on Clinical Trial Networks supported by the US National Cancer Institute

The rising cost and complexity of conducting cancer clinical trials, that has threatened the viability of our institutional clinical research infrastructure, reached record levels even before the outbreak of the COVID-19 pandemic (1). In the context of the extraordinary social and economic stress on the American health care system engendered by wide-spread COVID-19-related illness, the regulatory and procedural requirements that have underpinned NCI-supported clinical trial conduct for decades were recognized to be unsustainable within weeks of the pandemic's outbreak (<https://deainfo.nci.nih.gov/advisory/joint/0420/Doroshov.pdf>). Despite early recognition that clinical trial resources would, of necessity, need to be reassigned to direct patient care, and the subsequent, related introduction of major

alterations to standard clinical trial procedures for NCI's clinical trials networks over a remarkably rapid time frame (https://ctep.cancer.gov/content/docs/Memorandum_on_Interim_Guidance_for_Clinical_Trial_Activities_Affected_by_the_Novel_Coronavirus), clinical trial accrual for NCI-funded investigations will have decreased by 15-20% for calendar year 2020 due to the COVID-19 pandemic.

It is important to point out that the observed decrease in clinical trial accrual for 2020 would likely have been substantively worse without major changes to the NCI's clinical trials system that were introduced by NCI and its grantees, in consultation with the FDA. These changes included, as outlined in Table 1: acceptance of an electronic informed consent process, transfer of care for both administration of therapy and trial monitoring to local oncology providers, shipping of oral investigational agents to local clinics, promoting remote protocol auditing, minimizing the impact of minor protocol deviations on the validity of established clinical trial endpoints, and the facilitation of clinical trial assessments using telemedicine approaches (2).

However, despite these adjustments to the NCI's clinical trial procedures, the ongoing effects of the COVID-19 pandemic continue to reveal that many aspects of NCI's established processes act as a deterrent to facile participation by both underserved and rural cancer patient populations in novel programs of clinical research. This is particularly true in the context of the adverse economic impact of the pandemic that has limited access to health insurance (3). It is also the case that changes to the NCI's clinical trials procedures have not dealt fully with the major effect that clinical co-morbidities play in limiting trial accrual by underserved minorities (4, 5). Thus, it is incumbent upon the NCI and the investigators it supports to envision continuing improvements to its clinical trials program.

As outlined in Table 1 and in a recent white paper from the NCI's Clinical Trials and Translational Research Working Group (<https://deainfoc.nih.gov/advisory/ctac/1120/SPWGREportpdf2020>), it is strongly recommended that all of the important changes detailed above become permanent fixtures of the trials programs supported by NCI's clinical research networks. In our current health context, furthermore, every effort must be made to extend the cancer clinical research process further into the community setting, including provision of investigational intravenous therapeutics at the local level, reduction in reporting requirements for adverse events and low value laboratory data in late-stage trials where these data are unlikely to have an adverse impact on patient safety, and use of patient reported outcomes as primary study endpoints. Finally, all cancer clinical trials, including those supported by the NCI, would be dramatically streamlined by a national effort to make it possible to collect clinical trial data directly from a patient's electronic health record (Figure 1B). In all of these ways, the COVID-19 pandemic could serve as a stimulus for the introduction of major changes to the NCI's clinical trials programs, changes that have the potential to dramatically broaden access to cancer clinical trials while, potentially, reducing requirements for research resources in a time of social and economic uncertainty.

Impact on the biopharmaceutical industry

At the beginning of the COVID-19 pandemic, as investigational sites came under significant pressure with increased in-patient load, and research trial staff sometimes diverted to other priorities, it became clear that rapid assessments of which clinical trials could continue, and other modifications would be required. At AstraZeneca, by the end of December 2020, around 15% of phase 3 trials had been impacted by at least a 3 month delay to projected accrual, although this was less than reported across the industry and a lower figure than for phase 3 trials in other therapeutic areas. This is in general as the balance of potential benefit-risk of such trials was felt to be favorable even with the pandemic-associated increased risks of hospital or clinic visits. For early phase trials, a higher percentage were delayed or paused at 18%, since such programs have less clinical efficacy data to support a positive benefit-risk profile.

Key changes that were made included allowing electronic virtual consents, a reduction of on-site visit requirements, enabling home or local blood collection, and also modification to treatment regimens to permit more infrequent dosing of investigational agents where appropriate (Table 1). Infusional products, which were part of the treatment regimen and which were already approved, were in some cases administered at home rather than requiring clinic or hospital visits. Furthermore, at most sites remote monitoring visits were encouraged to reduce the requirement for on-site access and a reduction in investigational site staff time. For some new studies, there has been increased adoption of digital health technology, such as remote pulse, blood pressure, ECG and pulse oximetry, as well as collection of patient reported outcome data. As these changes have become acceptable, and shown to be feasible across different sites and in multiple countries around the world, it is now very reasonable to ask which of these modifications can stay as part of the ‘new-normal’ way of running trials (Table 1 and Box 1). The answer is almost all of these represent a more efficient and effective way of running clinical trials with the potential to reduce the burden we place on patients who volunteer for our trials.

Impact at the US Food and Drug Administration

As COVID-19 advanced throughout the U.S. and across the globe, FDA proactively released guidance for sponsors of clinical trials in anticipation of operational challenges with trial conduct during the COVID-19 pandemic. FDA initially issued the Guidance for Industry, Investigators, and Institutional Review Boards, *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency*, on March 18, 2020, to assist sponsors of clinical trials by providing general considerations to assure the safety of trial participants, maintain compliance with good clinical practice, and minimize risks to trial integrity during the COVID-19 public health emergency (<https://www.fda.gov/media/136238/download>). This guidance, and its multiple subsequent updates, discussed expected clinical trial conduct issues including meeting protocol-specified procedures, such as adherence to protocol-defined study visits for clinical or laboratory safety assessments, imaging or other evaluations to determine disease status and response to therapy, and administration of investigational products at Study sites. The Oncology Center of Excellence (OCE) met with professional societies, patient advocacy organizations, and clinical trial

sponsors from the outset of the COVID-19 pandemic to determine immediate impacts and long-term challenges for oncology trials. As stakeholders gained experience with contingency measures for continuing clinical trial conduct, a common theme in these OCE stakeholder interactions concerned whether “flexibilities” described in this FDA guidance would be permitted once the COVID-19 public health emergency ends. It was, however, generally recognized by all stakeholders that the impact of such measures on maintaining patient safety, good clinical practice, and trial integrity was largely unknown. Importantly, many key flexibilities identified by stakeholders in this guidance likely to be necessary to minimize exposure to COVID-19 generally existed already based on pre-COVID-19 pandemic initiatives, including decentralizing aspects of clinical trials, to create efficiencies in clinical trial conduct and evidence generation while also creating opportunities for trial participation to historically underserved populations in clinical trials.

Prior to the COVID-19 pandemic, FDA published guidance documents, held public workshops and meetings, and formed public-private partnerships to advance potential efficiencies in the clinical trial paradigm such as those described in Table 1. In particular, FDA laid the groundwork that supported the ability to allow remote conduct of aspects of cancer trials during COVID-19 pandemic through issuance of guidance documents on electronic informed consent (2016) (<https://www.fda.gov/media/116850/download>), electronic source data capture in clinical investigations, such as from electronic health records and laboratory or imaging data, (2013) (<https://www.fda.gov/media/85183/download>), use of electronic health record data in clinical investigations (2018) (<https://www.fda.gov/media/97567/download>), and remote monitoring of clinical investigations (2013) (<https://www.fda.gov/media/116754/download>). Additionally, FDA engagement with external stakeholders on decentralized trials, such as the Clinical Trials Transformation Initiative, a public-private partnership co-founded by Duke University and FDA, included discussions of telemedicine for study visits, remote clinical assessments, such as laboratory and imaging assessments, alternate delivery and administration of investigational products, and mobile/local health care providers, all aspects of a decentralized trial paradigm which have the potential to streamline clinical trials and facilitate access of underserved and rural populations (https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/dct_recommendations_final.pdf). Moreover, as a result of 21st Century Cures Act and amendment to the Federal Food, Drug, and Cosmetic Act, FDA has generated a framework for evaluating potential use of real-world evidence to help support the approval of a new indication of a previously approved drug or help support or satisfy post-approval study requirements (<https://www.fda.gov/media/120060/download>)(<https://www.fda.gov/drugs/news-events-human-drugs/meetings-conferences-workshops-drugs>). Within this framework, FDA describes considerations for clinical trial use of real-world data, which is defined as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, including electronic health records and mobile devices.

Ultimately, increasing potential efficiencies in the clinical trial and evidence generation paradigm, has been a consistent priority of the OCE, and of the Agency more broadly, to accelerate patient recruitment and retention, facilitate evaluation of rare patient populations, and increase diversity of the trial population. To this end, the OCE has initiated programs to advance the science of patient-reported outcomes, digital health technologies, real-world

evidence and health equity that focused specifically on cancer product development. While many flexibilities described within the COVID-19 Clinical Trials Guidance had pre-dated COVID-19, the impact of the COVID-19 pandemic on the conduct of cancer clinical trials has led to a renewed sense of purpose and conceivable alignment across stakeholders for reimagining the conduct of oncology trials where patient accessibility and, potentially, resource efficiency may prevail (Table 1).

Conclusions

The COVID-19 pandemic forced academic medical centers, clinical trial sponsors and the FDA to streamline oncology clinical trial procedures in order to preserve potential patient benefit while minimizing risk associated with investigational therapies and COVID-19. This process has redefined the essential processes and data capture needed to achieve both aims. Additionally, a more patient-centric approach has been rapidly adopted in response to COVID-19. Guided by lessons learned, many of the remote assessments and trial efficiencies deployed during the pandemic can be preserved and improved upon. We strongly encourage use of these streamlined procedures where appropriate in future prospectively designed cancer clinical trials. There remain some domains of trial conduct for which further process improvements and technology development are needed to make clinical trial participation more inclusive and less onerous, while still optimizing risk/benefit.

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Box 1.**Additional potential changes in clinical trial conduct taking advantage of improvements in technologies for safety and efficacy assessments.**

- Electronic data collection methods could be developed to move data into CTM systems from EHRs instead of having clinical trial data collected exclusively from the clinical trial site
- To eliminate gross duplication of effort across institutions for procedures and clinical trial orders “Beacon Builds” could be systematized within vendors. This would alleviate the issue of clinical trial site-specific standard operating procedures and study orders, even for multicenter trials with similar electronic medical record systems
- In efficacy clinical trials, investigate utility of new study endpoints (time to event; PROs) as a means of decrease cost/improve efficiency instead of relying exclusively on multiple specialized tumor measurements
- Decrease collection of low grade adverse events and minimize effect of minor protocol deviations on protocol conduct, rather than collect every recorded event irrespective of importance and relationship to the study endpoints.
- Collect less low value laboratory and clinical data per patient to minimize non-essential testing, instead of collecting all laboratory values despite not being related to the research being conducted (e.g. normal values for red cell distribution width).

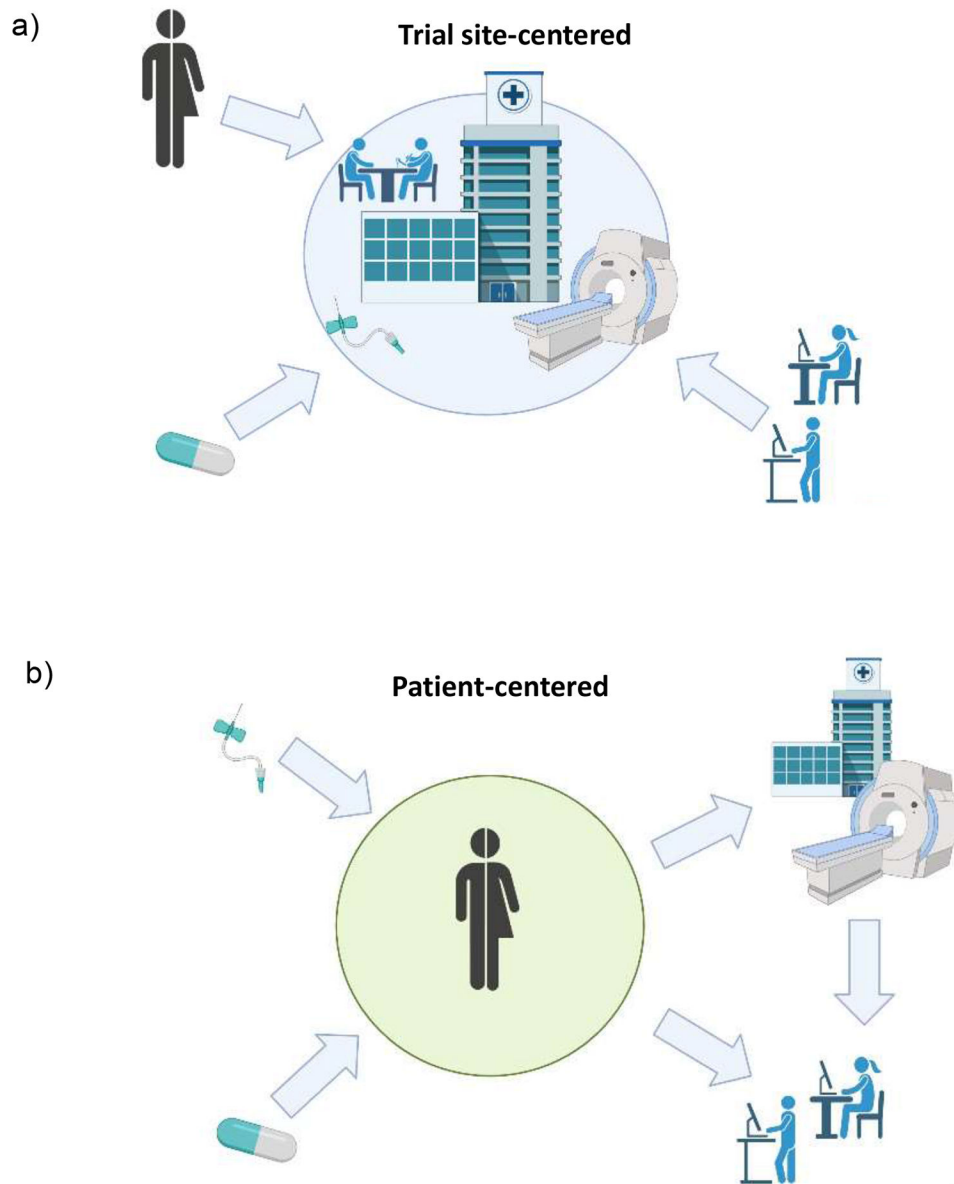


Figure 1. Change in the clinical trial conduct accelerated by the COVID-19 pandemic. A) The clinical trials enterprise had evolved over decades to have the clinical trial site as the center of the action, where patients would need to go for consenting, clinical trial procedures and experimental therapies were provided, regardless if they were oral or infused. Also, monitors and auditors performed their work onsite. B) Accelerated by the need to adapt to the COVID-19 pandemic, the patient was put at the center of the clinical trials activity, allowing remote consenting without having to go to the clinical trial site, being able to do laboratory tests at home or at a local facility, having drugs delivered at home, and having monitoring and auditing remotely.

Table 1.

FDA and NCI guidance for changes in clinical trial conduct early in the COVID-19 pandemic, and how they could be incorporated as new standard for modern clinical trial conduct.

Clinical trial issue	FDA/NCI 2020 guidance during COVID-19	Post-COVID-19 roadmap
Requirement of in-person consent	Obtaining signed informed consent remotely	Make electronic remote consenting permanent
Requirement to use clinical trial-specified laboratories and imaging	Allowed use of alternate laboratories and imaging centers	Allow use of any laboratory and imaging center that meet specifications
Recording of safety and clinical assessments based on in-person visits at investigator sites and investigator-based recording	Allowed alternative methods for safety and clinical outcome assessments (e.g., virtual visits, phone contact)	Add patient-reported outcomes and telehealth approaches to routine clinical trial methodologies
Administration of investigational products exclusively at clinical trial sites	Alternative delivery/administration methods of investigational products.	Increased use of community-based network sites as opposed to clinical trials sites only.
Requirement for in-person visits to receive investigational oral products	Allow home delivery of investigational oral products	Direct-to-patient investigational product (oral drugs) and concomitant medication reporting via digital tools
Requirement for in-person visits to receive investigational infusional products	Allow at-home or local health care provider infusion	Aspire to 100% remote infusions and monitoring when feasible based on a risk assessment
Limited clinical trial access for underserved populations	Shipping of investigational product intended for infusion to a local health care provider for administration.	Decentralize clinical trial conduct and make it more accessible to rural areas and underserved populations: <ul style="list-style-type: none"> • Increase funding mechanisms for trials conducted in underserved communities • Markedly broaden trials available for patients with wide range of co-morbidities
Requirement to administer “experimental clinical trial products” even if the same drug was approved and available commercially	Commercial procurement by patient of investigational product already approved for other indications	Discuss mechanisms for use of clinical trial products obtained as commercially approved drugs.

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