

COVID-19, Social Justice, and Clinical Cancer Research

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Abstract

The COVID-19 pandemic and related socioeconomic events have markedly changed the environment in which cancer clinical trials are conducted. These events have resulted in a substantial, immediate-term decrease in accrual to both diagnostic and therapeutic cancer investigations as well as substantive alterations in patterns of oncologic care. The sponsors of clinical trials, including the United States National Cancer Institute, as well as the cancer centers and community oncology practices that conduct such studies, have all markedly adapted their models of care, usage of health care personnel, and regulatory requirements in the attempt to continue clinical cancer investigations while maintaining high levels of patient safety. In doing so, major changes in clinical trials practice have been embraced nationwide. There is a growing consensus that the regulatory and clinical research process alterations that have been adopted in response to the pandemic (such as the use of telemedicine visits to reduce patient travel requirements and the application of remote informed consent procedures) should be implemented long term. The COVID-19 outbreak has also refocused the oncologic clinical trials community on the need to bring clinical trials closer to patients by dramatically enhancing clinical trial access, especially for minority and underserved communities that have been disproportionately affected by the pandemic. In this Commentary, changes to the program of clinical trials supported by the National Cancer Institute that could improve clinical trial availability, effectiveness, and diversity are proposed.

Better understanding of cancer biology, new forms of targeted therapies, and the explosion of immuno-oncology has resulted in an unprecedented expansion of United States Food and Drug Administration (FDA)-approved therapeutic options for cancer patients as well as an increase in life expectancy (1). At the heart of this progress have been clinical trials supported by the National Cancer Institute (NCI), industry, and cancer centers across the country. However, even before devastating recent political, economic, and health-related events unfolded, the extensive resources required to support the current clinical cancer research enterprise have deeply stressed the capacity of both community oncology practices and academic sites to carry out their research missions, especially in underserved populations (2-4). Hence, at the conclusion of this commentary, we wish to suggest a series of changes to the NCI's clinical trials programs that could markedly enhance their availability, operational efficiency, and implementation across a much wider segment of the populace.

The deleterious effect of the COVID-19 pandemic on the American health care system has been substantial. Oncologists have appropriately de-prioritized non-emergent clinical cancer care and non-COVID-19-related translational research. The responsibilities of many clinical and cancer research staff have been shifted from investigational programs to assist in studies of COVID-19-associated medical interventions. For these reasons, access to cancer clinical trials as well as to many standard-of-care treatments has plummeted over the past months, particularly at academic medical centers and community sites located in those geographic regions hardest hit by the pandemic (5,6). If current trends continue, clinical trial accrual for NCI-funded studies alone will decrease by approximately 20-25% (or ~3,500 patients) in 2020 (7). By default, decreased accrual will prolong the time needed to determine whether new treatments and other interventions can improve therapeutic outcomes, and in the process increase the costs of drug

development. These delays will adversely affect the rate of progress resulting from recent advances in cancer research and most likely diminish the rapid pace of FDA approvals of new cancer therapies observed before COVID-19. Decreased accrual will also delay clinical research efforts designed to reduce cancer incidence rates and to ameliorate acute and long-term sequelae of cancer treatments (8,9).

Furthermore, the rising cost of treatment for cancer patients is not sustainable, particularly in the context of the enormous economic impact of the pandemic (10-12). Patients must now weigh the potential for financial hardship that can accompany a diagnosis of cancer in the context of rising unemployment levels that are associated with loss of health insurance provided by employers (11). These observations suggest that a renewed focus on prevention, detection, and cost-effective implementation and treatment is needed to assure that all patients benefit from advances in cancer care, especially patients in rural and underserved regions of the United States.

The dramatic effects of the COVID-19 pandemic on the cancer research enterprise have coincided with the realization that the exponential growth in the complexity and expense associated with cancer clinical trials may threaten the vitality of the clinical trials endeavor. Hence, developing less expensive trials that are more convenient for patients and that demand meaningful clinical outcomes rather than simple statistical significance should become a clinical research imperative. Adapting to current clinical realities by dramatically streamlining the clinical research paradigm in oncology is an urgent need. We must modernize the process of clinical trial design and execution, decrease regulatory hurdles, and focus new studies on fewer essential endpoints while increasing the efficiency of data collection and analysis (13).

The impact of these trends is magnified in underserved populations that, before COVID-19, had already experienced diminished access to state-of-the-art clinical trials (14). COVID-19 and cancer disproportionately produce adverse outcomes in African Americans, Hispanics, and Native Americans patients (15). The Johns Hopkins University and American Community Survey found that the infection rate in 131 predominantly Black counties in the United States was over three-fold greater than in predominantly White counties. At least some of these differences may be attributable to a higher incidence of pre-pandemic risk factors among Black patients, such as diabetes, obesity, hypertension, and cardiovascular disease, which are associated with reduced access to health care (16,17).

Oncologists have long recognized the poorer health outcomes in African Americans compared to their White counterparts. Death from all cancer types is 13% higher in Black patients compared to White patients (18). Putative causes of these disparities include socioeconomic issues and decreased access to care; but at the core is a lack of attention to what Berwick and others call the moral determinants of health (19). These determinants include an individual's condition of birth, education, work environment, the social concerns of elders, community resilience, social and economic security, and the basic equity level in society. Our current cancer clinical trial paradigm has also presented substantive obstacles to the inclusion of underserved populations, including African Americans. By design, cancer clinical trials have developed rigid eligibility criteria and often include frequent and expensive "standard of care" tests and procedures, such as functional imaging examinations, that often exclude patients with multiple co-morbid conditions, transportation issues, and inadequate health insurance—including substantial co-pays (20,21). Recent evidence from the NCI-supported clinical trials performed by SWOG indicates, furthermore, that barriers to minority accrual appear to be worse for

industry versus NCI-sponsored investigations (22). Finally, the emerging economic crisis resulting from the COVID-19 pandemic has further heightened socioeconomic disparities between white patients and patients of color. Black patients are experiencing disproportionate loss of employment and health insurance, which may limit the feasibility of participating in complex trials requiring frequent health care visits and procedures (23).

In the last several months, regulatory agencies and clinical trial sponsors (including the NCI) have demonstrated the ability to adapt rapidly to the exigencies imposed by the infection of a proportion of the US population with SARS-CoV-2 (24,25). These changes have included: broad acceptance of electronic informed consent, transfer of the clinical care of trial patients to local providers to diminish travel requirements, shipping of oral investigational agents to local sites, decreasing the impact of minimal protocol deviations on the assessment of clinical trial site performance, remote auditing of clinical trial documents, and, perhaps most importantly, accepting the validity of clinical trial assessments performed using telehealth approaches. All these adaptations to minimize disruptions to ongoing clinical studies and to maximize access to clinical trials during the COVID-19 pandemic demonstrate clearly that major changes to the currently accepted standards for the conduct of cancer clinical investigations are feasible. And that the time horizon to implement such changes need not be excessive.

In the context of the current health care milieu, which is likely to continue for the foreseeable future, there is an urgent need to adapt our clinical research enterprise to a “new normal”. This “new normal” must facilitate simpler, faster, flexible, and less expensive trials that seamlessly integrate with the needs of daily clinical practice. It is imperative that we begin testing new approaches to address essential modifications of our clinical trials system. Taking advantage of the adaptations affected during this pandemic as a starting point (e.g. telemedicine,

verbal informed consents, allowances for diminished travel to cancer centers for diagnostics and treatments), additional novel strategies to improve the efficiency of clinical cancer research should be promulgated.

Clinical Trial Initiatives

We propose that the current environment demands consideration of a series of initiatives throughout NCI-supported clinical trials networks, and hopefully elsewhere, that will address impediments to rapid clinical trial execution. These initiatives include the following:

Enhancing patient access

Cancer clinical trials must be brought to the patient—rather than the converse--without regard to geography. Additional local clinical trial sites should be developed at affordable costs that utilize advances in telemedicine pioneered during the COVID-19 pandemic. This has major implications for patients with rare malignancies as well as for underserved populations and the institutions that serve them. This effort, building on the recent activities of Friends of Cancer Research, ASCO and others (26), should include designing trials that permit entry of patients with a wide variety of chronic comorbidities, thus broadening the range of patients eligible for clinical study. It should also include developing studies conducive to implementation in safety-net hospitals. In part, this will involve adequately supporting and training clinical research teams that now lack the necessary infrastructure needed to enroll underserved patient populations in cancer clinical investigations.

Improving operational efficiency

Electronic data collection methods should be developed that are fully compatible with remote auditing and trial monitoring by way of electronic health records (EHRs). These methods must complement current electronic data entry techniques, minimize in-person visits to distant clinical trials sites, and promote more uniform and robust data collection. This effort should be coupled with a program to ease the administrative burden and cost of repeatedly creating custom local versions of study records and forms compatible with local EHRs and clinical trial monitoring systems. We do not suggest generating so-called ‘shadow charts’ for patients enrolled on clinical studies. Rather, working with the major EHR vendors, the NCI should support a national effort at its clinical trial sites to harmonize the electronic representation of clinical data in a fashion that will facilitate simpler, automated cross validation and usage of standardized electronic order sets, auditing, and data entry for its clinical investigations at all centers.

Transforming statistical designs

Clinical trial design should strive to provide meaningful endpoints that require less data acquisition. We need to test new trial formats that simplify data management compared with current NCTN, ETCTN, or NCORP standards—to answer the question of whether the current approach is actually needed to change clinical practice or to meet regulatory endpoints. One example is to investigate and compare whether electronically collected patient-reported outcomes or simpler time to event endpoints could reduce the need for more frequent imaging studies while still providing reliable information sufficient to support the results of cancer clinical trials.

Minimizing the review process

It will be important to create more innovative processes to enable rapid evaluation of clinical trial documents, such as letters of intent, protocols, and protocol amendments. This is especially true for the evaluation and approval of trials for rare tumors that would not typically be opened at non-academic sites because of the allocation of resources for higher incidence malignancies.

Rethinking strategic research infrastructure

The personnel requirements for the review, activation, and monitoring of clinical trials have expanded dramatically. Tools and processes should be developed to substantively diminish the person-hours required for study development and conduct (including the development of electronic rather than in-person protocol auditing) to decrease time to trial completion.

Simplifying the regulatory framework

In concert with FDA, regulatory obligations for cancer clinical trials need to be simplified without jeopardizing patient safety. This includes re-evaluating mandatory requirements for reporting certain data elements, such as minor protocol deviations and low-grade adverse events. We need a much better understanding of the impact of different reporting thresholds for an array of data elements on meeting pre-defined clinical research and safety endpoints.

Minimizing non-essential tests

We need to more rigidly identify essential and non-essential testing on clinical trials. Many extraneous “standard-of-care” tests are included in trials because of the possibility that they may be needed for registration of a drug by the FDA. This leads to excessive trial costs, including costs for the collection of unnecessary data that must then be borne by patients and insurers.

Promoting the use of electronic consent

In accordance with the 2016 FDA guidance to reduce paperwork, we should provide improved flexibility to allow for an informed consent process that can be conducted remotely.

Conclusions

At the crossroads of cancer, COVID-19, and growing social inequities, substantive opportunities to improve the current methodology of oncologic clinical investigation have manifested themselves in dramatic fashion. Now is the time to make fundamental changes that will lead to sustainable improvements in our approach to and conduct of clinical cancer research, changes that will provide broad, long lasting benefit to all patients and to society.

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