



Commentary

COVID-19 Challenges Confronted by Smoking Cessation Clinical Trials for People Living With HIV: The Experience of Grantees of the US National Cancer Institute

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Introduction

Clinical trials are critical to science and medicine, leading to novel therapeutics that address major diseases and disorders. In addition to the devastating effects on morbidity and mortality, the COVID-19 pandemic has led to unprecedented disruption to clinical trials, reducing access to treatments and slowing scientific discovery.^{1–3} Scientists engaged in tobacco control research have faced similar disruptions.⁴ Since individuals who use tobacco may be at heightened risk for COVID-19 infection and poor clinical outcomes if infected,⁵ the adverse impact of the disruption of clinical trials for smoking cessation interventions may have salient importance to the field.

For the many smokers who lack access to evidence-based tobacco dependence treatments, clinical trials represent a critical opportunity for effective care. People with HIV (PWH) report rates of tobacco use that are two to three times higher (ie, 30–40%) than the general population.^{6,7} They are an underserved community with unique comorbidities and disparities such as mental health and substance use disorders, HIV-related stigma, and race/ethnicity, educational, and economic disparities.⁶ The combined effects of COVID-19 on reduced access to smoking cessation clinical trials and disparities among PWH may further increase the inequality in tobacco-related disease morbidity and mortality among PWH,^{8,9} versus the general

population. The potential for compromised immune function among PWH to increase COVID-19 infection risk is also a unique concern.¹⁰

In late 2019, the NCI funded seven smoking cessation clinical trials for PWH to improve knowledge about effective models of tobacco use treatment for this community.¹¹ These studies provide evidence-based treatment across all study arms and within academic medical centers, the Veterans Affairs health care system, and through mobile health (mHealth) applications. To help ensure that these studies advance the science of treating tobacco use among PWH, NCI fostered a grantee group linking teams through annual meetings and working groups.

However, in the spring of 2020, the pandemic shut down the majority of clinical research in many countries. In the United States, academic health centers and research institutes relied on guidance from federal and state authorities as to when clinical trials could resume, and under what conditions. Many institutions drafted guidelines to promote the safety of staff and participants, addressing use of personal protective equipment, social distancing, occupancy of clinical spaces, and ventilation. Grantee group members discussed the ways in which the COVID-19 pandemic has affected the conduct of their trials and the efforts they made to overcome these challenges. Here, similar to other scientific groups,¹² we describe these challenges and mitigation efforts to support others who face similar challenges, currently, or in the future.

Challenges to Clinical Trials From COVID-19

In November 2020, grantees met, virtually, to discuss the challenges they were facing to continue their trials during the COVID-19 pandemic, as well as strategies each group was utilizing to continue their

research. Below, and in [Table 1](#), we present the results of our discussion and summaries from our group.

Procedural Challenges

As described by others,¹³ an immediate challenge faced by grantee group members was that in-person screening, consenting, assessments, and intervention visits were not feasible at all, initially, and posed a risk in the longer term. The most difficult aspect of this challenge concerned the collection of biological samples (urine, sputum, breath), often used to verify self-reported smoking cessation, which is the primary outcome across these trials. Grantees reconceived study protocols to reduce the number of in-person visits and/or their duration. Although telephone-based interventions and assessments ensured feasibility, the limitations of participant telephone minutes, data plans, and access to, willingness to use, and skills to engage with, video-conferencing technology emerged as a new challenge.^{14,15}

Analytic and Statistical Challenges

As with other scientific areas,¹⁶ study teams experienced concerns related to accrual and missing data. Inability to accrue projected samples may reduce statistical power and the stress posed by the pandemic may reduce quit motivation and treatment response.¹⁷ Reduced accrual came as a result of (1) institutionally mandated moratoria on enrollment; (2) reduced occupancy of clinical spaces and fewer clinical appointments mandated by institutions; and (3) potential participant reluctance. Additionally, the inability to collect some measures (eg, breath samples or end-of-treatment viral load) may undermine the ability of trials to address certain aims (eg, the effects of cessation on HIV viral suppression). Last, the conversion of many studies from in-person to remote platforms may affect the

Table 1. Challenges to Smoking Cessation Clinical Trial Research From COVID-19 and Strategies to Resume Activities

Challenge	Strategy
Procedural <ul style="list-style-type: none"> Inability to conduct in-person: Assessments, Intervention visits, Collection of biosamples for laboratory tests and verification of smoking status relevant for outcome ascertainment and intervention implementation (eg, contingency management) 	<ul style="list-style-type: none"> Telephone, digital, clinically derived, and self-reported assessments (height and weight, end-of-treatment HIV viral load) in lieu of in-person assessments, removal of certain measures, and expanded windows for assessments Optimizing flexibility and pivoting programs to telephone and video-based intervention visits Outdoor collection of biosamples or in adequately ventilated rooms (breath carbon monoxide), mail-in biosamples (eg, saliva for cotinine testing), video assessment (eg, participants conducting salivary cotinine swab or breath carbon monoxide)
Analytical and statistical <ul style="list-style-type: none"> Participant accrual Impact of COVID-19 on treatment response Missing data Tracking mode of intervention delivery (ie, in person, video, telephone) Tracking reasons for missed visits, including COVID-19 	<ul style="list-style-type: none"> Increased enrollment incentive, described safety protocols, remote consenting options Included survey to assess potential impact of COVID-19 on response to treatments under study New analytic model that better accommodates missing data
Financial/administrative <ul style="list-style-type: none"> Staff employment Grant support Delayed administrative reviews and timelines 	<ul style="list-style-type: none"> Shifted staff to projects that were not yet focused on participant recruitment and engaged staff in paper writing Restructure the award to allow additional time (a sixth year) to accomplish proposed aims Actively worked with administrative staff to attempt to expedite reviews and approvals, including bringing staff from multiple sites together to address concerns in tandem rather than in sequence

characteristics of the sample and response to the interventions under investigation.

Financial and Administrative Challenges

Most studies had hired and trained staff and initiated accrual prior to or during the pandemic, which necessitated continual staffing to ensure continuity and safety for patients and staff. As such, study teams maintained staff employment during research shutdowns, while continuing to utilize fixed resources. Consistent with NIH guidance since the start of the pandemic, the stoppage of accrual while maintaining staff employment meant the use of portions of the first- and second-year's funding.¹⁸ Some institutions implemented hiring freezes, resulting in partial teams unable to conduct all of the work required within the study for a period of time. Additionally, the extensive methodological changes necessitated by the pandemic led to frequent protocol revisions, requiring repeated IRB review and approval that, in some cases, delayed study start-up once research was allowed to resume. Some sites also required additional review and approvals from institutional safety committees and subcontract or data use agreements were delayed.

Strategies to Address Clinical Trial Challenges From COVID-19

Grantee group members worked to develop solutions to the challenges with conducting clinical trials during the pandemic (Table 1).

Procedural Strategies

Although some trials were originally designed to use remote procedures, most studies transitioned to remote protocols, either through the internet (eg, survey platforms like REDcap), by videoconference (eg, HIPAA compliant Zoom), or by telephone to improve safety. Not all procedures could adapt to remote protocols, and some studies were permitted to collect breath samples outdoors or in ventilated indoor areas. Other studies used ride-share vouchers to address concerns that participants had with using public transportation. Several studies created procedures to collect informed consent using REDcap and e-consent. Some studies that transitioned to, or provided the option for, telephone- or video-based visits, were planning to provide participants with prepaid cell phones to address a shortage of minutes as a barrier. As required by their institutions, studies developed and implemented protocols to increase safety of staff and participants (eg, mandatory masking, reduced staffing, fewer in-person visits, participant and staff COVID-19 screening), which were communicated to prospective participants to minimize their risk of infection. Overall, key procedural modifications reflected a shift toward pragmatic designs, which can have benefits and disadvantages.¹⁹

Analytic and Statistical Strategies

Many sites have increased staffing, advertisements, incentives, and recruitment sources to speed accrual rate. Sites that arranged to extend their studies for an additional year may make-up ground in the later study years. All studies added assessments of COVID-19 infection and exposure as a treatment moderator and some studies may be unable to fully address certain secondary aims (eg, effects of cessation treatment or cessation on HIV viral load). Some study teams are considering use of new longitudinal analyses that accommodate missing data.¹⁶ Finally, although protocol changes have been enacted with rigor, a key empirical question is whether remote study procedures will influence participant

characteristics, accrual, and retention, and treatment adherence and response.

Financial/Administrative Strategies

In some cases, staff were retained, but some sites temporarily shifted proportions of their effort to other funding sources to save money and keep staff employed and productive. During the initial shutdown, staff continued to administer the protocol to enrolled participants, prepared protocol documents for revision and IRB approval, and assisted with data analysis using other data sets and manuscript writing. NCI was committed to supporting studies and allowed flexibilities where possible, such as revising aims, allowing carry-over of funds, and working with grantees to restructure grants into 6-year awards (extending 5-year projects by 1 year). This flexibility will be critical to allowing for potential modifications to address slowed or reduced accrual. Last, project managers worked to modify study protocols and coordinate with their respective IRBs, which were flexible and collaborative.

Conclusions

The COVID-19 pandemic led to unprecedented disruptions to tobacco dependence clinical trials, reducing access to evidence-based care and slowing scientific discovery. The impact of this disruption has been uniquely detrimental for underserved populations like PWH. However, commonalities between COVID-19 and clinical research with PWH, such as racial disparities and the use of telehealth, can help guide clinical trial redesign efforts.²⁰ This commentary described the disruptions to tobacco cessation clinical trials for PWH, which were more detrimental to the 2-year R21 studies than the 5-year R01 studies, and the strategies employed to press forward. The effectiveness of strategies to overcome these challenges and address original study aims remains uncertain. But, our hope is that by describing these efforts, our colleagues across the field of tobacco control research—and in other areas of substance abuse treatment and beyond—may moderate the impact of the COVID-19 pandemic on their work. Furthermore, when the COVID-19 crisis has been mitigated, adopting some of these innovations to increase trial efficiency may be useful.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

Funding

This work is supported by the following grants from the National Cancer Institute (NCI): R01 CA243914, R01 CA243552, R21 CA243911, R21 CA243906, R01 CA243800, R01 CA243910, and R01 CA243907. The NCI reviewed the final version of this manuscript, but had no influence over the decision to submit for publication.

Authors' Contributions

Conception, Design, and Writing: KC, RS, SLB, AK. Writing, Review, and/or Revision: KC, RS, SLB, AK, RG, EJE, PC, BH, SM, EL, LRP, DV, RV, RLA, and JBM.

Declaration of Interests

Dr. Schnoll received medication and placebo free of charge from Pfizer for clinical trials and has provided consultation to Pfizer, GlaxoSmithKline, and Curaleaf. Dr. Hitsman has received free placebo and varenicline from Pfizer for past trials. Dr. Gross served on a DSMB for Pfizer for a drug unrelated to HIV or smoking cessation. All other authors report no conflicts of interest.

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