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Review

Remote Methods for Conducting Tobacco-Focused Clinical Trials

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Abstract

Most tobacco-focused clinical trials are based on locally conducted studies that face significant challenges to implementation and successful execution. These challenges include the need for large, diverse, yet still representative study samples. This often means a protracted, costly, and inefficient recruitment process. Multisite clinical trials can overcome some of these hurdles but incur their own unique challenges. With recent advances in mobile health and digital technologies, there is now a promising alternative: Remote Trials. These trials are led and coordinated by a local investigative team, but are based remotely, within a given community, state, or even nation. The remote approach affords many of the benefits of multisite trials (more efficient recruitment of larger study samples) without the same barriers (cost, multisite management, and regulatory hurdles). The Coronavirus Disease 2019 (COVID-19) global health pandemic has resulted in rapid requirements to shift ongoing clinical trials to remote delivery and assessment platforms, making methods for the conduct of remote trials even more timely. The purpose of the present review is to provide an overview of available methods for the conduct of remote tobacco-focused clinical trials as well as illustrative examples of how these methods have been implemented across recently completed and ongoing tobacco studies. We focus on key aspects of the clinical trial pipeline including remote: (1) study recruitment and screening, (2) informed consent, (3) assessment, (4) biomarker collection, and (5) medication adherence monitoring.

Implications: With recent advances in mobile health and digital technologies, remote trials now offer a promising alternative to traditional in-person clinical trials. Remote trials afford expedient recruitment of large, demographically representative study samples, without undo burden to a research team. The present review provides an overview of available methods for the conduct of remote tobacco-focused clinical trials across key aspects of the clinical trial pipeline.

Introduction

Most tobacco-focused clinical trials are based on locally conducted studies that face significant challenges to implementation and successful execution. Most prominent among these challenges is the need for large, diverse, yet still representative study samples. This

often means a protracted, costly, and inefficient recruitment process. Many trials struggle or fail to meet their target sample size[1] and/or have largely unrepresentative samples.[2] Trials that target lower prevalence behaviors (eg, tobacco use comorbid with a physical or mental health disorder) face even greater challenges, to the point where locally conducted trials may be infeasible. Multisite clinical

trials can overcome some of these hurdles but incur their own unique challenges, including the need for sizable and costly infrastructure, site training and monitoring, regulatory hurdles, and centralized versus local data management.

With recent advances in mobile health (mHealth) and digital health technologies, there is now a promising alternative: Remote Trials. These trials, which may also be referred to as decentralized trials, are led and coordinated by a local investigative team, but are based remotely, within a given community, state, or even nation. The remote approach affords many of the benefits of multisite trials (more efficient recruitment of larger study samples) without the same barriers (cost, multisite management, and regulatory hurdles). The conduct of remote tobacco-focused trials is now all the more timely in light of the Coronavirus Disease 2019 (COVID-19) global health pandemic, which has resulted in rapid requirements to shift ongoing clinical trials to remote delivery and assessment platforms. Indeed, guidance from numerous global health agencies now highlights that clinical trials procedures should shift, where possible, to alternative remote methods of delivery.[3–5]

During the 2020 Annual Meeting of the Society for Research on Nicotine and Tobacco, our group presented a symposium focused on remote methods for the conduct of tobacco-focused clinical trials. The present review serves as an extension of this symposium with the primary purpose to provide an overview of available methods for the conduct of remote tobacco-focused clinical trials. In addition, we provide illustrative examples where appropriate of how our team and others have implemented these methods across recently completed and ongoing federally funded research programs. We focus on key aspects of the clinical trial pipeline including remote: (1) study recruitment and screening, (2) informed consent, (3) assessment, (4) biomarker collection, and (5) medication adherence monitoring. Our focus is on the general procedures for remote trials, and thus we do not focus on the remote delivery of any one intervention, as that is idiographic to a specific study. Many, but not all, of these methods involve the use of Research Electronic Data Capture (REDCap),[6,7] a secure web application for building and managing online surveys and databases. REDCap is specifically geared toward supporting online and offline data capture for research studies and operations and is capable of compliance with Health Insurance Portability and Accountability Act (HIPAA), Part 11, and Federal Information Security Management Act (FISMA) standards (low, moderate, or high). REDCap is freely licensed to nonprofit institutions who join the REDCap Consortium and at the time of this writing, more than 4100 institutions in 137 countries have joined the Consortium, including all Clinical and Translational Science Awards program hubs.

Remote Recruitment and Screening

Numerous platforms currently exist to remotely recruit study participants for tobacco-focused clinical trials. These platforms include websites such as Craigslist, social media outlets (eg, Facebook, Instagram, and Twitter), and other online avenues for research recruitment such as ResearchMatch. Through these platforms, investigators can place ads targeted toward their population of interest. These ads can either directly link interested individuals to online study screeners (eg, via REDCap or Qualtrics) or can include a phone number or e-mail address from which the potential participant can contact the study team.

There are at least two key considerations when recruiting via these remote platforms. First, any of these online methods risks sampling bias; that is, recruiting certain demographics to the exclusion of others.[8–10] Although the digital divide is shrinking, disparities still exist. In the United States specifically, residents of rural areas own smartphones at lower rates than residents of suburban areas (71% vs. 83%) and are less likely to have home broadband Internet access (63% vs. 79%).[11] Lower income Americans similarly have lower levels of technology adoption, such that 71% of Americans with household income less than $30K per year own smartphones as compared to 90% of those with income between $50K and $74 999.[11] Beyond the digital divide, certain demographic groups, including women,[12] white adults,[13] and younger individuals[14] may be more likely to volunteer for research and click-through screening links posted online. The benefits of remote trials could be undercut if they are disproportionately weighted toward any of these groups.

In an ongoing nationwide remote clinical trial (NCT03453385) which recruits primarily via ads posted on Craigslist, our group has developed a proactive method within REDCap[6] to ensure sample diversity and representativeness. At the study outset, we set an enrollment quota for both gender and race such that no more than 60% of our planned study sample would be comprised of any one gender, and no more than 70% of the sample would be comprised of any one race. These enrollment quotas serve as additional inclusion criteria. For example, if a potential study participant is otherwise eligible for the study, but her inclusion would result in a total study sample comprised of 61% women, that individual is excluded from the study through the online eligibility screener. Of 405 participants enrolled thus far, 30% are non-white and 57% are female. Although this quota system is study-specific, we are currently in the process of turning this platform into a plug-in that can be installed in other REDCap projects, both within our institution and across others that have REDCap access. Via this plug-in, investigators will be able to enforce quotas on any variable within their dataset to ensure sample representativeness in more nuanced ways. For example, a study might require a certain proportion of the study sample to be menthol smokers or unmotivated to quit. Another study might have requirements for enrollment of nested demographics (eg, female smokers who have never tried vaping), and this too can be automated during the remote screening process via the quotas plug-in. One potential limitation to this proactive quotas system, whether instituted using our planned REDCap plug-in or via another means, is that the system will only work as intended if the planned study sample size is met. For example, if a study is recruiting 1000 participants and institutes a maximum of 60% female enrollees, the first 600 participants enrolled into the trial could be women. Within our ongoing REDCap plug-in development work, we are incorporating additional optional functionality to institute customized block sizes. If total planned study enrollment is 1000, the investigator could opt for example to split enrollment into four blocks of 250 participants and enrollment quotas will be applied separately to each enrollment block. This will ensure that enrollment quotas are equally applied throughout the entire trial enrollment period.

Another threat to remote screening, particularly through automated processes such as demonstrated above, is the potential for individuals to "game the system." That is, a potential participant who completes an online screening and is deemed ineligible may then use the same screening link to recomplete the screening, this time providing inaccurate responses in an attempt to falsely gain study entry. Potential participants may provide inaccurate demographic information which would negatively impact representativeness and may also inaccurately portray a disease state (eg, indicating that they smoke more cigarettes per day than they actually do, or

indicating that they recently quit smoking when they did not).[15–17] *A study by Devine et al.*[18] specifically recruited experienced research participants (average participation in 12 studies in the past year, lifetime-reported income of more than $20 000 as a research participant) and found that 25% had fabricated a symptom to enter a trial and 75% withheld information to avoid study exclusion. Within the same ongoing remote trial mentioned previously, our team has instituted procedures to proactively identify and disqualify "gamers." To do this, we created a visual database that identifies when a potential participant has completed study screening, but has provided demographic information (first name, last name, age, sex) that is identical to information provided within a prior screening record deemed ineligible. Research staff can sort and scan this visual database prior to enrolling a new participant to ensure unique screening attempts. As with procedures to institute enrollment quotas, our team is also currently working on the development of a REDCap plug-in that would allow other research teams with REDCap access to utilize this platform for detecting "gamers." Depending on institutional regulatory guidelines, additional identifiers such as Internet protocol (IP) address, mailing address, phone number, and/or e-mail address could be captured at the screening to aid in the detection of duplicates. For example, Bricker et al.[19] utilized CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart) authentication, review of IP addresses for duplicates or non-US origin, and review of survey logs for suspicious response times to identify screening records that required additional staff contact prior to enrollment. Similar functionality to proactively screen out individuals using Virtual Private Servers to disguise location or who are responding from a county not currently being targeted for study enrollment has also been developed within Qualtrics.[20]

Remote Consent

Informed consent is a critical entry point for all clinical research. As noted in the United States Food and Drug Administration's regulations relating to good clinical practice and clinical trials, informed consent shall be documented by the use of a written consent form approved by the Institutional Review Board (IRB) and signed and dated by the subject or subject's legally authorized representative at the time of consent with a copy given to the person signing the form. Several options exist for remote informed consent that adhere to good clinical practice guidelines. First, following completion of study screening, a physical consent form can be mailed to eligible research participants. Depending on the nature of the study and approved procedures for local IRBs, this consent form can either be reviewed independently by the participant, signed, and mailed back to the research team, or a phone/video call can be scheduled with a member of the research team to synchronously review the consent form prior to signing and return mailing. In our own prior studies that have utilized mailed consent procedures, return rates have been somewhat low, with nonresponse rates of approximately 45%–50%.[21,22] To improve upon this process, we are currently exploring the added utility of a $5 noncontingent incentive, mailed with consent forms in a similar manner as many paper-based household surveys are conducted.[23,24] Study recruitment is ongoing and early results should be interpreted with caution; nonetheless, among mailed consent forms sent to date (775 total), response rates to mailings with the $5 incentive versus not have been 45.5% versus 35%, which equates to a cost of $48.78 per additional participant enrolled.

However, antiquated mailed consent procedures do not capitalize on the opportunities given by mHealth technologies. Several alternative electronic forms of consent now exist that can be applied broadly within remote clinical trials.[25] Such electronic approaches have been associated with improved patient comprehension, usability, and workflow as compared to standard paper-based consent approaches.[26–30] First, within REDCap, there is electronic consent (e-consent) functionality with included support for electronic signatures which has been deployed across numerous institutions (including our own, with IRB approval).[31] Via REDCap e-consent, an electronic version of the consent form can be shared with the research participant and this can be paired with a synchronous audio or video phone call. After review of the e-consent form, both the study participant and the consenter electronically sign and date the form, each retaining a digital copy. In the event of an institutional compliance audit of the research study, all signed consent forms are stored within REDCap and can be downloaded and/or printed as needed by an approved member of the research team.

Additional methods exist for e-consent that, within a single platform, pair synchronous review of a consent form with an audio or a video call with a consenter. One such platform is doxy.me, a lightweight telehealth platform with minimal hardware requirements for both research staff and research participants. Adopted for a clinical research workflow, doxy.me supports e-consent with simultaneous video communication (teleconsent). A waiting room within doxy.me allows the research staff member to manage multiple participants who may simultaneously be awaiting consent while still protecting privacy. Aside from video communication, a key feature that differentiates teleconsent from REDCap e-consent is shared control of the screen. This shared control allows the consenter to scroll through the consent form as she/he reviews the consent form, with this scrolling also visible to the research participant. Users on both sides can provide their electronic signatures using a stylus on touch screens or via a photo snapshot for identity verification. After completion of the informed consent process, researchers and participants can download signed copies of consent forms along with a self-contained audit trail.

A critical concern with all e-consent options is the maintenance of the quality of the informed consent process. Several e-consent systems (particularly asynchronous online options) may add informational multimedia along with contact information to address comprehension issues. Our group is in the process of examining the quality of informed consent for some of these e-consent options and data collection is still underway. Preliminary results suggest a slight advantage of synchronous video consent (teleconsent) over consent by phone, and no disadvantage of e-consent when compared to a face-to-face informed consent process.

Remote Assessment

Many, but certainly not all, research assessments for ongoing clinical trials can be delivered via remote collection formats. Various self-report assessments are likely amenable to some form of remote assessment, either via phone follow-ups in which a member of the research team reads questions to participants or via electronic surveys that can be e-mailed or text messaged to study participants (the latter options requiring text/e-mail access as an additional eligibility criterion).

E-mail and/or text-based surveys can be administered via a variety of survey platforms, including REDCap, Qualtrics, and

SurveyMonkey, to name a few. The Twilio platform is a secure, third-party app that has been integrated with REDCap to send survey invitations and messages to participants via text message or voice calls. The use of the Twilio platform incurs a nominal fee for each text message sent (at $0.0075) and phone call made (at $0.013/min). The study survey is initially created in REDCap and then sent to the participant via either a text message or a phone call. Study assessments can be sent at any frequency, including as daily diaries to capture outcomes in granular detail. As examples, we have utilized this approach to text message participants links to complete assessments of smoking up to three times per day and as daily diaries to augment data collection in an in-person clinical trial (NCT02737358).[32] Individuals who completed the study reported that the assessment platform was easy to use and 78.9% preferred this electronic assessment platform to traditional paper measures.[32] Recent meta-analyses suggest that participants complete approximately 80% of electronic daily diaries, on average,[33] and certain design characteristics may help to minimize the frequency of missing data. Strategies to improve daily survey completion include sending surveys at fixed times, adequately compensating for participants' time, and keeping the number of daily assessments to the minimum necessary to answer the research questions.[33]

Remote Biomarkers Collection

Many tobacco research teams already deploy methods outlined previously within their clinical trials, but still rely on in-person collection of biomarkers of nicotine exposure. Thus, one of the biggest hurdles to overcome in the conduct of remote trials is the need for remote biomarker collection to objectively identify tobacco use status.[34] To date, studies that have incorporated remote biochemical verification have typically utilized mailed saliva to assess cotinine.[35–38] Within these studies, saliva sampling kits are usually mailed to participants after reporting abstinence at study follow-up. The saliva sample is then mailed back to the research team and analyzed for cotinine. Limitations to the remote collection of salivary cotinine include high cost ($125/sample[36]), inability to distinguish between combustible tobacco use and other nicotine exposure (eg, nicotine replacement therapy and electronic cigarettes),[39–41] lack of synchronicity between reporting of abstinence and collection of a saliva sample, and potential for biased responding, with those who misrepresent abstinence on self-report measures less likely to return saliva samples.[36] Point-of-contact cotinine screenings also exist[42] (eg, NicAlert), which address issues related to cost, but only provide semiquantitative results.

Expired-air (ie, breath) carbon monoxide (CO) is an alternative biological indicator of recent smoking that can be utilized to verify smoking status.[43–45] Although CO can be confounded by environmental CO exposure, there are several benefits to the utilization of breath CO as compared to cotinine: (1) CO collection is noninvasive, (2) CO samples can be captured at multiple study timepoints without increasing costs, and (3) CO is sensitive to combustible tobacco use and is unaffected by electronic cigarette or nicotine replacement therapy use.[44] Several research groups have pioneered procedures to remotely collect expired-air CO.[46–51] The most common approach involves providing study participants with a stand-alone gold standard CO monitor and then prompting them to submit video recordings (via computer or mobile device) of themselves providing CO samples. In the largest remote and nationwide trial to our knowledge to date that has used these procedures with

adults (N = 94), participants were randomized to earn incentives based either on video-verified abstinence or solely on video submission of providing a CO sample (ie, noncontingent control group).[46] Compliance was high with both CO submission protocols (78% and 85%, respectively) indicating the feasibility of remote CO collection.[46] However, compliance with similar protocols has been somewhat lower among adolescent smokers, with a recent trial finding that only 37% and 51% of possible CO samples were submitted among active (incentive earned based on abstinence) and control (incentive earned based on CO submission only) participants, respectively.[52] Similarly low compliance rates were found in the UK-based BupaQuit trial such that only 25% of participants who self-reported abstinence submitted CO remotely using Bedfont's COmpactUSB Smokerlyzer, a device that required connection to a Windows PC to function.[53]

A key downside to most remote CO collection procedures published to date is the cost of the stand-alone CO monitors. These protocols rely on gold standard monitors which typically cost $700–1200 per monitor. This cost is reasonable when CO verification is to occur in person and the device is kept secure by the research team. However, when applied to a remote collection procedure, cost limitations prohibit widespread application. Recently, lower cost smartphone-enabled CO monitors have become available which could address this issue. The only commercially available smartphone-enabled CO monitor to our knowledge that is not sold exclusively with a cessation program is Bedfont Scientific's iCO Smokerlyzer. The current version of iCO can be used with any iOS or Android mobile device for a period of up to 3 years (or 200 tests, whichever comes first) and detects continuous CO concentrations of 0–100 ppm. The current iCO connects to the smartphone's audio jack, although Bedfont plans to release a Bluetooth-enabled device during the third quarter of 2020. Beyond the benefits of utilizing CO outlined above, the iCO is well suited for remote, large-scale use because it is much more affordable (~$60) than other remote tools including standalone CO monitors and salivary cotinine. A recent qualitative study documented that smokers are interested in using the iCO, particularly for purposes of smoking cessation.[54] Although the iCO has the potential to make remote CO collection possible in any smoking study, existing video verification protocols cannot be used with the iCO because the device does not have a screen to directly display a CO reading. The iCO functions only when used in conjunction with a mobile app developed by Bedfont. Bedfont has made the Application Programming Interface for the iCO available to investigators and software developers so that the device can be integrated into other mobile apps for CO collection. Our own team has recently completed initial technology development which integrates the iCO with the web-based REDCap system (R21 CA241842), eliminating the need for a separate mobile app. Via this platform, participants complete web-based self-report questionnaires as per usual and then are prompted to provide remote CO within the same web-based platform. The iCO/REDCap integration video records the participant providing CO and syncs all data in an individual study record in REDCap. Researchers can confirm participant identity and directly link CO outcomes to other trial outcomes. Taken together, the iCO, whether utilized with the mobile app developed by Bedfont, a mobile app developed by another investigative team, or with our iCO/REDCap integration, may offer one low-cost option to remotely biochemically verify smoking status.

Remote Medication Adherence Monitoring

An additional challenge to remote clinical trials that involve pharmacotherapy evaluation (not specific to tobacco clinical trials, but applicable) is the rigorous assessment of medication adherence. Several remote methods have been explored to capture medication adherence, with wide variation in cost and burden for participants and research staff. For medications that can be directly detected in saliva (eg, varenicline[55]), mailed saliva sample kits can be used to test for the presence of the medication. This has the unique advantage of allowing for biological outcome detection (ie, salivary cotinine) at the same time as testing for medication adherence. However, this method is limited to those medications with corresponding assays and available laboratories to test such specialized assays.

A common method for detecting medication adherence is via Medication Event Monitoring System or MEMS. A microprocessor or memory chip is inserted into a pill bottle cap or pill box and will signal when the device is opened and closed.[56] MEMS is used to confirm the timing and frequency of pill container openings but cannot be used to objectively confirm ingestion. In contrast, ingestible sensors ("digital pills") have been developed that can be added to capsules to allow for both timing/frequency and confirmation of ingestion.[57] Participants wear a device that receives a signal when the sensor enters the stomach.

Synchronous or asynchronous video observation of medication-taking is a recent advance in clinical trials and well suited for inclusion in remote trials. Medication-taking can be observed via video connection with a staff member in real time (ie, synchronously[58,59]), recorded via video on a mobile device and uploaded for subsequent staff review (ie, asynchronously[32,60,61]), or automatically detected using a mobile app with facial recognition software, such as AICure.[62] Limitations of these methods include high participant burden, required access to technology with video capabilities, and the need for staff to observe dosing in real time or review videos at a later date (for synchronous and asynchronous methods, respectively). Use of REDCap for remote video observation of medication-taking addresses some of these limitations and our group has used this approach to capture medication adherence as part of several clinical trials.[32] This approach involves asynchronous video capture of dosing, upload of video files, and later review by staff members.[32] While there is participant burden in the upload of videos, this functionality is free through REDCap and does not require specialty programming. Video capture and upload do require the participant to have a smartphone, but since the survey is web-based, the operating system is not critical to successful survey/video completion.

In summary, several rigorous methods for remotely monitoring medication adherence in pharmacological smoking cessation trials exist. These methods vary in availability depending on the medication, cost, participant and staff burden, and required technology and the optimal method depends on the specifics of each trial. It is also important to note that many of these methods work well for pill/tablet dosing formulations, in which the medication is ingested as a discrete event. However, nicotine replacement therapy products (eg, patches and lozenges) are not as easily amendable to remote adherence capture.

Conclusions and Future Directions

The methods of remote clinical trials have particular relevance in the context of COVID-19-related research restrictions. Many investigators face the prospect of indefinite halts to their research trials versus adapting to remote delivery. Any given study might consider the adoption of some or all methods described herein, with appropriate IRB approvals. However, our belief is that remote methods have enduring potential beyond COVID-19 restrictions and indeed can be a priori designed as such. Remote clinical trials cannot and should not replace traditional in-person studies and safety considerations for certain novel treatments may play a key role in the decision as to whether a trial can be conducted remotely. Moreover, remote trials that test interventions are also only viable to the extent that the intervention under examination is also viable for remote delivery. Nevertheless, remote trials do allow expedient recruitment of larger, demographically representative study samples, without undo burden to a research team.

There are a number of important future directions for the broader field of remote clinical trials research and for remote tobacco-focused trials in particular. First, particularly for trials in which there is some potential for study-related risks, adverse event monitoring is critical. Trials have begun to implement remote procedures for adverse event monitoring including via phone and automated electronic surveys,[21] but there is great potential to improve real-time adverse event monitoring and response to such events within the context of remote trials. Second, for tobacco-focused trials, innovating methods for real time, continuous, remote measurement of cotinine will improve the options for remote biochemical verification of tobacco use status and address limitations to current remote cotinine collection options. Third, the issue of potential bias will be critical to consider as the field of remote tobacco-focused trials continues to innovate and move forward. Each of the methods reviewed in this manuscript and future methods will likely be subject to different potential forms of bias, which should be considered when determining whether a remote method is appropriate to implement within a given trial. For example, although remote CO collection may potentially help to address barriers that lower income smokers may face when attempting to attend an in-person lab visit (eg, transportation barriers), the requirement to video record one's self and/or download a mobile app may result in disproportionate study attrition for older smokers who may have lower levels of technology literacy. Fourth, although remote trials likely will be associated with cost-savings, particularly as compared to large, multisite clinical trials, no studies to our knowledge have comprehensively examined the cost-effectiveness of remote versus in-person approaches. These types of analyses, especially if focused on specific methods (eg, cost-effectiveness of remote vs. in-person CO collection and of remote vs. in-person consent) may help research teams to determine which remote methods they would like to adopt within their trials. Finally, although some studies have adapted traditionally lab-based assessments, such as behavioral analog tasks, for remote delivery,[63–66] integration of such tasks with existing data capture systems like REDCap would improve the ease with which data from these tasks can be analyzed.

In summary, methods for remote clinical trials are regularly evolving, and new tools using mHealth and other digital platforms offer rapidly expanding options. The key to success for any remote trial is to maintain study rigor in a manner consistent with in-person trials. Whether this has yet been or will ever be achieved is debatable, but the overall trend is in that direction, particularly with new capacities for remote, yet still feasible, biomarker collection.

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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.

Declaration of Interests

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