METHODS FOR REMOTE CLINICAL TRIALS

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Background

Nearly all clinical trials are conducted locally, with recruitment limited to those who live proximal to a clinical trial site. These local trials struggle to recruit large, diverse, representative study samples. Consequently, many fail to meet their target enrollment and/or have unrepresentative samples. Trials that target specific subgroups of participants (e.g., low socioeconomic status, rural) or that address rare clinical conditions face even greater challenges, to the point where local trials may not even be feasible. Multi-site clinical trials can overcome some of these hurdles but incur their own unique challenges, most notably the need for sizable and costly infrastructure. With recent advances in telehealth and mobile health technologies, there is now a promising alternative: Remote clinical trials. Remote clinical trials (sometimes referred to as "decentralized clinical trials") are led and coordinated by a local investigative team, but are based remotely, within a community, state, or nation. Such trials rely on remote methods to recruit participants into trials, consent study participants, deliver interventions, and maintain all follow-up assessments from a distance. Because participants are not required to attend in-person visits, remote trials improve sample representativeness, expand trial access, and enhance study feasibility[1, 2]. Remote clinical trials are now timelier 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].

Remote Methods

The purpose of this technical assistance report is to provide a brief review of available methods for conducting remote clinical trials. We focus this report on key aspects of the clinical trial pipeline including remote: 1) study recruitment and screening, 2) informed consent, 3) assessment, 4) intervention delivery, 5) biomarker collection, and 6) remuneration (*Figure 1*). Many, but not all, of these methods involve the use of 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 is compliant with HIPAA, Part 11, and FISMA standards (low, moderate, or high). REDCap is freely licensed to non-profit institutions who join the REDCap Consortium and at the time of this writing, over 4,600 institutions in 139 countries have joined the Consortium, including all Clinical and Translational Science (CTSA) program hubs.

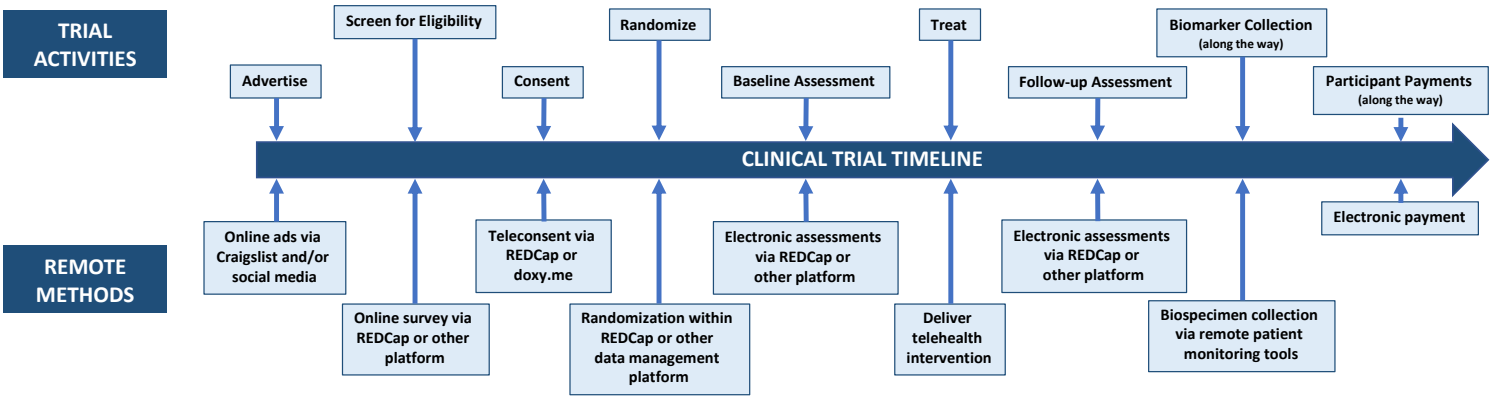

Figure 1: The clinical trial pipeline and remote methods that can be utilized at each stage of a clinical trial. See Appendix A for a larger format of Figure 1.

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Study Recruitment. Numerous platforms currently exist to remotely recruit study participants for remote clinical trials. These platforms include websites such as Craigslist, social media outlets (e.g., Facebook, Instagram, and Twitter), and other online avenues for research recruitment such as ResearchMatch. Via these platforms, investigators can place ads targeted toward their population of interest. These ads can either directly link interested individuals to online study screeners (e.g., via REDCap or Qualtrics) or can include contact information for potential participants to contact the study team.

One risk of remote recruitment via social media and other online platforms is fraudulent or otherwise low-quality data. A study by Devine and colleagues[8] 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. Methods for increasing the quality of data have been detailed previously[9] and include: 1) ensuring that study eligibility criteria are not explicitly stated in advertisements, 2) requiring respondents to pass a Completely Automated Public Turing test to tell Computers and Humans Apart (CAPTCHA), 3) collecting respondent IP addresses, 4) collecting verifiable information such as telephone number or physical address, 5) including at least one hidden item (e.g., by adding the @HIDDEN action tag to an item in REDCap) which will be visible to bots, but invisible to human participants, 6) including timestamps at the beginning and end of each instrument to identify suspiciously quick responding, 7) reviewing completed assessments for evidence of "straight lining" (i.e., responding with the same response down a line for all questions within an assessment), 8) including and requiring responses to open-ended items which can be reviewed for illogical responses, and 9) language in the study protocol that allows the study team to verify respondent identity if needed and language in the consent document stating that participants will be removed from the study without remuneration in cases of fraud.

Informed 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 (GCP) and clinical trials, informed consent shall be documented by the use of a written consent form approved by the 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[10]. Remote informed consent must adhere to these same guidelines. One option is to mail a hardcopy of the consent form to eligible research participants. Depending on the nature of the study and approved procedures for local Institutional Review Boards, this consent form can either be reviewed, signed, and returned independently by the participant, or if needed, a phone/video call can be scheduled with a research team member to synchronously review the consent form prior to signing and return mailing.

Mailed consent procedures do not capitalize on the opportunities given by mHealth technologies, and thus often incur unwanted recruitment delays. Several options for e-consenting now exist that can be applied broadly within remote clinical trials[11]. Such electronic approaches have been associated with improved patient comprehension, usability, and workflow as compared to standard paper-based consent approaches[12-16]. REDCap now allows for e-consent functionality, including capture of electronic signatures[17]. With this approach, an electronic version of the consent form is shared with the research participant and can be paired with a synchronous audio or video phone call. Upon review, 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[18] that, within a single platform, pair synchronous review of a consent form with an audio or video call with a consenter. One such platform is doxy.me, a 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

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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 s/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.

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. Direct phone assessment between study staff and research participants is perhaps the most common and has the advantage of averting errant responding. However, this approach is resource intensive (e.g., staff time for multiple calls, scheduling, etc.). Newer options allow assessments to be sent via e-mail or text message and can be auto sent on a scheduled basis if needed. These methods have the advantage of increased efficiency while still maintaining data integrity through sophisticated survey programming. There is enduring concern that these methods might have the unintended effect of excluding participants across a 'digital divide'[19]. However, most recent surveys indicate that >80% of the US population, including those across older and disadvantaged strata, are regular users of smartphones with internet access[19].

For researchers who opt for electronic survey methods, several options exist. Email 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. Use of the Twilio® platform incurs a nominal fee for each text message sent (@ $0.0075) and phone call made (@ $0.013/minute). The study survey is initially created in REDCap and then sent to the participant via either a text message or a phone call. Procedures detailed above to decrease fraud and improve the quality of data may also be useful within remote follow-up assessments.

Intervention Delivery. Various telehealth interventions lend themselves well to evaluation within the context of a remote clinical trial. Following completion of informed consent and randomization, study participants can be linked to a remote telehealth intervention such as a text messaging intervention, a mobile app-based treatment, telephone counseling, a website, or another remote intervention. Many of these platforms (e.g., mobile apps, websites, text messaging) allow for passive collection of usage data to determine engagement with the intervention. Other interventions, such as medication-based interventions or patient education materials, can also be delivered remotely by mailing the treatment to the study participant. Mailing of medications and/or other intervention materials can eliminate the need for a participant to complete a study visit in person to receive their intervention.

Biomarker Collection. One of the biggest hurdles to overcome in the conduct of remote trials is the need for remote biomarker collection to objectively identify clinical outcomes and/or to characterize the study sample. The field of remote patient monitoring tools is increasing rapidly and many of these devices can be utilized to remotely capture biomarkers. For example, Bluetooth-enabled devices such as scales, glucometers, thermometers, and blood pressure cuffs can be integrated with mobile apps that allow researchers to access patient data[20]. Individual research groups across the country have also developed procedures for and demonstrated feasibility of mailing and returning saliva, blood, urine, and buccal samples to/from participants[21-26]. These samples, once returned to the research team, can be assayed for relevant biomarkers.

Remuneration. Participant remuneration is a standard component of many clinical trials. Management of this process in a remote context has its own challenges, but electronic forms of payment are well suited for this purpose. Many online

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vendors offer electronic gift codes that can be e-mailed, or text messaged to participants to provide compensation for completion of study procedures. Greenphire's ClinCard system can also be used to remotely compensate participants. The ClinCard, which is similar to a preloaded debit card, can be mailed to study participants and remotely loaded with payments by the study team[27]. Finally, physical gift cards may also be mailed to participants to remotely provide compensation. Audit trails are possible for each of these methods, ensuring compliance with university accounting guidelines.

Conclusion

Remote clinical trials have the potential to extend clinical trial access beyond brick-and-mortar academic silos into the communities that are most in need of innovative, efficacious interventions. Any given study might consider adoption of some or all methods described herein, with appropriate IRB approvals. 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 allow for expedient recruitment of larger, demographically representative study samples, without undue burden to a research team.

For more information on remote clinical trial methods or a consultation with our Center of Excellence, please contact us at telehealthcoe@musc.edu.

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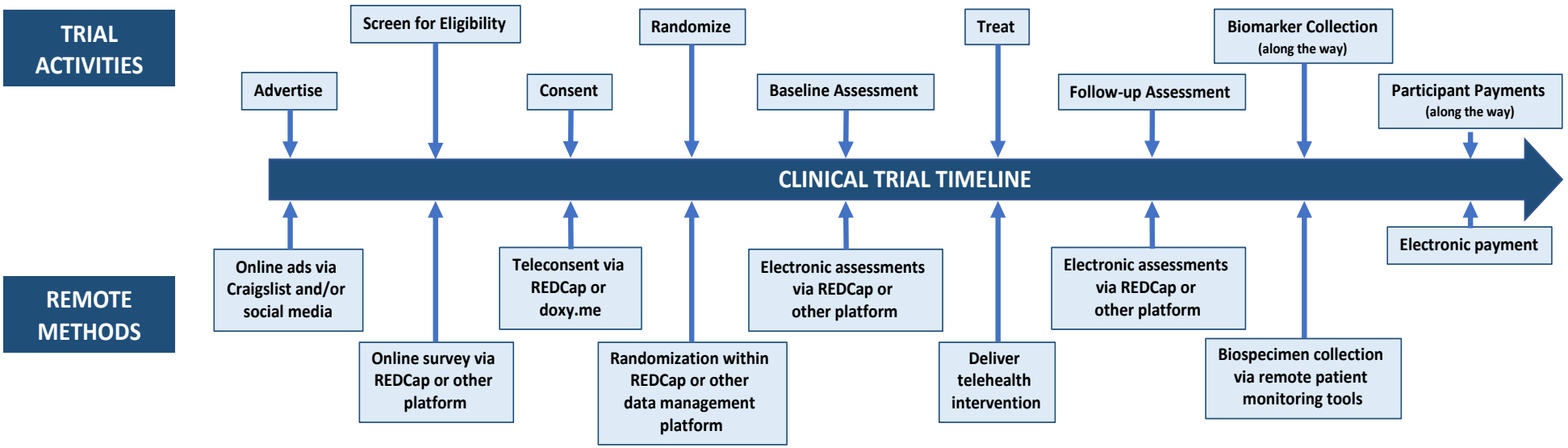
Appendix A

Figure 1: The clinical trial pipeline and remote methods that can be utilized at each stage of a clinical trial.



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