

Digital Clinical Trials for Substance Use Disorders in the Age of Covid-19

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As a result of the coronavirus 2019 (Covid-19) pandemic, clinical research for substance use disorders (SUDs) has been impeded due to widespread stay-at-home mandates limiting the operations of “non-essential” work. Although appropriate to proceed with an abundance of caution to prevent viral spread, there will be detrimental consequences for patients with SUDs if clinical trials research cannot adapt and continue uninterrupted. The field of digital health has strong evidence for its feasibility and effectiveness and offers tools that can facilitate the continuation of SUD clinical trials research remotely in accordance with Covid-19 precautions. Some digital tools have been used as components of SUD research in the past; however, no published clinical trial in SUDs to-date has been entirely virtual. This has important implications for disrupted clinical care, as providers seek guidelines for best digital practices. This paper provides a roadmap for integrating the fields of digital health and SUD clinical trials by proposing methods to complete recruitment,

screening, informed consent, other study procedures, and internal lab operations digitally. The immediate future of SUD research depends on the ability to comply with social distancing. Investment in research of digital clinical trials for SUDs provides an opportunity to cultivate benefits for research and clinical care long-term as we can (1) define regulatory requirements for the implementation of digital systems, (2) develop consensus on system-wide standards and protocols in the appropriate use of technology, and (3) gain experience that can translate to the treatment of patients with SUDs through telehealth in the community.

Key Words: clinical trials, Covid-19, substance use disorders, technology, digital

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All sectors have had to adapt to the novel coronavirus 2019 (Covid-19) pandemic or cease operations in response to widespread transmission mitigation policies.¹ This includes clinical care for substance use disorders (SUDs), which has rapidly converted to telehealth,^{2,3} in addition to research operations, including clinical trials for SUDs, as institutions and Internal Review Boards (IRBs) have appropriately overseen limitations of “nonessential” activities to protect staff and participants.⁴ This is significant for 2 reasons: (1) the massive paradigm shift to telehealth as a primary means of providing clinical care precludes evidence-based guidance on best practices and how to implement them rapidly,² and (2) research on the efficacy and safety of novel therapeutics and processes are on hold or reduced.

Historically, clinical research has made use of technology to serve some functions of a study⁵; however, none have completed their operations entirely through remote, and thereby, digital means.⁶ In the field of SUDs, telehealth has been underutilized in clinical practice and understudied for treatment.⁷ No clinical trial to date examining a medication-based intervention has occurred without in-person visits, though a number of studies have examined and demonstrated feasibility for delivering components of SUD treatment, such as internet based psychotherapies.^{8,9} As experts anticipate the world during the pandemic will require phases of social distancing,¹⁰ clinical trials in SUDs can only continue their essential functions of testing and validating novel treatments and their safety and determining best practices for implementation in clinical management, if they are able to quickly create a pathway for a comprehensive digital platform or hybrid model with reduced in-person functions to prevent future interruptions.⁴

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The field of digital health, a multidisciplinary domain defined as the convergence of digital technology with health and healthcare and includes categories such as mobile health (mhealth), health information technology (IT), wearable devices, telehealth and telemedicine, digital analytics, artificial intelligence, and personalized medicine,¹¹ offers solutions for research that is compliant with social distancing. Existing technologies and evidence of digital health interventions for many medical specialties,¹² including previous work in SUD,^{7,13} can be applied to the design and execution of clinical trials in SUDs.¹⁴ This paper outlines a roadmap for the conduction of SUD clinical research utilizing digital technology as it applies to recruitment, screening, informed consent, enrollment, retention, study procedures, and research staff operations. Investment in digital health applications for clinical research in SUDs will have far reaching implications, especially for clinical care, as best practices and guidelines are defined in adapting SUD treatment to social distancing. While possible, this new digital world has limitations as compared to in-person functions and brings challenges as a result of the time, financial investment, and physical effort these modifications will require. All stakeholders will need support to adequately address these hurdles, though the possible long-term benefits of improving health disparities in accessing clinical trials, decreasing burden on staff and participants by automating and improving flexibility of research functions, and creating standards and safeguards for digital infrastructure in research outweigh many of the costs.

RECRUITMENT

Recruitment is a component of the clinical trial process that researchers have experience doing remotely and, in the age of social media and modern advertising, is conducive to digital processes.^{15,16} Reduced foot-traffic to clinics and hospitals limits the effectiveness of onsite recruitment. Radio, television, print media, and advertising on public transportation (eg, bus stops, subways, etc) can continue to be used in a digital trial; however, they may also be less effective as fewer people engage in traditional routines, such as commuting to work. Social media, internet, and other online platforms may provide opportunities and larger, more diverse pools of prospective participants as location limitations are eroded if physical attendance in the clinic is not necessary or is less frequent.^{16,17} Recruitment across a state or potentially from multiple states enhances diversity by allowing for inclusion of individuals in rural areas or participants who have had trouble with transportation to research sites and who historically have not been well represented in clinical research.¹⁸ In doing so, researchers will need to address challenges in working competently with unfamiliar communities. Outreach efforts should be made to identify liaisons to assist in understanding different needs based on geography, race, and ethnicity, and to enhance the development of social and cultural competencies. Expanding the scope of the boundaries for recruitment may also bring about challenges that require differentiated messaging, support, and tailored resources.¹⁹

Digital recruitment strategies can target characteristics outlined in inclusion criteria such as demographics (eg, age, sex) and the substance of interest (eg, “alcohol treatment”).^{17,16} However, this form of advertising can be expensive as popular “key words” such as “addiction” drive up

costs, and many researchers have limited experience in optimizing these platforms.²⁰ Partnerships with advertising experts or hiring staff with past experience in this area may be fruitful. Principal investigators (PIs) will be incentivized to have engaging, user-friendly websites that are updated with information on current trials. PIs and their staff should develop a greater awareness of their online presence. Since IRBs approve advertising, it will be critical to have IRB members well-versed in digital advertising techniques, ethics, and risks to ensure that these methods are not prevented due to inexperience or approved without proper considerations.^{21–23} Institutions might provide training in the following competencies: (1) practical use of digital health tools, (2) privacy and confidentiality, (3) history of digital health regulations and policy, (4) digital research ethics, and (5) possible risks and breaches of data and safeguards. Many academic institutions have experts in digital media, ethics, and policy. Collaborative relationships across disciplines can facilitate and enhance the needed learning to embark on the use of digital advertising and digital health research. A final, novel recruitment strategy involves utilization of social media directly through “word of mouth.” Several recent studies for the treatment and prevention of Covid-19 have been recruited largely by word of mouth as well as unpaid media coverage of the study.²⁴ These strategies are especially worthy of consideration for larger, government sponsored multi-site clinical trials.

SCREENING, INFORMED CONSENT, AND ENROLLMENT

During the pandemic, it is important to limit unnecessary contact. Previous screening that occurred by “walk-in” to a research clinic should be ended. Potential participants should access screening via a website, phone call, direct messaging through social media, email address, or online portal. To achieve this, a filter should be implemented to assess the appropriateness of screening participants for studies before scheduling a virtual visit. This filter should consist of an online screening questionnaire or a brief phone screen. The screening filter should identify individuals that DO meet inclusion criteria and DO NOT meet exclusion criteria. Only these participants should have the option of scheduling a virtual screening session via an online portal or scheduling system, having study staff contact them to schedule a virtual assessment upon review of their screening questionnaire, or if via phone, have the study staff schedule them personally for their next assessment.⁵ The screening filter should assess an individual’s access to internet enabled devices (eg, computer, smart-phone, or tablets). Although the vast majority of the US population has access to the internet (75%–90%+), only a third of the population has access to residential, high-speed, broadband technology.²⁵ Most of the current broadband utilization consists of cell-phone based mobile coverage that allows for synchronic video conferencing, though the bandwidth and flow of data are often unreliable or costly. If it is within the study budget, subjects may be mailed a study device.^{26,27} As screening and study procedures may require additional supplemental tools that need to be shipped to participants, a mailing address that participants can receive packages should be recorded. Researchers may want to

consider alternative shipping options such as parcel lockers where participants can pick up packages from a secure site in the community. Confirmation and reliable timing of receiving a delivery as well as videoconferencing should be tested before the initiation of study participation. These are notable challenges to overcome as part of conducting a digital trial, and currently, the literature does not present solutions.

Virtual visits should be conducted on HIPAA compliant platforms provided by the PI's institution or subscriptions in the case of stand-alone sites.¹² Screening participants may receive screening consent forms and information to review before their virtual visit via text or email. These forms can be reviewed and then signed via secure e-signature platforms. Software may require HIPAA Business Associate Agreements (BAAs) if operating outside of a research institution to ensure compliance with confidentiality and privacy measures. Data usage agreements may be needed if third party systems collect or store data. PIs should consult with their IT departments if using digital technology not provided by their institutional licenses. Execution of these external contracts creates barriers as it contributes to additional time and effort needed for approval. If the software is provided by the parent institution, researchers should confirm with their IT departments that it is appropriate for use in clinical research. Generally, institutionally licensed software and tools have fewer barriers as they have previously been vetted. The legal framework for remote consent has existed and been part of the clinical trial repertoire for years.²⁸ Many secure video-platforms allow for screen sharing which can facilitate the informed consent process. These video platforms also permit multiple individuals to join, allowing for group gatherings with participant contacts, such as family members, or other research staff. Recording functions exist and may be relevant to study procedures (eg, if a psychotherapy component is being monitored for compliance).

Digital self-assessments can be completed via emailed or texted links, if not through an online portal, and interviews via video can include medical or psychiatric assessments. Other meaningful data can be collected passively through the utilization of an individual's "digital phenotype."²⁹ This concept, introduced by Jain and colleagues, is defined as a set of observable characteristics of an individual's health manifested through use of social media, internet forums and online communities, wearable technologies and mobile devices that can shape understanding of both human health and illness beyond traditional medical approaches to characterizing disease such as the physical exam, laboratory values and clinical imaging data. As an example, decreased activity as measured by wearable accelerometers is consistently observed in individuals who are depressed.³⁰ Data as part of a digital phenotype has the added benefit of being mostly passive in its collection and requiring no or limited additional burden on the part of the participant. Data collection can occur directly through other digital platforms, like social media.³¹ Digitally completed assessments and passive data have many benefits including higher rates of completion, ease of collection, decreased burden on the participants and staff, and decreased errors over paper assessments which require transcription to electronic form.³²

Virtual visits may need to be enhanced with "screening kits," that can be shipped to the participant, a neighborhood

partner (eg, medical office or other research site), picked up from the primary research site, or delivered by staff or courier service with safety protocols to limit physical contact. These kits can include supplies, such as sensors, that participants can learn to use independently or in collaboration with community clinics, laboratories, or health centers. As an example, a kit might include a home blood pressure and pulse monitor, drug testing cups for biological samples such as urine or saliva, mobile sensors such as breathalyzers, accelerometers, and heart rate monitors. There is a strong existing literature for the self-assessment of home blood pressure,³³ pulse, and weight, and remote use of breathalyzers.³⁴ However, remote drug testing on biological samples, a key treatment and research outcome for SUDs, requires investigation of its feasibility and development of protocols and guidelines for best practice.³⁵ Video facilitation of observed salivary drug testing is one option. Other options include creating a standardized, observed urine testing process completed via video or having an in-home observed urine test or blood collection by study staff or lab technicians. Contracting with external providers, such as phlebotomists, lab technicians or nurses, requires greater investment from researchers and risks virus exposure. Research should attempt to define best practices for video-observed urine drug testing which can build on existing processes of in-person observed testing,³⁶ such as: (1) confirming test cup is intact before collection (eg, twist tops that record number and times of openings), video assessment of bathroom, placement of video device to confirm specimen is collected by individual identified as participant in real-time (use of pH and temperature strips), audio confirmation of micturition, and no use of faucets until visual confirmation the specimen is sealed in tamper-proof container. Although all of this requires additional, creative work on the part of the researchers, it is feasible and has the potential to enhance data collection options for SUD clinical research.³⁷ As clinical providers struggle with a radical shift towards telehealth and limitations to in-person clinical practice, these procedures developed in clinical trials can help inform treatment guidelines for remote, video-assisted drug testing.

Alternatively, eligible screening participants may need to have an in-person visit with their primary care provider or study staff physicians to complete a physical exam, electrocardiogram, or local laboratory for blood work and other specimen testing. If permitted, supplemental in-person visits to the research site with appropriate virus transmission mitigation processes in place (eg, protective equipment, sanitation procedures, limiting staff and participants in one setting, etc) may be needed. The Food and Drug Administration supports and encourages clinical trial researchers to work with IRBs to adapt to the current environment and collaboratively develop ways to complete research virtually, providing some guidelines in support of the above processes.⁴

STUDY PROCEDURES

Eligible participants can progress to informed study consent using similar methods as screening consent. Participants should be provided information and tutorials regarding the digital study procedures and timeline. Additional assistance and coaching may be required if the participant

struggles using or is unfamiliar with technology and the digital interface. For a medication-based clinical trial, a brief delay may precede start of study medication as shipment and delivery to participants is coordinated. Confirmation of receipt by signature, from parcel lockers, and video observed medication administration as with Cell Phone Assisted Remote Observation of Medication Adherence (CAROMA) is recommended.^{27,38} Return shipping labels and containers should be provided for missed doses or to accommodate dose reductions and safe medication return.

As with screening, well-labeled study-procedure kits may need to be mailed with tools, sensors, and testing. If partnership with community providers, such as outside physicians or laboratories, is required, research staff should try to coordinate and facilitate these visits to aid participants and enhance adherence. If qualitative drug testing is acceptable as a binary outcome, as with cocaine or opioid use disorder treatment, home drug testing or breathalyzer testing in the case of alcohol can occur during virtual visits.³⁵ However, if quantitative levels are needed as with some drug treatment studies,³⁹ close collaboration with local patient service centers can facilitate this.

As participants complete self-report and interview assessments through electronic means, PIs may consider the use of ecological momentary assessments (EMA) or ecological momentary interventions (EMI), that are self- or investigator- initiated on internet-enabled devices in vivo and logged in real-time.⁴⁰ This increased specificity of time-scale for assessments and interventions may be useful for some trials and expand utilization and access for underserved communities as investigators develop more comfort with digital processes improving retention and engagement of participants with the research study process.⁴¹ Although assessments may have previously been confined to in-person study visits, digital study design allows for greater flexibility for completion of self-reports in an expanded time frame where participants can pace themselves. Research staff can make use of automated text, voicemail, or email messages with links reminding participants what assessments remain. Quality of study data can also be enhanced as assessments may not be submitted until all responses are complete. As with other clinical trials and if required by the IRB, the study PI should consider including access to a study physician who is on-call 24 hours per day, 7 days a week, in case there is a study emergency or different staff member if support is needed to trouble shoot a technological issue after hours. This may raise other considerations if a participant reports a concerning response (eg, suicidal ideation) after hours. PIs and study staff will need to work closely with IT and IRBs to assess what is feasible and safe for participants.

Payment for participants' time and adherence to study procedures can be completed remotely, and there is a wide literature to support different methods.¹³ Many remote options exist that can be emailed or mailed to the participant,⁴ such as electronic gift cards or payment cards. Complex automated digital systems of providing cash through software have been developed, especially as they are tethered to intermittent random reinforcement, such as those used in Community Reinforcement Approach.⁴² One FDA-cleared

product, ReSET/ReSET-O, allows for the dynamic modification of payment based on a variety of therapeutic goals as part of Contingency Management.⁴³ In the future, financial incentives can be tailored using real-time, biologically driven methods that maximize reinforcing effects, linking computational psychiatry with real-world applications.⁴⁴

RESEARCH STAFF OPERATIONS

Covid-19 also greatly affected research staff operations not involving participants. Some institutions have implemented hiring freezes. As current employees transition on to new positions, some groups are understaffed. Onsite work, particularly in large lab groups with limited space or in geographical areas with high rates of infection, has been temporarily prohibited or reduced. Lab meetings are now virtual, using group synchronous video conferencing. Communication transpires predominantly over email, phone calls, or video. For operations that must occur onsite, staff safety must be a priority, and labs are devoting more resources to personal protective equipment, frequent sanitation of commonly used surfaces, protocols for Covid-19 symptom and contact screening, temperature checks, and air circulation. Research groups should consider how staff commute to work, especially if taking public transportation, and might consider providing accommodations to staff with preexisting medical conditions, older age, or other vulnerabilities that may make the risk of onsite work too great. Collaboration with buildings and facilities management on plans for elevators, contactless soap dispensers and garbage cans, restroom management, and processes of communication and contact tracing if employees test positive is necessary in creating a safe return to work.⁴⁵ Parent institutions and departments are making recommendations and rules contingent upon local infection rates. Labs might consider identifying a key person to stay informed and compliant. All of this requires time and resources. Coupled with stress of the current environment, the risk for burnout and negative mental health effects is great.⁴⁶ It is not clear what impact this will have on the trajectories of research careers. Guidance and assistance with navigating all of these changes is needed.

LIMITATIONS

Limitations with implementing the digital trial for SUD include (1) the lack of clearly defined regulatory requirements, (2) no consensus for system-wide standards and protocols for virtual clinical trial technology applications, (3) inexperience for most PIs and study staff on structuring a digital study, (4) inconsistent or limited access to compatible technology, internet, or privacy for participants, (5) initial increased costs and time to learn and implement this methodology and systems, and (6) the need for some "in-person" encounters. Most of these issues can be addressed over time by funding digital clinical trials in SUD.¹⁴ This will initially feel overwhelming for researchers. The large investment of time and financial resources upfront is great. However, this investment may provide longitudinal benefits by bringing more comprehensive technological advances into the operations and systems of clinical research, and hopefully translate into how providers administer clinical care for SUD

through telehealth as evidence based digital procedures dictate treatment, expand access, improve recruitment and retention of diverse and larger samples, decrease data entry errors, and automate processes to relieve some burdens on research staff and participants over time. As funding bodies, researchers, regulators, and participants gain experience in these operations and technology advances, digital clinical trials research has the potential to be as common-place as current brick-and-mortar operations.¹² The assessment of research staff and participants' preferences in conjunction with federal and institutional guidance will elucidate feasibility, regulatory standards, benefits, outcomes, and costs for digital processes.

CONCLUSIONS AND FUTURE DIRECTIONS

Although the Covid-19 pandemic has been highly disruptive, this crisis may present opportunities to enhance clinical trials research in SUDs and ultimately treatment. Experience in this area may yield ongoing benefits for future research as these digital methods can continue to be utilized after recovery from the pandemic through hybrid virtual and in-person processes. Through embracing digital opportunities, the field of SUD research can help (1) define regulatory requirements for implementing digital systems, (2) develop consensus for system-wide standards and protocols on the appropriate digital applications for clinical trials, and (3) gain experience that applies to the clinical care of patients with SUDs through digital health platforms and tools. Finally, enhancing digital health applications has the potential to improve access to historically disadvantaged groups. Investment in research assessing the feasibility and limitations of these proposed changes is necessary to guide future digital practices.

REFERENCES

- Galbadage T, Peterson BM, Gunasekera RS. Does COVID-19 spread through droplets alone? *Front Public Health*. 2020;8:163.
- Jain S, Khera R, Lin Z, Ross JS, Krumholz HM. Availability of telemedicine services across hospitals in the United States in 2018: a cross-sectional study. *Ann Intern Med*. 2020;173(6):503–505.
- Lin L (Allison), Fernandez AC, Bonar EE. Telehealth for substance-using populations in the age of coronavirus disease 2019: recommendations to enhance adoption. *JAMA Psychiatry*. Published online July 1, 2020.
- Commissioner O of the. Coronavirus (COVID-19) Update: FDA Issues Guidance for Conducting Clinical Trials. FDA. Published March 27, 2020. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-guidance-conducting-clinical-trials>. Accessed May 18, 2020.
- Rosa C, Campbell ANC, Miele GM, Brunner M, Winstanley EL. Using e-technologies in clinical trials. *Contemp Clin Trials*. 2015;45(Pt A):41–54.
- Ginige JA, Boulamatsis C, Heffernan M, et al. Fully-online, interoperable clinical trial management system for multi-interventional RCT: maintain your brain digital platform. *Stud Health Technol Inform*. 2020;268:97–112.
- Lin LA, Casteel D, Shigekawa E, Weyrich MS, Roby DH, McMenamin SB. Telemedicine-delivered treatment interventions for substance use disorders: a systematic review. *J Subst Abuse Treat*. 2019;101:38–49.
- Beckham JC, Adkisson KA, Hertzberg J, et al. Mobile contingency management as an adjunctive treatment for co-morbid cannabis use disorder and cigarette smoking. *Addict Behav*. 2018;79:86–92.
- Campbell ANC, Nunes EV, Matthews AG, et al. Internet-delivered treatment for substance abuse: a multisite randomized controlled trial. *Am J Psychiatry*. 2014;171(6):683–690.
- Hick JL, Biddinger PD. Novel coronavirus and old lessons — preparing the health system for the pandemic. *N Engl J Med*. 2020;382(20):e55.
- Bucci S, Schwannauer M, Berry N. The digital revolution and its impact on mental health care. *Psychol Psychother*. 2019;92(2):277–297.
- Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. *N Engl J Med*. 2020;382(23):e82.
- Marsch LA, Dallery J. Advances in the psychosocial treatment of addiction: the role of technology in the delivery of evidence-based psychosocial treatment. *Psychiatr Clin North Am*. 2012;35(2):481–493.
- Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *Npj Digit Med*. 2020;3(1):1–7.
- Applequist J, Burroughs C, Ramirez A, et al. A novel approach to conducting clinical trials in the community setting: utilizing patient-driven platforms and social media to drive web-based patient recruitment. *BMC Med Res Methodol*. 2020;20(1):58.
- Akers L, Gordon JS. Using Facebook for large-scale online randomized clinical trial recruitment: effective advertising strategies. *J Med Internet Res*. 2018;20(11):e290.
- Borodovsky JT, Marsch LA, Budney AJ. Studying cannabis use behaviors with Facebook and web surveys: methods and insights. *JMIR Public Health Surveill*. 2018;4(2):e48.
- Myers US, Birks A, Grubaugh AL, Axon RN. Flattening the curve by getting ahead of it: how the VA healthcare system is leveraging telehealth to provide continued access to care for rural veterans. *J Rural Health*. Published online April 13, 2020.
- Bhutada NS, Rollins BL. Disease-specific direct-to-consumer advertising of pharmaceuticals: an examination of endorser type and gender effects on consumers' attitudes and behaviors. *Res Soc Adm Pharm RSAP*. 2015;11(6):891–900.
- Kong T, Scott MM, Li Y, Wichelman C. Physician attitudes towards-and adoption-of mobile health. *Digit Health*. 2020;6:1–10.
- Jain SH. Practicing medicine in the age of Facebook. *N Engl J Med*. 2009;361(7):649–651.
- Samuel G, Buchanan E. Guest editorial: ethical issues in social media research. *J Empir Res Hum Res Ethics JERHRE*. 2020;15(1–2):3–11.
- Burr C, Taddeo M, Floridi L. The ethics of digital well-being: a thematic review. *Sci Eng Ethics*. 2020;26(4):2313–2343.
- A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 | NEJM. Available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2016638>. Accessed August 4, 2020.
- NW 1615 L. St, Suite 800 Washington, Inquiries D 20036USA202-419-4300 | M-857-8562 | F-419-4372 | M. Demographics of Internet and Home Broadband Usage in the United States. Pew Research Center: Internet, Science & Tech. Available at: <https://www.pewresearch.org/internet/fact-sheet/internet-broadband/>. Accessed May 13, 2020.
- Wycoff AM, Metrik J, Trull TJ. Affect and cannabis use in daily life: a review and recommendations for future research. *Drug Alcohol Depend*. 2018;191:223–233.
- D'Souza DC, Cortes-Briones J, Creatura G, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. *Lancet Psychiatry*. 2019;6(1):35–45.
- Welch BM, Marshall E, Qanungo S, et al. Teleconsent: a novel approach to obtain informed consent for research. *Contemp Clin Trials Commun*. 2016;3:74–79.
- Jain SH, Powers BW, Hawkins JB, Brownstein JS. The digital phenotype. *Nat Biotechnol*. 2015;33(5):462–463.
- Alosco ML, Spitznagel MB, Miller L, et al. Depression is associated with reduced physical activity in persons with heart failure. *Health Psychol*. 2012;31(6):754–762.
- Ramo DE, Kaur M, Corpuz ES, et al. Using Facebook to address smoking and heavy drinking in young adults: protocol for a randomized, controlled trial. *Contemp Clin Trials*. 2018;68:52–60.

32. Palen L-A, Graham JW, Smith EA, Caldwell LL, Mathews C, Flisher AJ. Rates of missing responses in personal digital assistant (PDA) versus paper assessments. *Eval Rev*. 2008;32(3):257–272.
33. Shimbo D, Abdalla M, Falzon L, Townsend RR, Muntner P. Role of ambulatory and home blood pressure monitoring in clinical practice: a narrative review. *Ann Intern Med*. 2015;163(9):691–700.
34. Koffarnus MN, Bickel WK, Kablinger AS. Remote alcohol monitoring to facilitate incentive-based treatment for alcohol use disorder: a randomized trial. *Alcohol Clin Exp Res*. 2018;42(12):2423–2431.
35. Melanson SEF. The utility of immunoassays for urine drug testing. *Clin Lab Med*. 2012;32(3):429–447.
36. Hadland SE, Levy S. Objective testing: urine and other drug tests. *Child Adolesc Psychiatr Clin N Am*. 2016;25(3):549–565.
37. Samuels EA, Clark SA, Wunsch C, et al. Innovation during COVID-19: improving addiction treatment access. *J Addict Med*. 2020;14(4):e8–e9.
38. Walker R, Hillhouse M, Perrochet B, Sparenborg S, Mooney L, Ling W. Medication adherence monitoring using smartphone video dosing in an open-label pilot study of monthly naltrexone plus once-daily bupropion for methamphetamine use disorder: feasibility and acceptability. *J Addict Med*. 2019;13(5):372–378.
39. Brezing CA, Levin FR. The current state of pharmacological treatments for cannabis use disorder and withdrawal. *Neuropsychopharmacol*. 2018;43(1):173–194.
40. Ferreri F, Bourla A, Mouchabac S, Karila L. e-Addictology: an overview of new technologies for assessing and intervening in addictive behaviors. *Front Psychiatry*. 2018;9:51.
41. Colombo D, Palacios AG, Alvarez JF, et al. Current state and future directions of technology-based ecological momentary assessments and interventions for major depressive disorder: protocol for a systematic review. *Syst Rev*. 2018;7:233.
42. Petry NM, Alessi SM, Rash CJ, Barry D, Carroll KM. A randomized trial of contingency management reinforcing attendance at treatment: do duration and timing of reinforcement matter? *J Consult Clin Psychol*. 2018;86(10):799–809.
43. reSET® & reSET-O®. Pear Therapeutics. Available at: <https://peartherapeutics.com/products/reset-reset-o/>. Accessed May 18, 2020.
44. Liu S, Dolan R, Heinz A. Translation of computational psychiatry in the context of addiction. *JAMA Psychiatry*. Published online July 1, 2020.
45. CDC. Coronavirus Disease 2019 (COVID-19) - Interim Guidance for Businesses and Employers. Centers for Disease Control and Prevention. Published February 11, 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/community/guidance-business-response.html>. Accessed August 4, 2020.
46. Lin K, Yang BX, Luo D, et al. The mental health effects of COVID-19 on health care providers in China. *Am J Psychiatry*. 2020;177(7):635–636.