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The application of Digital Health to the Assessment and Treatment of Substance Use Disorders: *The past, current, and future role of the National Drug Abuse Treatment Clinical Trials Network*

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Abstract

The application of digital technologies to better assess, understand, and treat substance use disorders (SUDs) is a particularly promising and vibrant area of scientific research. The National Drug Abuse Treatment Clinical Trials Network (CTN), launched in 1999 by the U.S. National Institute on Drug Abuse, has supported a growing line of research that leverages digital technologies to glean new insights into SUDs and provide science-based therapeutic tools to a diverse array of persons with SUDs.

This manuscript provides an overview of the breadth and impact of research conducted in the realm of digital health within the CTN. This work has included the CTN's efforts to systematically embed digital screeners for SUDs into general medical settings to impact care models across the nation. This work has also included a pivotal multi-site clinical trial conducted on the CTN platform, whose data led to the very first "prescription digital therapeutic" authorized by the U.S. Food and Drug Administration (FDA) for the treatment of SUDs. Further CTN research includes the study of telehealth to increase capacity for science-based SUD treatment in rural and under-resourced communities. In addition, the CTN has supported an assessment of the feasibility of detecting cocaine-taking behavior via smartwatch sensing. And, the CTN has supported the conduct of clinical trials entirely online (including the recruitment of national and hard-to-reach/under-served participant samples online, with remote intervention delivery and data collection). Further, the CTN is supporting innovative work focused on the use of digital health technologies and data analytics to identify digital biomarkers and understand the clinical trajectories of individuals receiving medications for opioid use disorder (OUD).

This manuscript concludes by outlining the many potential future opportunities to leverage the unique national CTN research network to scale-up the science on digital health to examine optimal strategies to increase the reach of science-based SUD service delivery models both within and outside of healthcare.

1.0 Introduction

Advances in digital technologies and data analytics have created unprecedented opportunities to assess and enhance health behavior and to accelerate the ability of science to understand and contribute to improved health behavior and health outcomes. Over 5 billion people in the world have access to mobile phone services (Silver, 2019). And access to these technologies is not confined to high income populations or countries but is also increasingly evident in many low and middle income countries and traditionally underserved populations (Collins et al., 2016; Deloitte, 2017; GSMA Intelligence, 2019; Mitchell & Kan, 2019; Naslund, Aschbrenner, Araya, et al., 2017).

Digital health refers to the use of digital technologies and data analytics to understand people's health-related behavior and provide personalized health care resources (Bhavnani, Narula, & Sengupta, 2016; Dallery, Kurti, & Erb, 2015). Given the widespread access to technology worldwide, digital health offers great promise to enable widespread reach and scalability of evidence-based treatments to promote health behavior and collectively lead to transformations in the delivery of science-based health care.

The application of digital technologies to better assess, understand and treat substance use disorders (SUDs) is a particularly promising and vibrant area of scientific research (Budney, Borodovsky, Marsch, & Lord, 2019; Marsch & Borodovsky, 2018; Marsch, Lord, & Dallery, 2014). Among the many applications of digital technologies, digital tools may be useful in the screening and assessment of SUD. Indeed, research evaluating the use of electronic screeners (e.g., assessments completed by a patient on a tablet) has demonstrated that individuals more accurately report risk behavior, including substance use and sexual risk behavior, when responding to questions posed by an electronic screener instead of by another individual (Perlis, Des Jarlais, Friedman, Arasteh, & Turner, 2004). Embedding standardized, validated clinical assessments of SUD into electronic health records may also facilitate the assessment and treatment of SUDs as part of the routine clinical workflow in a wide variety of clinical settings (Tai, Wu, & Clark, 2012).

Digital health interventions (called "digital therapeutics") are interactive, self-directed software tools that can overcome some of the striking disparities in treatment access and treatment quality evident in healthcare settings across the globe (Hixon, 2015). For example, digital therapeutics can teach people effective, scientifically validated skills to recognize and change unhealthy thoughts and behavior (such as drug use) and provide tools to help people apply these skills to their everyday lives. Digital therapeutics can be available 24/7 and thus allow for "on-demand" access to therapeutic support, thereby creating unprecedented models of intervention delivery and reducing barriers to accessing care. Treatments delivered via digital platforms can be widely accessible at a population level.

Telehealth, the use of telecommunication technologies to deliver long-distance clinical care, may also allow SUD expert clinicians to deliver care in communities (e.g., rural settings) where SUD treatment needs are high but SUD workforce capacity is limited (Lin et al., 2019). Telehealth can be used in concert with digital therapeutics to provide real-time distance communication with SUD clinicians via video technology, complemented by digital therapeutic software that does not rely on synchronous communication with another individual but rather can be available at all times.

Digital therapeutics and telehealth models of care may be transformative in the treatment of SUDs in many ways (Budney et al., 2019; Marsch, 2012; Marsch & Borodovsky, 2018; Marsch & Dallery, 2012; Rosa, Campbell, Miele, Brunner, & Winstanley, 2015). As most persons with SUDs spend the majority of their time outside of a treatment facility, digital technologies can extend the reach and impact of treatment by offering anytime/anywhere SUD care. Digital tools can function like a therapist "in your pocket" and can be accessible at times when individuals struggling with SUDs may be in greatest need of therapeutic support. Additionally, a large part of care offered in SUD treatment settings does not reflect

the state of the science of SUD care (Center on Addiction, 2012). Digital therapeutics can ensure the delivery of SUD care with fidelity to the most evidence-based practices. Further, the behavioral health clinician workforce cannot meet the large population-level needs for SUDs or offer anytime/anywhere care (Hyde, 2013). Digital therapeutics provide science-based, scalable solutions to meet SUD needs at a population-level. This may be particularly relevant in tackling the current U.S. opioid crisis, in which the number of Americans with an opioid use disorder (OUD) has surged, especially in rural communities, while the trained SUD workforce has not grown at a comparable rate (Health Resources & Services Administration (HRSA), 2019).

Digital technologies also afford new opportunities to examine clinical trajectories and identify novel digital biomarkers within-individuals through intensive collection of individual-level data using mobile devices, wearable sensors, and mapping digital footprints. Indeed, digital tools may capture information about individual's physiology "in vivo" as they live their daily lives (Jain, Powers, Hawkins, & Brownstein, 2015). Specifically, mobile technologies enable ecological momentary assessment (EMA; (Shiffman, Stone, & Hufford, 2008) a method that prompts individuals to respond to queries on mobile devices, and which enables near real-time monitoring, of individuals' behavior (including exposure to individual risk factors for drug use and drug-taking behavior) while they engage in daily activities. Because EMA allows for intensive longitudinal assessment in naturalistic contexts, these data offer promise to enhance our understanding of mechanisms of health behavior, including drug-taking behavior (McCarthy et al., 2008; Panlilio et al., 2019).

Digital technologies also enable passive sensing and inference from smartphones or sensing devices worn on the body, which is transforming how we understand human behavior (Cornet & Holden, 2018). Mobile sensing allows for the continuous measurement of physiological and behavioral data in the real world. This sensor data can be streamed to a smartphone and processed immediately to infer information about a person's health behavior, physiology, and context. These data from sensors can be combined with data from self-report EMA assessments to enhance an understanding of the individual's behavior in context (Marsch, 2018). This information can then be used to trigger the delivery of interventions in real time (e.g., to respond to a person's in-the-moment needs, such as craving of a substance of abuse) (Burns et al., 2011; Gustafson et al., 2014).

Further, the use of social media sites (e.g., online forums, social blogs) has exploded in recent years. Social media enables multi-directional communication anywhere and anytime. Social media may be leveraged to recruit individuals into research, often allowing for rapid, cost-effective recruitment of national and hard-to-reach populations (Borodovsky, Marsch, & Budney, 2018; Reagan et al., 2019). Social media data have also been used to predict many phenomena, ranging from purchasing patterns to disease epidemics (Brownstein, Freifeld, & Madoff, 2009; Darden & Perreault, 1976), and a growing body of literature shows how social media data may enable a rich understanding of the topology and functioning of social networks and their relationships to health/risk behavior (Kazemi, Borsari, Levine, & Dooley, 2017; Kim, Marsch, Brunette, & Dallery, 2017; Naslund, Kim, et al., 2017). For example, social media has been shown to contain signals of depression among individuals, such as decreased social activity, increased negative affect, highly clustered egocentric networks,

and heightened concerns about relations and medications (Choudhury, Gamon, Counts, & Horvitz, 2013). Also, data derived from social media has been shown to predict a range of sensitive personal attributes including sexual orientation, political views, personality traits, and use of addictive substances (Hassanpour, Tomita, DeLise, Crosier, & Marsch, 2019; Kosinski, Stillwell, & Graepel, 2013; Ricard, Marsch, Crosier, & Hassanpour, 2018).

Digitally-derived data offer great potential to refine and advance our understanding of health behavior, including SUDs. These granular-level data captured in daily life allow for the development of dynamic models of SUDs to understand behavior in real-time and in response to changing environmental, social, physiological, and intrapersonal factors (Naslund, Aschbrenner, Kim, et al., 2017; Spruijt-Metz & Nilsen, 2014). And, they can help us understand when individuals may be most receptive to interventions (Nahum-Shani, Hekler, & Spruijt-Metz, 2015), with a goal of providing the right type/amount of therapeutic support at the right time by adapting to an individual's changing internal and contextual state (Goldstein et al., 2017; Nahum-Shani et al., 2018).

Collectively, these digital technologies enable an entirely new offering of tools for collecting rich data about individuals' behavior, health, and environment, provide personalized interventions and resources based on individuals' needs and preferences, and enable dynamic computational models to predict and characterize individuals' changing needs and health trajectories over time.

The National Drug Abuse Treatment Clinical Trials Network (CTN), launched in 1999 by the U.S. National Institute on Drug Abuse (NIDA), has supported a growing line of research that leverages digital technologies to glean new insights into SUDs and provide science-based therapeutic tools to a diverse array of persons with SUDs. The CTN is a unique research infrastructure for conducting practical, rigorous, and highly impactful trials focused on improving the treatment of SUDs and promoting widespread implementation and sustainability of effective and accessible SUD care in community systems across the nation. Among its many contributions, the CTN has supported a broad array of innovative and impactful research projects that have leveraged digital health.

This manuscript provides an overview of the digital health portfolio of the CTN and outlines a vision for the many future opportunities to leverage the unique national CTN research network to scale-up the science on digital health to examine optimal strategies to increase the reach of, and reduce barriers in access to science-based SUD service delivery models both within and outside of healthcare.

Note that we recognize that additional, rigorous research supported by NIDA focused on the application of digital health to SUDs has been conducted outside of the CTN (e.g., Bickel, Marsch, Buchhalter, & Badger, 2008; Budney et al., 2011; Garrison et al., 2018; Getty, Morande, Lynskey, Weaver, & Metrebian, 2019; Kiluk et al., 2018; Ondersma, Svikis, Thacker, Beatty, & Lockhart, 2014); however, consistent with the focus of this journal Special Issue, this article focuses on the breadth of work within the CTN.

Collectively, this research within the CTN is focused on addressing important scientific questions such as how to use digital health to routinize and standardize validated SUD

screening in health care settings; how to use digital health to detect substance use in real time and in "the wild"; how to implement and scale up effective SUD treatment; and how to leverage social media for recruitment and intervention.

2.0 Methods

We reviewed the study designs and resulting publications from all studies (past and active) conducted on the CTN platform since its inception in 1999 (n=107 CTN studies at the time of this writing). Studies that centrally included any of the following types of digital health technologies as a key part of the study aims or methods were identified and included in this overview: (1) digital SUD screening and/or assessment (n=6), (2) digital therapeutics (n=2), (3) telehealth (n=2), (4) EMA and passive sensing technologies (n=2), and (5) social media platforms (n=1). This manuscript is not intended to provide a comprehensive literature review of all the digital health studies conducted within the CTN but rather to provide an overview of the breadth and impact of the CTN's work in the digital health space. For detailed information on every study within the CTN, the interested reader should visit: https://www.drugabuse.gov/about-nida/organization/cctn/ctn.

3.0 Results

3.1 CTN Studies that employed Digital SUD Screening and/or Assessment

The majority of digital health studies in the CTN have focused on the use of electronic health records (EHRs) for SUD screening and/or assessment. One of the earliest projects in this area was the development and validation of a brief screening and assessment instrument, the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool, for use in primary care patients (CTN-0059). The TAPS tool is comprised of a 4-item screening survey, followed by a more detailed, substance-specific assessment of risk for any substances for which an individual has a positive initial screen (Wu et al., 2016). An early multi-site CTN trial with 2000 adult patients in 5 adult primary care clinics compared an interviewer-administered version of the TAPS tool to a version of the tool that was self-administered on a tablet computer (in which individuals had the option to hear questions read to them by a recorded voice on the computer) (McNeely et al., 2016). Results demonstrated that the interviewer- and self-administered versions of the TAPS tool had comparable diagnostic characteristics, but the self-administered version yielded higher rates of reporting of past year alcohol, illicit drug and prescription medication misuse (Gryczynski et al., 2017). The most notable discrepancy was for reports of prescription medication misuse, such that disclosure rates were 50% higher on the self-administered version. In addition, the tool showed promising sensitivity and specificity for detecting several types of substance use disorders, including tobacco and alcohol. It also identified adult primary care patients with high risk scores on the World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) as well as moderate risk scores for tobacco, alcohol and marijuana (Schwartz et al., 2017). Overall, the TAPs tool showed a more modest ability to identify some illicit and prescription medication SUDs in comparison to the ASSIST. Despite this, the TAPS tool is much briefer than the ASSIST and provides primary care providers with information about current substance use, thus underscoring its

strong appeal for use in primary care. Given that visits to primary care represent an important window of opportunity to systematically screen and identify SUDs among a broad population (John et al., 2018; John et al., 2019; Wu et al., 2017), the TAPS tool is an example of a validated, brief and practical resource that can be routinely delivered, including in a digital format, in general medical settings. The TAPS tool is now available online for widespread use at: https://www.drugabuse.gov/taps/.

The CTN's work has extended beyond development and validation of the TAPS SUD screening tool to evaluate the feasibility of embedding SUD screeners into EHRs in primary care and integrating screening into the primary care workflow. One trial (CTN-0065) evaluated how implementation of drug screening in primary care impacts rates of SUD assessment and subsequent care and demonstrated that screening led to an increase in SUD diagnoses, particularly cannabis use disorder diagnoses (Richards et al., 2019). Another multi-site study (CTN0062) being conducted in both urban primary care and rural Federally Qualified Health Centers (FQHCs) has identified barriers and facilitators of embedding screening into these settings and underscored the importance of clearly communicating with patients about the goals of screening to counteract stigma, addressing staff concerns regarding time and workflow, and providing SUD education and treatment resources to primary care clinicians (McNeely et al., 2018; Saunders et al., 2019). Several ongoing CTN projects have further extended this work to evaluate the feasibility, usability, acceptability (CTN-0076 and CTN-0090) and impact (CTN-0095) of OUD clinical decision support tools embedded in EHRs to help guide primary care providers in evidence-based treatment of OUD. Of considerable promise, and influenced by the research conducted within the CTN, the U.S. Preventive Services Task Force has just released a draft recommendation to screen for drug use among adults in general medical settings (U.S. Preventive Services Task Force (USPSTF), 2019).

3.2 CTN Studies that Employed Digital Therapeutics

The CTN has had a marked impact in the field of digital therapeutics for SUDs -- interactive software used to treat SUDs. The most impactful clinical trial with a digital therapeutic conducted within the CTN evaluated the clinical effectiveness of the web-based Therapeutic Education System (TES) (CTN-0044) (A. N. Campbell et al., 2014). TES is a web-based, self-directed version of the strongly evidence-based Community Reinforcement Approach (CRA) to behavior therapy (Bickel et al., 2008) developed by Azrin (Azrin, 1976). This intensive behavioral treatment is designed to teach individuals with SUDs how to better understand and disrupt harmful behaviors and cognitions related to their drug-taking behavior and to develop new skills to restructure their lives. In this pivotal CTN trial, the CRA-based behavioral treatment was offered along with incentives targeting drug abstinence and treatment participation. In this trial, conducted in partnership with 10 SUD treatment sites, individuals in outpatient SUD treatment were randomly assigned to receive either 12 weeks of standard outpatient SUD treatment or a treatment model in which TES partially replaced 2 hours of patient-clinician therapy time or psychoeducation (approximately 2 hours weekly). This study found that participants who received TES as part of their care model had a markedly lower rate of treatment dropout (hazard ratio=0.72, 95% CI=0.57, 0.92) and a higher rate of drug abstinence (odds ratio=1.62, 95% CI=1.12, 2.35), an effect

that was most evident among patients who had a drug-positive urine and/or alcohol-positive breath screen at the time of entering the study (odds ratio=2.18, 95% Cl=1.30, 3.68). This pattern highlighting the effectiveness of TES was evident across diverse groups of patients, including those with stimulant, cannabis and alcohol use disorders (Cochran et al., 2015), those with and without criminal justice involvement (Lee et al., 2017) those with and without Internet access (Tofighi et al., 2016), and across both males and females (A. N. Campbell, Nunes, et al., 2015) and diverse racial and ethnic groups (A. N. C. Campbell et al., 2017). TES was also found to have promising cost-effectiveness (Murphy et al., 2016).

This CTN trial built on a prior body of NIDA-funded single site trials showing, for example, that adding TES to buprenorphine treatment produces synergistic treatment effects; that replacing part of counselor-delivered treatment with TES treatment in methadone treatment systems greatly improves patients' treatment outcomes, and that TES offered to incarcerated individuals can produce comparable treatment outcomes to those produced by exclusively clinician-delivered care (Bickel et al., 2008; Chaple et al., 2014, 2016; Christensen et al., 2014; Marsch, Guarino, et al., 2014). By conducting a national, highly rigorous multi-site trial, the CTN study was well-poised to demonstrate the safety and effectiveness of the TES digital intervention when reviewed by the FDA, leading to the very first FDA-authorized prescription digital therapeutic in the U.S. (now called re-SET®, Pear Therapeutics). This reflects a new category of FDA-regulated devices and allows for digital therapeutics to be prescribed by clinicians, in a manner similar to FDA-approved medications. This is a compelling example of how CTN research can change the landscape of care to scale-up access to evidence-based treatments for SUDs.

This work led to several ancillary CTN studies focused on enhancing TES (in the form of a mobile app) to be modified for American Indians and Alaskan Natives (A. N. Campbell, Turrigiano, et al., 2015). And, several mobile digital therapeutics will be included in a new national CTN trial that will test strategies to improve treatment retention in medication treatment for OUD and to improve outcomes among individuals who are stabilized on OUD medications but wish to discontinue such medications (CTN-100).

3.3   CTN Studies that Employ Telehealth.

Although treatments for SUDs, including OUD, have been shown to be life-saving (Larochelle et al., 2018), many communities across the nation are challenged by not having sufficient clinician capacity to conduct universal screening and medication induction and maintenance to the large population who may need it. This is particularly challenging in rural contexts which have lower capacity for evidence-based opioid treatment, including fewer waivered buprenorphine prescribers, behavioral health clinicians, and opioid treatment programs and often lack of a widespread public transportation system. To address this challenge, the CTN is launching a large multi-site trial to evaluate the effectiveness of a tele-health model of care for the medication treatment of OUD (MOUD), designed to help ensure sufficient and sustainable capacity to offer evidence-based opioid treatment in rural communities (CTN-102). This cluster-randomized, comparative effectiveness trial will examine the utility of adding tele-MOUD to outpatient MOUD treatment compared to outpatient MOUD treatment alone in rural areas highly impacted by the U.S. opioid crisis.

Tele-MOUD will flexibly offer patients remote access (via video) to a core team of OUD experts who can assess and prescribe medications to individuals with OUD, provide therapy, and/or provide remote urine and/or saliva drug testing. Another new primary care-based CTN trial (CTN-101), which seeks to identify an effective strategy to address unhealthy opioid use and prevent escalation to an opioid use disorder, will also offer remote tele-counseling to participants to enhance onsite care centrally led by a nurse care manager. The collective learning from this research will inform innovative models that can scale access to a suite of evidence-based treatment for OUD in high need, low resource settings.

3.4 CTN Studies that Employ Ecological Momentary Assessment (EMA) and Passive Sensing Technologies.

Two CTN trials have employed EMA and passive sensing technologies. The first of these studies (CTN-0073-Ot) developed and evaluated the ability of a wrist-worn sensor suite (embedded in a smartwatch) to detect cocaine use (Holtyn et al., 2019). This work builds on prior promising work demonstrating that a chestband with electrodes can detect cocaine use via a computational model that uses heart rate (interbeat intervals) and physical activity data (Hossain et al., 2014; Kennedy et al., 2015). The present study seeks to evaluate whether similar cocaine detection algorithms will work, that have been modified for use with sensor data collected via a less obtrusive, more user-friendly smartwatch that can be worn in daily life. Data from the smartwatch is compared to chestband data (because prior work demonstrated the chestband can detect cocaine use) as well as EMA reports of cocaine use (as "ground truth") of cocaine use.

Cocaine use is often measured via self-report, which can be inaccurate, and/or use is measured via urine drug tests which can be intrusive and may not capture the temporal granularity of cocaine use patterns (Donovan et al., 2012). If smartwatch sensing is determined to be an acceptable and accurate way to measure cocaine use, it may offer rich information about the precise timing and duration of use events and could allow us to glean new insights into contextual factors that may serve as triggers for use events. Additionally, detecting cocaine use with greater precision may enhance our outcomes measurement in clinical trials that evaluate potential therapeutics for cocaine use disorder.

The second of these CTN studies (CTN-0084-A2) is, to our knowledge, the first study to employ passive mobile sensing, social media data, and active responses to queries on mobile devices using EMA to obtain moment-by-moment quantification of individual-level data (including contextual and momentary factors) that may lead to opioid use events, medication non-adherence and/or MOUD treatment dropout/retention (as measured via EHR data) in a population of persons with OUD in buprenorphine treatment.

In this study, participants are asked to wear a smartwatch and carry a smartphone continuously for a period of 12 weeks. The smartwatch passively collects data regarding location and distance traveled, physical activity (including metrics of energy expenditure and steps), sleep, and heart rate. Participants are also prompted to respond to questions (EMA) through a smartphone multiple times per day. Questions assess sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, location, substance use, self-regulation, and MOUD adherence. In addition to the

EMA prompts, individuals are asked to self-initiate EMAs if substance use occurred. App usage, audio/conversation, call/text, GPS, screen on/off, phone lock/unlock, phone notification information, Wi-Fi & Bluetooth logs, sleep, ambient light, and proximity are passively collected via smartphone. Participants are also asked if they are willing to share their social media data from any social media platforms they may use (e.g., Facebook, Instagram, Twitter). Sharing social media data is an optional component of study participation. The primary objective of the study is to evaluate the feasibility of utilizing digital health technology with OUD patients as measured by a 12-week period of continuous assessment using EMA and digital sensing. A secondary objective of this study is to examine the utility of EMA, digital sensing, and social media data (separately and compared to one another) in predicting OUD treatment retention and buprenorphine medication adherence.

Overall, this line of research may inform which subset(s) of digitally-derived data (digital biomarkers) may be most useful to employ as part of outcome measurement in future clinical trials research. Digital data that capture the richness of clinical status and clinically trajectories as individuals go about their daily lives may greatly complement and enhance the learning from standardized, clinical outcomes assessment. And predicting OUD treatment retention and medication adherence via continuous digital assessments may be used to identify early (and with relatively low participant burden) those participants who show signs of non-adherence and trigger additional intervention to prevent ultimate non-response to treatment.

3.5   CTN Studies that Employ Social Media Platforms

In addition to the CTN-0084-A2 study referenced above which includes social media data as part of a broader set of digitally-derived data, the CTN supports a trial that centrally evaluates the relative utility of various social media platforms in recruiting a national sample from a hard-to-reach population. Specifically, this trial (CTN-0083) compares the relative effectiveness of using social media sites vs. online informational sites vs. online dating sites to promote HIV self-testing and seamless linkage to pre-exposure prophylaxis (PrEP) medication among young (aged 18-30), racial/ethnic minority, high-risk men who have sex with men (MSM). In this study, individuals in the targeted sample who click on culturally-tailored study advertisements and who provide online consent will be offered a free HIV self-test kit (OraSure®) to be discreetly sent to their home with seamless linkage to PrEP for those who test HIV-negative, and linkage to HIV care resources for those who test positive. Among other outcomes, the primary outcome is the monthly rate (number of study participants requesting an HIV home self-test kit per 30-day period) by promotional platform (social media, informational, dating sites). The modifying role of substance use on observed outcomes will also be examined.

Online recruitment strategies allow for targeted recruitment of select audiences. The CTN-0083 study will target recruitment in the states that have hard-to-reach, high risk populations and limited availability of risk reduction services (e.g., Georgia, Louisiana, Maryland, Mississippi, and Nevada). This study illustrates how a targeted national sample

can be recruited for clinical trials participation and how all intervention delivery and data collection in a clinical trial can be conducted remotely online.

4.0 Discussion

This manuscript provides an overview of the breadth and impact of research conducted within the U.S. National Drug Abuse Treatment Clinical Trials Network in the realm of digital health. This work has included the CTN's efforts to systematically embed digital screeners for SUDs into general medical settings to increase the diagnosis and treatment of SUDs across the nation. This work has also included a pivotal multi-site clinical trial conducted on the CTN platform, whose data led to the very first "prescription digital therapeutic" authorized by the U.S. Food and Drug Administration (FDA) for the treatment of SUDs. Further CTN research includes the study of telehealth to increase capacity for science-based SUD treatment in rural and under-resourced communities. In addition, the CTN has supported an assessment of the feasibility of detecting cocaine-taking behavior via smartwatch sensing. The CTN has also supported the conduct of clinical trials entirely online (including the recruitment of national and hard-to-reach/under-served participant samples online, with remote intervention delivery and data collection). Further, the CTN is conducting innovative work focused on the use of digital health technologies and data analytics to identify digital biomarkers and understand the clinical trajectories of individuals with OUD in buprenorphine medication treatment for OUD.

Given its unique national research infrastructure and access to a broad array of community and healthcare partners, the CTN is uniquely poised to accelerate the scope and impact of its work applying digital health to the assessment and treatment of SUDs. Among these opportunities, the CTN is positioned to evaluate the role of digital technologies in SUD care transitions. For example, offering persons with SUDs access to a digital therapeutic and/or telehealth when they transition from a period of incarceration, hospitalization, or inpatient SUD care to the community would provide them with 24/7 access to therapeutic support as they reintegrate into the community and/or community-based care. Digital tools may also be offered directly to individuals recruited online who are not engaged, and do not wish to engage in SUD care within the health care system. Given that only about 10% of persons with SUDs are engaged in treatment, there is tremendous opportunity to creatively use digital technology to provide the other 90% with evidence-based SUD resources (Center for Behavioral Health Statistics and Quality, 2016).

The CTN is optimally poised to conduct national implementation science trials and/or hybrid implementation-effectiveness trials to evaluate optimal strategies to implement and sustain digitally-enhanced models of care. Such trials could integrate the various digital health tools and approaches that the CTN has previously studied in separate studies to instead embed a suite of complementary digital tools spanning an entire model of care within an integrated implementation strategy. That is, a digitally-enhanced model of care could include digital screeners and assessments in medical settings, linkage to electronic clinical decision support tools to enhance providers' ability to deliver state-of-the-science care, as well as provision of digital therapeutics that are available directly to patients to ensure evidence-based care is available to them anytime and anywhere and can complement

the care they receive in the healthcare sector. Importantly, digital therapeutics offered to patients do not need to reflect static models of behavioral treatment that work exactly the same way with every end user. Rather, these tools can be adaptive and flexibly offer evidence-based therapeutic resources to individuals that are responsive to their changing clinical needs, preferences, and goals.

There is tremendous opportunity to integrate the science of digital assessment and digital therapeutics for SUDs to help us understand (in real time) when individuals may be most receptive to health promotion interventions. They can, in turn, inform optimal delivery of "Just-in-Time Adaptive Interventions" or in-the-moment interventions for SUDs that provide the right type/amount of therapeutic support at the right time (Nahum-Shani et al., 2015; Nahum-Shani et al., 2018). The large and diverse samples that can be recruited within the CTN offer many opportunities to conduct novel experimental approaches (e.g., Micro-Randomized Trials, Sequential Multiple Assignment Randomized Trials, Factorial Designs) to systematically investigate who would benefit from which intervention and when (i.e., under what conditions), as well as to apply novel statistical machine learning methods to personalize SUD interventions at the individual level (Dempsey, Liao, Kumar, & Murphy, 2017; Walton, Nahum-Shani, Crosby, Klasnja, & Murphy, 2018).

Importantly digital therapeutics do not need to have a siloed focus on SUD treatment (Marsch, 2014). Indeed, we have the opportunity to maximally benefit from what digital technology offers to embrace the co-occurring needs of patients. Digital therapeutics can arguably embrace whatever combination of needs a patient may have. They may focus on, for example, SUD and mental health care, SUD and chronic pain management, SUD and infectious diseases such as HIV and hepatitis, and/or SUD care and care for chronic physical health conditions. Because patients typically do not experience SUD in isolation but often have many care needs and because various comorbidities interact in clinically meaningful ways (Druss & Walker, 2011; Hooten, 2016; Onyeka, Hoegh, Eien Em, Bi, & I., 2019; Schulte & Hser, 2014), digital technologies can transcend the artificial constraints of siloed care models to provide therapeutic resources across many health domains and disease states. Digital health offers great promise for increasing the breadth and potency of models of SUD healthcare delivery.

Although applying digital health to the assessment and treatment of SUDs offers great promise, many challenges remain in this work. Indeed, there is tremendous opportunity for expanding research focused on how to best balance the promise of digital health with its potential limitations. For example, we can examine ethical questions (Capon, Hall, Fry, & Carter, 2016; Labrique, Kirk, Westergaard, & Merritt, 2013) such as "how do we best ensure that the benefit of digital tools outweighs potential risks?" And "how do we best ensure protections of patient privacy and sensitive information while still allow for data to be shared (e.g., between persons in SUD treatment and their providers and/or support network) in accordance with patient preferences and treatment goals?" Additionally, some sources of digitally-derived data, although rich and often voluminous, may contain biases and/or methodological challenges (Codella, Partovian, Chang, & Chen, 2018; Olteanu, Castillo, Diaz, & Kiciman, 2019). For example, data collected via EMA questions on mobile devices or via computerized SUD screeners are based on individuals' self-report and may be subject

to reporting bias. Additionally, identifying the optimal source of "ground truth" when making inferences about behavior using mobile sensing data remains a challenge (National Academies of Sciences, 2018). And best practices in preserving privacy when capturing and analyzing sensitive data (e.g., para-linguistic aspects of speech captured on mobile devices; consumer-generated social media data) need to prioritized (Pentland, Lazer, Brewer, & Heibeck, 2009). Further, although many populations across the world are increasingly getting access to mobile devices, some populations (such as some populations with SUDs) may have inconsistent access to mobile technology and/or live in communities (e.g., rural settings) with limited connectivity (Collins et al., 2016). And, patient engagement with digital therapeutic tools is an ongoing challenge (Wagner et al., 2017). Further, although interest in digital therapeutics among providers and healthcare systems has markedly increased in recent years, challenges remain with implementation and sustainability as well as payment models of digital health tools in many health care contexts (Messner EM et al., 2019). Indeed, as the application of digital health to SUDs continues to expand, it is important that we have a parallel examination of ways in which to support the optimal and pragmatic measurement of patient privacy and ethics and widespread implementation in digital health research.

Digital health and data analytics are transforming our world. As we consider the striking unmet SUD treatment needs as well as the variability in quality of SUD care across the national and global landscape, digital technologies promise to extend and enhance our SUD clinical workforce to make on-demand, state of the science SUD treatment a reality worldwide.

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References

Azrin NH (1976). Improvements in the community-reinforcement approach to alcoholism. Behav Res Ther, 14(5), 339–348. doi:10.1016/0005-7967(76)90021-8 [PubMed: 971207]

Bhavnani SP, Narula J, & Sengupta PP (2016). Mobile technology and the digitization of healthcare. European Heart Journal, 37(18), 1428–1438. doi:10.1093/eurheartj/ehv770 [PubMed: 26873093]

Bickel WK, Marsch LA, Buchhalter AR, & Badger GJ (2008). Computerized behavior therapy for opioid-dependent outpatients: A randomized controlled trial. Experimental and Clinical Psychopharmacology, 16(2), 132–143. doi:10.1037/1064-1297.16.2.132 [PubMed: 18489017]

Borodovsky JT, Marsch LA, & Budney AJ (2018). Studying cannabis use behaviors with Facebook and web surveys: Methods and insights. JMIR Public Health and Surveillance, 4(2), e48. doi:10.2196/publichealth.9408 [PubMed: 29720366]

Brownstein JS, Freifeld CC, & Madoff LC (2009). Digital disease detection--harnessing the Web for public health surveillance. N Engl J Med, 360(21), 2153–2155, 2157. doi:10.1056/NEJMp0900702 [PubMed: 19423867]

Budney AJ, Borodovsky JT, Marsch LA, & Lord S (2019). Technological innovations in addiction treatment In Danovitch I & Mooney I (Eds.), The Assessment and Treatment of Addiction: Best Practices and New Frontiers (pp. 75–90). New York, NY: Elsevier.

Budney AJ, Fearer S, Walker DD, Stanger C, Thostenson J, Grabinski M, & Bickel WK (2011). An initial trial of a computerized behavioral intervention for cannabis use disorder. Drug Alcohol Depend, 115(1–2), 74–79. doi:10.1016/j.drugalcdep.2010.10.014 [PubMed: 21131143]

Burns MN, Begale M, Duffecy J, Gergle D, Karr CJ, Giangrande E, & Mohr DC (2011). Harnessing context sensing to develop a mobile intervention for depression. Journal of Medical Internet Research, 13(3), e55. doi:10.2196/jmir.1838 [PubMed: 21840837]

Campbell AN, Nunes EV, Matthews AG, Stitzer M, Miele GM, Polsky D, … Ghitza UE (2014). Internet-delivered treatment for substance abuse: A multisite randomized controlled trial. American Journal of Psychiatry, 171(6), 683–690. doi:10.1176/appi.ajp.2014.13081055 [PubMed: 24700332]

Campbell AN, Nunes EV, Pavlicova M, Hatch-Maillette M, Hu MC, Bailey GL, … Greenfield SF (2015). Gender-based outcomes and acceptability of a computer-assisted psychosocial intervention for substance use disorders. Journal of Substance Abuse Treatment, 53, 9–15. doi:10.1016/j.jsat.2014.12.006 [PubMed: 25613105]

Campbell AN, Turrigiano E, Moore M, Miele GM, Rieckmann T, Hu MC, … Nunes EV (2015). Acceptability of a web-based community reinforcement approach for substance use disorders with treatment-seeking American Indians/Alaska Natives. Community Mental Health Journal, 51(4), 393–403. doi:10.1007/s10597-014-9764-1 [PubMed: 25022913]

Campbell ANC, Montgomery L, Sanchez K, Pavlicova M, Hu M, Newville H, … Nunes EV (2017). Racial/ethnic subgroup differences in outcomes and acceptability of an Internet-delivered intervention for substance use disorders. Journal of Ethnicity in Substance Abuse, 16(4), 460–478. doi:10.1080/15332640.2017.1300550 [PubMed: 28368740]

Capon H, Hall W, Fry C, & Carter A (2016). Realising the technological promise of smartphones in addiction research and treatment: An ethical review. Int J Drug Policy, 36, 47–57. doi:10.1016/j.drugpo.2016.05.013 [PubMed: 27455467]

Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. (2016). Results from the 2015 National Survey on Drug Use and Health: Detailed tables. Retrieved from http://www.samhsa.gov/data/report/results-2015-national-survey-drug-use-and-health-detailed-tables

Center on Addiction. (2012). Addiction medicine: Closing the gap between science and practice. Retrieved from https://www.centeronaddiction.org/addiction-research/reports/addiction-medicine-closing-gap-between-science-and-practice

Chaple M, Sacks S, McKendrick K, Marsch LA, Belenko S, Leukefeld C, … French M (2014). Feasibility of a computerized intervention for offenders with substance use disorders: A research

note. Journal of Experimental Criminology, 10, 105–127. doi:10.1007/s11292-013-9187-y [PubMed: 24634641]

Chaple M, Sacks S, McKendrick K, Marsch LA, Belenko S, Leukefeld C, … French M (2016). A comparative study of the Therapeutic Education System for incarcerated substance-abusing offenders. The Prison Journal, 96(3), 485–508. doi:10.1177/0032885516636858

Choudhury MD, Gamon M, Counts S, & Horvitz E (2013). Predicting depression via social media. Paper presented at the Seventh International AAAI Conference on Web and Social Media, North America, Boston, MA.

Christensen DR, Landes RD, Jackson L, Marsch LA, Mancino MJ, Chopra MP, & Bickel WK (2014). Adding an Internet-delivered treatment to an efficacious treatment package for opioid dependence. Journal of Consulting and Clinical Psychology, 82(6), 964–972. doi:10.1037/a0037496 [PubMed: 25090043]

Cochran G, Stitzer M, Campbell AN, Hu MC, Vandrey R, & Nunes EV (2015). Web-based treatment for substance use disorders: Differential effects by primary substance. Addict Behav, 45, 191–194. doi:10.1016/j.addbeh.2015.02.002 [PubMed: 25697725]

Codella J, Partovian C, Chang H, & Chen C (2018). Data quality challenges for person-generated health and wellness data. IBM Journal of Research and Development, 62(1). doi:10.1147/JRD.2017.2762218

Collins KM, Armenta RF, Cuevas-Mota J, Liu L, Strathdee SA, & Garfein RS (2016). Factors associated with patterns of mobile technology use among persons who inject drugs. Subst Abus, 37(4), 606–612. doi:10.1080/08897077.2016.1176980 [PubMed: 27092425]

Cornet VP, & Holden RJ (2018). Systematic review of smartphone-based passive sensing for health and wellbeing. Journal of Biomedical Informatics, 77, 120–132. doi: 10.1016/j.jbi.2017.12.008 [PubMed: 29248628]

Dallery J, Kurti A, & Erb P (2015). A new frontier: Integrating behavioral and digital technology to promote health behavior. Behaviora Analyst, 38(1), 19–49. doi:10.1007/s40614-014-0017-y

Darden WR, & Perreault WD (1976). Identifying interurban shoppers: multiproduct purchase patterns and segmentation profiles. J Marketing Res, 13(1), 51–60. doi:10.2307/3150901

Deloitte. (2017). Global Mobile Consumer Trends. Retrieved from https://www2.deloitte.com/content/dam/Deloitte/us/Documents/technology-media-telecommunications/us-global-mobile-consumer-survey-second-edition.pdf

Dempsey W, Liao P, Kumar S, & Murphy SA (2017). The stratified micro-randomized trial design: Sample size considerations for testing nested causal effects of time-varying treatments. Annals of Applied Statistics. Retrieved from https://arxiv.org/pdf/1711.03587.pdf

Donovan DM, Bigelow GE, Brigham GS, Carroll KM, Cohen AJ, Gardin JG, … Wells EA (2012). Primary outcome indices in illicit drug dependence treatment research: Systematic approach to selection and measurement of drug use end-points in clinical trials. Addiction, 107(4), 694–708. doi:10.1m/j.1360-0443.20n.03473.x [PubMed: 21781202]

Druss BG, & Walker ER (2011). Mental disorders and medical comorbidity. Retrieved from Atlanta, GA: https://www.rwjf.org/en/library/research/2011/02/mental-disorders-and-medical-comorbidity.html

Garrison KA, Pal P, O'Malley SS, Pittman BP, Gueorguieva R, Rojiani R, … Brewer JA (2018). Craving to Quit: A Randomized Controlled Trial of Smartphone app-based Mindfulness Training for Smoking Cessation. Nicotine Tob Res. doi:10.1093/ntr/nty126

Getty CA, Morande A, Lynskey M, Weaver T, & Metrebian N (2019). Mobile telephone-delivered contingency management interventions promoting behaviour change in individuals with substance use disorders: a meta-analysis. Addiction, 114(11), 1915–1925. doi:10.1111/add.14725 [PubMed: 31265747]

Goldstein SP, Evans BC, Flack D, Juarascio A, Manasse S, Zhang F, & Forman EM (2017). Return of the JITAI: Applying a just-in-time adaptive intervention framework to the development of m-health solutions for addictive behaviors. International Journal of Behavioral Medicine, 24(5), 673–682. doi:10.1007/s12529-016-9627-y [PubMed: 28083725]

Gryczynski J, McNeely J, Wu LT, Subramaniam GA, Svikis DS, Cathers LA, … Schwartz RP (2017). Validation of the TAPS-1: A four-item screening tool to identify unhealthy substance use in

primary care. Journal of General Internal Medicine, 32(9), 990–996. doi:10.1007/s11606-017-4079-x [PubMed: 28550609]

Intelligence GSMA. (2019). The Mobile Economy 2019. Retrieved from https://www.gsmaintelligence.com/research/?file=b9a6e6202ee1d5f787cfebb95d3639c5&download

Gustafson DH, McTavish FM, Chih MY, Atwood AK, Johnson RA, Boyle MG, … Shah D (2014). A smartphone application to support recovery from alcoholism: A randomized clinical trial. JAMA Psychiatry, 71(5), 566–572. doi:10.1001/jamapsychiatry.2013.4642 [PubMed: 24671165]

Hassanpour S, Tomita N, DeLise T, Crosier B, & Marsch LA (2019). Identifying substance use risk based on deep neural networks and Instagram social media data. Neuropsychopharmacology, 44(3), 487–494. doi:10.1038/s41386-018-0247-x [PubMed: 30356094]

Health Resources & Services Administration (HRSA). (2019, April 2019). Opioids strain health workforce. Retrieved from https://www.hrsa.gov/enews/past-issues/2019/april-18/opioids-strain-health-workforce

Hixon T (2015). Digital therapeutics have huge promise and they are real today. Retrieved from https://www.forbes.com/sites/toddhixon/2015/12/09/digital-therapeutics-have-huge-promise-and-they-are-real-today/#13dc884f26f0

Holtyn AF, Bosworth E, Marsch LA, McLeman B, Meier A, Saunders EC, … Ghitza UE (2019). Towards detecting cocaine use using smartwatches in the NIDA Clinical Trials Network: Design, rationale, and methodology. Contemporary Clinical Trials Communications. doi:10.1016/j.conctc.2019.100392

Hooten WM (2016). Chronic pain and mental health disorders: Shared neural mechanisms, epidemiology, and treatment. Mayo Clinic Proceedings, 91(7), 955–970. doi:10.1016/j.mayocp.2016.04.029 [PubMed: 27344405]

Hossain SM, Ali AA, Rahman M, Ertin E, Epstein D, Kennedy A, … Kumar S (2014). Identifying drug (cocaine) intake events from acute physiological response in the presence of free-living physical activity. IPSN, 2014, 71–82. doi:10.1109/IPSN.2014.6846742 [PubMed: 25531010]

Hyde PS (2013). Report to Congress on the Nation's Substance Abuse and Mental Health Workforce Issues. Retrieved from https://www.cibhs.org/sites/main/files/file-attachments/samhsa_bhwork_0.pdf

Jain SH, Powers BW, Hawkins JB, & Brownstein JS (2015). The digital phenotype. Nature Biotechnology, 33(5), 462–463. doi:10.1038/nbt.3223

John WS, Zhu H, Mannelli P, Schwartz RP, Subramaniam GA, & Wu LT (2018). Prevalence, patterns, and correlates of multiple substance use disorders among adult primary care patients. Drug Alcohol Depend, 187, 79–87. doi:10.1016/j.drugalcdep.2018.01.035 [PubMed: 29635217]

John WS, Zhu H, Mannelli P, Subramaniam GA, Schwartz RP, McNeely J, & Wu LT (2019). Prevalence and patterns of opioid misuse and opioid use disorder among primary care patients who use tobacco. Drug and Alcohol Dependence, 194, 468–475. doi:10.1016/j.drugalcdep.2018.11.011 [PubMed: 30513477]

Kazemi DM, Borsari B, Levine MJ, & Dooley B (2017). Systematic review of surveillance by social media platforms for illicit drug use. J Public Health (Oxf), 1–14. doi:10.1093/pubmed/fdx020

Kennedy AP, Epstein DH, Jobes ML, Agage D, Tyburski M, Phillips KA, … Preston KL. (2015). Continuous in-the-field measurement of heart rate: Correlates of drug use, craving, stress, and mood in polydrug users. Drug and Alcohol Dependence, 151, 159–166. doi:10.1016/j.drugalcdep.2015.03.024 [PubMed: 25920802]

Kiluk BD, Nich C, Buck MB, Devore KA, Frankforter TL, LaPaglia DM, … Carroll KM (2018). Randomized Clinical Trial of Computerized and Clinician-Delivered CBT in Comparison With Standard Outpatient Treatment for Substance Use Disorders: Primary Within-Treatment and Follow-Up Outcomes. Am J Psychiatry, 175(9), 853–863. doi:10.1176/appi.ajp.2018.17090978 [PubMed: 29792052]

Kim SJ, Marsch LA, Brunette MF, & Dallery J (2017). Harnessing Facebook for Smoking Reduction and Cessation Interventions: Facebook User Engagement and Social Support Predict Smoking Reduction. J Med Internet Res, 19(5), e168. doi:10.2196/jmir.6681 [PubMed: 28536096]

Kosinski M, Stillwell D, & Graepel T (2013). Private traits and attributes are predictable from digital records of human behavior. Proc Natl Acad Sci U S A, 110(15), 5802–5805. doi:10.1073/pnas.1218772110 [PubMed: 23479631]

Labrique AB, Kirk GD, Westergaard RP, & Merritt MW (2013). Ethical issues in mHealth research involving persons living with HIV/AIDS and substance abuse. AIDS Res Treat, 2013, 189645. doi:10.1155/2013/189645 [PubMed: 24171110]

Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, … Walley AY (2018). Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: A cohort study. Annals of Internal Medicine, 169(3), 137–145. doi:10.7326/m17-3107 [PubMed: 29913516]

Lee JD, Tofighi B, McDonald R, Campbell A, Hu MC, & Nunes E (2017). Acceptability and effectiveness of a web-based psychosocial intervention among criminal justice involved adults. Health Justice, 5(1), 3. doi:10.1186/s40352-017-0048-z [PubMed: 28285466]

Lin LA, Casteel D, Shigekawa E, Weyrich MS, Roby DH, & McMenamin SB (2019). Telemedicine-delivered treatment interventions for substance use disorders: A systematic review. Journal of Substance Abuse Treatment, 107, 38–49. doi:10.1016/j.jsat.2019.03.007 [PubMed: 31757263]

Marsch LA (2012). Leveraging technology to enhance addiction treatment and recovery. Journal of Addictive Disease, 31(3), 313–318. doi:10.1080/10550887.2012.694606

Marsch LA (2014). Envisioning the future: Transformation of health care systems via technology In Marsch LA, Lord SE, & Dallery J (Eds.), Behavioral Health Care and Technology: Using Science-Based Innovations to Transform Practice (pp. 317–328): Oxford University Press.

Marsch LA (2018). Opportunities and needs in digital phenotyping. Neuropsychopharmacology. doi:10.1038/s41386-018-0051-7

Marsch LA, & Borodovsky JT (2018). Digital health interventions for substance use disorders: The state of the science In Miller SC, Fiellin AA, Rosenthal RN, & Saitz R (Eds.), 6th Edition of the AS AM Principles of Addiction Medicine. Philadelphia, PA: Lippincott Williams and Wilkins.

Marsch LA, & Dallery J (2012). Advances in the psychosocial treatment of addiction: The role of technology in the delivery of evidence-based psychosocial treatment. Psychiatric Clinics of North America, 55(2), 481–493. doi:10.1016/j.psc.2012.03.009

Marsch LA, Guarino H, Acosta M, Aponte-Melendez Y, Cleland C, Grabinski M, … Edwards J (2014). Web-based behavioral treatment for substance use disorders as a partial replacement of standard methadone maintenance treatment. Journal of Substance Abuse Treatment, 46(1), 43–51. doi: 10.1016/j.jsat.2013.08.012 [PubMed: 24060350]

Marsch LA, Lord SE, & Dallery J (2014). The state of the science of technology-based behavioral health care: An editorial In Marsch LA, Lord SE, & Dallery J (Eds.), Behavioral Health Care and Technology: Using Science-Based Innovations to Transform Practice'. Oxford University Press.

McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, & Baker TB (2008). Psychological mediators of bupropion sustained-release treatment for smoking cessation. Addiction, 103(9), 1521–1533. doi:10.1111/j.l360-0443.2008.02275.x [PubMed: 18783504]

McNeely J, Kumar PC, Rieckmann T, Sedlander E, Farkas S, Chollak C, … Rotrosen J (2018). Barriers and facilitators affecting the implementation of substance use screening in primary care clinics: A qualitative study of patients, providers, and staff. Addiction, Science and Clinical Practice, 73(1), 8. doi :10.1186/s13722-018-0110-8

McNeely J, Wu LT, Subramaniam G, Sharma G, Cathers LA, Svikis D, … Schwartz RP. (2016). Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for substance use screening in primary care patients. Annals of Internal Medicine, 165(10), 690–699. doi:10.7326/ml6-0317 [PubMed: 27595276]

Messner EM, Probst T, O'Rourke T, Stoyanov S, Baumeister H, & Montag C. (2019). mHealth applications: Potentials, limitations, current quality and future directions In Baumeister H & Montag C (Eds.), Digital phenotyping and mobile sensing: New developments in psychoinformatics (pp. 235–248): Springer, Cham.

Mitchell M, & Kan L (2019). Digital Technology and the Future of Health Systems. Health Syst Reform, 5(2), 113–120. doi:10.1080/23288604.2019.1583040 [PubMed: 30908111]

Murphy SM, Campbell AN, Ghitza UE, Kyle TL, Bailey GL, Nunes EV, & Polsky D (2016). Cost-effectiveness of an internet-delivered treatment for substance abuse: Data from a multisite

randomized controlled trial. Drug and Alcohol Dependence, 161, 119–126. doi:10.1016/j.drugalcdep.2016.01.021 [PubMed: 26880594]

Nahum-Shani I, Hekler EB, & Spruijt-Metz D (2015). Building health behavior models to guide the development of just-in-time adaptive interventions: A pragmatic framework. Health Psychology, 34s, 1209–1219. doi:10.1037/hea0000306 [PubMed: 26651462]

Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, & Murphy SA (2018). Just-in-Time Adaptive Interventions (JITAIs) in mobile health: Key components and design principles for ongoing health behavior support. Annals of Behavioral Medicine, 52(6), 446–462. doi:10.1007/s12160-016-9830-8 [PubMed: 27663578]

Naslund JA, Aschbrenner KA, Araya R, Marsch LA, Unutzer J, Patel V, & Bartels SJ (2017). Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. Lancet Psychiatry, 4(6), 486–500. doi:10.1016/S2215-0366(17)30096-2 [PubMed: 28433615]

Naslund JA, Aschbrenner KA, Kim SJ, McHugo GJ, Unutzer J, Bartels SJ, & Marsch LA (2017). Health behavior models for informing digital technology interventions for individuals with mental illness. Psychiatric Rehabilitation Journal, 40(3), 325–335. doi:10.1037/prj0000246 [PubMed: 28182469]

Naslund JA, Kim SJ, Aschbrenner KA, McCulloch LJ, Brunette MF, Dallery J, … Marsch LA (2017). Systematic review of social media interventions for smoking cessation. Addict Behav, 73, 81–93. doi:10.1016/j.addbeh.2017.05.002 [PubMed: 28499259]

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Neuroscience and Nervous System Disorders. (2018). Transforming digital data into insight: collection, analysis, standardization, and validation. In Harnessing mobile devices for nervous system disorders: Proceedings of a workshop (pp. 9–20). Washington (DC) National Academies Press (US).

Olteanu A, Castillo C, Diaz F, & Kiciman E (2019). Social data: Biases, methodological pitfalls, and ethical boundaries. Front. Big Data, 2(13).

Ondersma SJ, Svikis DS, Thacker LR, Beatty JR, & Lockhart N (2014). Computer-delivered screening and brief intervention (e-SBI) for postpartum drug use: a randomized trial. J Subst Abuse Treat, 46(1), 52–59. doi:10.1016/j.jsat.2013.07.013 [PubMed: 24051077]

Onyeka IN, Hoegh C, Eien Em N, Bi N, & I., M. (2019). Comorbidity of physical disorders among patients with severe mental illness with and without substance use disorders: A systematic review and meta-analysis. Journal of Dual Diagnosis, 15(3), 192–206. doi:10.1080/15504263.2019.1619007 [PubMed: 31164045]

Panlilio LV, Stull SW, Kowalczyk WJ, Phillips KA, Schroeder JR, Bertz JW, … Preston KL (2019). Stress, craving and mood as predictors of early dropout from opioid agonist therapy. Drug and Alcohol Dependence, 202, 200–208. doi:10.1016/j.drugalcdep.2019.05.026 [PubMed: 31357121]

Pentland A, Lazer D, Brewer D, & Heibeck T (2009). Using reality mining to improve public health and medicine. Stud Health Technol Inform, 149, 93–102. doi:10.3233/978-1-60750-050-6-93 [PubMed: 19745474]

Perlis TE, Des Jarlais DC, Friedman SR, Arasteh K, & Turner CF (2004). Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. Addiction, 99(7), 885–896. doi:10.1111/j.1360-0443.2004.00740.x [PubMed: 15200584]

Reagan L, Nowlin SY, Birdsall SB, Gabbay J, Vorderstrasse A, Constance J, & D'Eramo Melkus G (2019). Recruitment of research participants through Facebook: An integrative review. Nursing Research. doi:10.1097/nnr.0000000000000385

Ricard BJ, Marsch LA, Crosier B, & Hassanpour S (2018). Exploring the utility of community-generated social media content for detecting depression: An analytical study on Instagram. Journal of Medical Internet Research, 20(12), e11817. doi:10.2196/11817 [PubMed: 30522991]

Richards JE, Bobb JF, Lee AK, Lapham GT, Williams EC, Glass JE, … Bradley KA (2019). Integration of screening, assessment, and treatment for cannabis and other drug use disorders in primary care: An evaluation in three pilot sites. Drug and Alcohol Dependence, 201, 134–141. doi:10.1016/j.drugalcdep.2019.04.015 [PubMed: 31212213]

Rosa C, Campbell AN, Miele GM, Brunner M, & Winstanley EL (2015). Using e-technologies in clinical trials. Contemporary Clinical Trials, 45(Pt A), 41–54. doi:10.1016/j.cct.2015.07.007 [PubMed: 26176884]

Saunders EC, Moore SK, Gardner T, Farkas S, Marsch LA, McLeman B, … McNeely J (2019). Screening for substance use in rural primary care: A qualitative study of providers and patients. Journal of General Internal Medicine. doi:10.1007/s11606-019-05232-y

Schulte MT, & Hser YI (2014). Substance use and associated health conditions throughout the lifespan. Public Health Reviews, 35(2). doi: 10.1007/bf03391702

Schwartz RP, McNeely J, Wu LT, Sharma G, Wahle A, Cushing C, … Subramaniam GA (2017). Identifying substance misuse in primary care: TAPS Tool compared to the WHO ASSIST. Journal of Substance Abuse Treatment, 76, 69–76. doi:10.1016/j.jsat.2017.01.013 [PubMed: 28159441]

Shiffman S, Stone AA, & Hufford MR (2008). Ecological momentary assessment. Annual Review of Clinical Psychology, 4, 1–32. doi:10.1146/annurev.clinpsy.3.022806.091415

Silver L (2019). Smartphone ownership is growing rapidly around the world, but not always equal. Retrieved from Washington, DC:https://www.pewresearch.org/global/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/

Spruijt-Metz D, & Nilsen W (2014). Dynamic models of behavior for just-in-time adaptive interventions. IEEE Pervasive Computing, 13(3), 13–17. doi:10.1109/MPRV.2014.46

Tai B, Wu LT, & Clark HW (2012). Electronic health records: Essential tools in integrating substance abuse treatment with primary care. Substance Abuse and Rehabiliatation, 3, 1–8. doi:10.2147/sar.S22575

Tofighi B, Campbell AN, Pavlicova M, Hu MC, Lee JD, & Nunes EV (2016). Recent internet use and associations with clinical outcomes among patients entering addiction treatment involved in a web-delivered psychosocial intervention study. Journal of Urban Health, 93(5), 871–883. doi:10.1007/s11524-016-0077-2 [PubMed: 27653383]

U.S. Preventive Services Task Force (USPSTF). (2019, August 2019). Draft recommendation statement: Illicit drug use, including nonmedical use of prescription drugs: Screening. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/drug-use-in-adolescents-and-adults-including-pregnant-women-screening

Wagner B 3rd, Liu E, Shaw SD, Iakovlev G, Zhou L, Harrington C, … Nahum-Shani I (2017). ewrapper: Operationalizing engagement strategies in mHealth. Proc ACM Int Conf Ubiquitous Comput, 2017, 790–798. doi:10.1145/3123024.3125612 [PubMed: 29362728]

Walton A, Nahum-Shani I, Crosby L, Klasnja P, & Murphy S (2018). Optimizing digital integrated care via micro-randomized trials. Clinical Pharmacology and Therapeutics, 104(1), 53–58. doi:10.1002/cpt.1079 [PubMed: 29604043]

Wu LT, McNeely J, Subramaniam GA, Brady KT, Sharma G, VanVeldhuisen P, … Schwartz RP (2017). DSM-5 substance use disorders among adult primary care patients: Results from a multisite study. Drug and Alcohol Dependence, 179, 42–46. doi:10.1016/j.drugalcdep.2017.05.048 [PubMed: 28753480]

Wu LT, McNeely J, Subramaniam GA, Sharma G, VanVeldhuisen P, & Schwartz RP (2016). Design of the NIDA clinical trials network validation study of tobacco, alcohol, prescription medications, and substance use/misuse (TAPS) tool. Contemporary Clinical Trials, 50, 90–97. doi:10.1016/j.cct.2016.07.013 [PubMed: 27444426]

Highlights

- The National Drug Abuse Treatment Clinical Trials Network (CTN) has supported a growing line of research that leverages digital technologies to glean new insights into substance use disorders (SUDs) and provide science-based therapeutic tools to a diverse array of persons with SUDs.

- This manuscript provides an overview of the breadth and impact of research conducted in the realm of digital health within the CTN – including in areas of digital screening and assessment, digital therapeutics, telehealth, mobile assessment and passive sensing, and social media.

- This manuscript outlines the many potential future opportunities to leverage the unique national CTN research network to scale-up the science on digital health to examine optimal strategies to increase the reach of science-based SUD service delivery models both within and outside of healthcare.