Document Title: CT-101-002 Sponsor Administration Letter and Protocol

Protocol Title: A Blinded, Randomized Controlled Clinical Trial of an Innovative Digital Therapeutic for Smoking Cessation with Biochemical Verification

NCT Number: NCT03694327

Date: 10Mar2022

Click Therapeutics

March 9, 2022

RE: Protocol: CT-101-002
A Blinded, Randomized Controlled Clinical Trial of an Innovative Digital Therapeutic for Smoking Cessation with Biochemical Verification

Administrative Letter

This letter serves to clarify that while the original CT-101-002 study, funded by NIH (NIDA) Grant 1 R43 DA045395-01 and conducted by Click Therapeutics, was intended as a randomized controlled trial of the commercially available Clickotine® (CT-101) mobile application compared to National Cancer Institute (NCI)'s QuitGuide, the study was transitioned to compare the efficacy of the minimally-viable-product version of Clickotine (CT-101-M) versus QuitGuide.

As disclosed to and confirmed by NIH on 06 & 07-Feb-2020 respectively, this transition was made due to availability limitations of the commercially available Clickotine® application for use in the study. The updated study design enabled a benchmarking assessment of CT-101-M that can be used as a stable baseline comparator in development studies of Clickotine®, including to support the development of future versions of Clickotine® for smoking cessation as well as FDA-regulated digital therapeutics for respiratory and other medical conditions that incorporate smoking cessation features from Clickotine®.

DocuSigned by:
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10-Mar-2022

Alankar Gupta, MD, MBA
Vice President, Clinical Development & Medical Affairs
Click Therapeutics, Inc.

Date

CONFIDENTIAL

TITLE: A Blinded, Randomized Controlled Clinical Trial of an Innovative Digital Therapeutic for Smoking Cessation with Biochemical Verification

Device Names: Clickotine and QuitGuide

Protocol Number: CT-101-002
Protocol Date: September 6, 2018

Principal Investigator: Brian M. Iacoviello, PhD

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1. INTRODUCTION

1.1 Smoking and the Need for Smoking Cessation

Tobacco smoking is the leading cause of preventable death in America, with numbers surpassing 480,000 each year (U.S. HHS, 2014). More than 16 million people live with diseases brought on by smoking, and every year secondhand smoke contributes to the death of more than 41,000 others (U.S. HHS, 2014). Nearly 20% of all Americans smoke tobacco in some form (King et al., 2012), and 9 out of 10 adult cigarette smokers become addicted before their eighteenth birthday (U.S. HHS, 2012).

Almost 70% of current smokers want to quit (U.S. HHS, 2014). Unfortunately, resisting tobacco presents a smoker with problems that contribute to low rates of cessation success (Gilbert et al., 1999). Nicotine cravings are perhaps the most dangerous moments in a smoker's quit journey, especially within the month following their last cigarette (Herd, et al., 2009). While treatments involving nicotine replacement can help reduce the severity of withdrawal symptoms, the frequent cravings must be managed and kept under control.

Not only is tobacco smoking dangerous for individuals' health, but negative national health economic repercussions also warrant a change. According to the Center for Disease Control, smoking costs the United States over 300 billion dollars a year, both from resulting necessary medical care and from a loss in workforce productivity due to early death and disease (U.S. HHS, 2014). Additionally, national marketing and publicity spending by the tobacco industry reaches billions of dollars each year (FTC, 2015), making it hard for any individual to ignore or escape messages advocating smoking.

Quit programs and pharmacological treatments can be helpful aids to smoking cessation. Without any assistance, a person's quit attempt is 50% likely to fail (U.S. HHS, 2014). Unfortunately, cessation therapies are not always widely accessible, and if they are, they tend to serve only a small population of heavy smokers (Fiore et. al, 1990). On top of this, smokers can face problems even *with* behavioral and pharmacological support in place, specifically in regard to participation and adherence. About 25% of patients looking to stop smoking don't take prescribed medicine as directed (DiMatteo, 2004).

When looking to reduce the large numbers of people who are affected by tobacco smoking each year, it is therefore important to focus not only on creating effective quit plans, but also on ways to ensure long-term compliance. To do this at the lowest cost, new technologies are being developed by which people can access treatment plans and cessation aids in the form of mobile applications. Now that the majority of the American population possesses smartphones (Smith, 2013), these apps are easily accessible and pervasive. However, the effectiveness of cessation apps to help users quit smoking is not well researched. The Sponsor, Click Therapeutics, Inc, has therefore developed Clickotine® (CKT), a mobile phone- based smoking cessation solution.

1.2 Description of Clickotine®

Clickotine® (CKT) is a novel app for iOS and Android smartphones, designed to provide smokers with essential features of the US Clinical Practice Guidelines (USCPG) for smoking cessation that are amenable to delivery via a mobile health solution ("the 5 A's for smoking cessation": advise/encourage to quit; assess willingness to quit and enhance motivation; assist with quit planning and connect with intervention- advice on pharmacotherapy, connect with counseling and medication treatments, provision of social support, and connect with a quit line; and arrange/provide follow-up) (Fiore et al., 2008).

Clickotine® embodies behavior modification Mechanisms of Action (MOAs) that have been supported by research: controlled breathing, personalized messaging, social engagement, treatment adherence, financial incentives, and digital diversions. These MOAs personalize cessation interventions to maximize effectiveness and user engagement. The MOAs are developed based on key features of clinical counseling services with advanced treatment personalization.

The controlled breathing Mechanism of Action provides a mindful breathing experience coupled with multisensory stimuli to reduce the negative symptoms of nicotine withdrawal, including cigarette craving and negative affect. This MOA was developed based on the works of multiple researchers, who demonstrated the effectiveness of controlled deep breathing on the severity of withdrawal symptoms (McClernon et. al, 2004; Shahab et. al, 2013; Westbrook et.al, 2013).

Personalized messaging involves sending customized text messages tailored to a user's profile, specifically to their motivations and daily schedules. As a user spends more time engaging with Clickotine®, information is collected in the database and the messaging adjusts to be more effective. Numerous text messaging studies demonstrate significant efficacy in aiding quit journeys (Free et. al, 2011; Whittaker et. al, 2012).

Social engagement provides real-life support from friends, family and the community. Social engagement adds meaning to quit messaging (Richardson et al, 2013.), and helps users change their behavior through real-time support, cooperative quit planning and goal setting, and mutual motivation.

The Sponsor acknowledges that Clickotine® is likely not the only quit aid a person will utilize to help them overcome their addiction. In fact, adding digital engagement to other smoking cessation therapies improves adherence to the therapies themselves, which is a potent predictor of successful cigarette abstinence (Hays et. al, 2010 and Stretcher et. al, 2005).

Cessation medications, including nicotine replacement therapies (NRTs; i.e., nicotine patch, gum, or lozenge), are proven to assist in management of the difficult withdrawal symptoms. However, the American Cancer Society states that they are not intended to be the *only* thing a person uses to help them overcome nicotine addiction ("Nicotine Replacement Therapy", ACS 2014). Clickotine® enhances access and adherence to pharmaceutical treatments and over-the-counter quit aids by helping a person track their usage, and navigate complex dosing schedules, and is fully adaptable to any prescribed and over-the-counter treatment.

Benefits from different smoking cessation treatments are seamlessly integrated across all MOAs by incorporating clinically tested cessation strategies in a single platform delivered through personal devices. Clickotine® provides users a timely and easily accessible solution to reduce cravings, anxiety, and other associated symptoms of smoking, improving the user's ability to quit.

1.3 Summary of Clinical Experience

In 2016, Click conducted an 8-week, open-label, single-arm, blinded clinical trial in which 416 subjects were enrolled. All study procedures were reviewed and approved by Western Institutional Review Board. The trial was registered with clinicaltrials.gov (NCT02656745) (Iacoviello et al., 2017).

Rationale: The goal was to initiate the process of gaining clinical validation for Clickotine by gaining data to guide improvements to the product and the design of further efficacy studies.

Aims: The primary aim was to assess engagement with Clickotine, hypothesized to be key to its effectiveness. Secondary aims were to assess Clickotine's effect on smoking behavior, its relationship to engagement, and the safety and tolerability of the digital therapeutic.

Results: The aims of the pilot were successfully met, recruiting 416 subjects in a three-month period and completing the trial in five months. Results were summarized as follows:

Recruitment, enrollment, and retention: Social media advertisement for current smokers interested in using a smartphone app to help quit proved effective in recruiting subjects. The average cost of advertisement was $28.91 per participant enrolled. Subjects had a mean age of 36 and an average of 6.1 on the Fagerstrom Test for Nicotine Dependence, with 18.1 years of smoking history and 16.7 cigarettes per day. The 87.7% retention rate was akin to other web-based smoking cessation trials with similar recruitment methods (Bricker et al., 2014; Munoz et al., 2009; Bricker et al., 2017).

Engagement: Subjects opened the Clickotine app (a standard and important metric for measuring engagement with a digital therapeutic) an average of 100.5 times. This translates to 1.8 app opens

per day over the course of 56 days. However, the app was engineered to emphasize active use (requiring app opens) during the period prior to the target quit date; in the week before target quit date, users opened the app 3.2 times per day.

Smoking: Results were analyzed in the intent-to-treat (ITT) population standard for clinical trials and recommended for smoking research (West, Hajek, Stead, & Stapleton, 2005), such that enrolled subjects who did not complete the 8-week survey were assumed to still be smoking. Since this methodology may bias the reported effects of interventions (Blankers et al., 2016), the data were also analyzed only in the population who completed the survey (case completer). In the ITT sample (n=416), at the end of the 8-week study period, 45.2% of subjects reported achieving 7-day abstinence and 26.2% of subjects achieved 30-day abstinence. Among the 365 case completers, 51.5% of subjects reported achieving 7-day abstinence and 29.9% of subjects achieved 30-day abstinence.

Summary: This single-arm clinical trial demonstrated Click's ability to conduct research using the methodology that will be used in the proposed two-arm RCT, generated the pilot data for Clickotine's impressive efficacy that were used to derive the power analysis, and provided the estimate of the enrollment yield and retention rate used to budget for recruitment to reach the target n of subjects.

1.4 Research Hypothesis

The purpose of the proposed study is to confirm the improved efficacy of CKT for short-term smoking cessation through a blinded randomized controlled trial (RCT) vs. QuitGuide. The hypothesis is that CKT will produce higher short-term quit rates than NCI Quitguide in a fully remote comparative efficacy trial, confirming pilot data and previous results (Iacoviello et al., 2017).

1.5 Rationale for Study Conduct

This study is being conducted as per NIH(NIDA) Grant 1 R43 DA045395-01 "Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification" to Brian M. Iacoviello, Ph.D.

Rationale: The demonstration of CKT's efficacy in producing superior smoking cessation rates in a sample of Medicaid users with biochemical verification of cessation, accomplished through establishing feasibility of conducting the research in Phase 1 and conducting a large-scale trial in this sample in Phase II, are the next steps in the clinical validation and commercialization of the product.

Comparison Arm: The active comparator app, the National Cancer Institute (NCI)'s QuitGuide (QG) was selected in acknowledgement of the fact that placebo interventions cannot be implemented in digital interventions of this type. Treatment-as-usual comparators could

introduce a negative bias among subjects denied access to CKT, would not allow for any level of blinding, and are fundamentally difficult to implement in a remote, digital trial. QuitGuide is a widely used smoking cessation app which like, CKT, follows USPCG guidelines, and has published quit rates in a controlled clinical trial setting. As an NIH-developed tool whose content is based on Smokefree.gov, the most-accessed cessation website, subjects would have reasonable expectancy that QuitGuide would be at least as effective as CKT. For these reasons, QuitGuide is widely used as an active comparator, for example in a published RCT of smoking cessation apps (Iacoviello et al., 2017) and in the each of the trials of this type registered at ClinicalTrials.gov, NCT02930200 and NCT01982110.

Randomization: The investigators considered dynamic randomization to ensure that covariates which may affect quit rates are equally distributed between study groups but decided at this Phase I stage to examine the effects of these covariates in post hoc tests. Data from these secondary analyses will be used to inform the design of a dynamic randomization procedure for the Phase II research.

1.6 Benefit-Risk and Ethical Assessment

Generally speaking, mobile applications for smoking cessation have been shown to increase quit rates (Whittaker et al., 2012), and thus may confer significant personal health benefit. Moreover, although documented risks of smoking cessation apps have rarely if ever been demonstrated, potential risks may be considered minimal and no greater than those associated with standard of care behavioral therapies for smoking cessation. In this context, the benefit-risk balance for study participation is considered highly favorable. Furthermore, this trial will ascertain potential adverse events via medical monitoring procedures and will be conducted in compliance with the protocol, good clinical practice (GCP), and the applicable regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to confirm the improved efficacy of CKT for short-term smoking cessation through a blinded randomized controlled trial (RCT) vs. QuitGuide. Acceptance criteria: Self-reported 30-day point prevalence quit rates will be significantly higher in the CKT arm than QuitGuide.

2.2 Secondary Objectives

A secondary objective of the study is to establish the feasibility of biochemical verification of smoking cessation in a fully remote, digital clinical trial. Concordance between self-reported abstinence and measurements of exhaled carbon monoxide (CO) at study outcome will be

assessed; Concordance rates between users that submit the CO measurement under video monitoring and those that do not will be assessed. Hypotheses are that groups will not demonstrate significantly different concordance rates, demonstrating the validity of both the self-report and biochemical verification procedures.

As some users are expected to choose to begin using smoking cessation pharmacotherapy or NRT during their quit attempt, users will be permitted to begin using smoking cessation pharmacotherapy or NRT during the trial if they so choose. A secondary objective of the study is to compare cessation rates between the CKT+NRT group and the CKT-only group, to address expected med/NRT use during the trial and to confirm the initial trial result that CKT+NRT is not superior to CKT-alone.

A secondary objective of the study is to demonstrate the feasibility of evaluating CKT in a Magellan Behavioral Health (A Click Therapeutics partner) value-based care population. Half of the study sample will be recruited from a Magellan value-based care population.

3. STUDY DESIGN

3.1 Overview of Study Design, Doses and Control Groups

The overarching study aim is to recruit a population of current smokers who are motivated to quit with the assistance of a mobile solution, enroll them into a study testing apps to help them quit, and randomize them into one of two arms. The core study period will consist of 8 weeks of usage of Clickotine or QuitGuide. At the end of this period, users will receive notifications to link them to an online survey, which will record their responses in a secure database. The primary outcome is successful short-term quitting, measured by 30-day point prevalence abstinence (self-reported and confirmed with expired CO < 7ppm). This study includes rigorous methodological standards to address potential limitations inherent to digital and behavioral interventions. In implementing an effective active control in a hypothesis-blind manner, the study sets a particularly high bar for establishing superiority of CKT. However, the investigators find it essential to use this strong control in order to demonstrate clear evidence of effectiveness that will be understood as clinically meaningful by Magellan Health and other providers, payers, and regulatory agencies.

All subjects will be encouraged to submit a CO sample using an iCO Smokerlyzer device at Week 4 and Week 8 (study completion). The iCO Smokerlyzer device will be mailed to participants after study randomization. Week 4 CO assessment submission is a compliance check and only recorded as a data point of successful submission. The CO assessment will be conducted during the outcome assessment after the 8-week study period regardless of self-reported smoking status.

<u>Duration of Subject Participation</u>

The proposed study will last for 8 weeks. Study data collection will end with the outcome survey; however, participants will have the opportunity to continue to use the Clickotine or QuitGuide apps for as long as they remain in commercial use.

3.2 Study Rationale and Choice of Study Population

After a successful single-arm trial of CKT, an RCT demonstrating CKT's efficacy in producing short-term smoking cessation is warranted. The choice of study population, to target one half of the sample from a Magellan Behavioral Health value-based care network, is important to demonstrate the ability to enroll smokers from this partner's network.

3.3 Justification of Study Design

This is a blinded, randomized controlled trial (RCT) of Clickotine (CKT) vs. NCI QuitGuide (QG), which is necessary to confirm the efficacy of CKT for smoking cessation after a positive open trial of CKT. This study design was reviewed and selected for funding by NIDA in grant number 1 R43 DA045395-01 "Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification".

3.4 Justification for Primary and Secondary Endpoints

An RCT demonstrating CKT's efficacy in producing short-term smoking cessation, demonstrating the capacity to biochemically verify smoking cessation, and to enroll a sample of users from a value-based care network, are important next steps in the clinical validation and commercial success of CKT.

3.5 Rationale for Duration of Treatment

The 8-week core duration of the trial was determined as this is a standard duration for low-intensity smoking cessation intervention trials.

4. SUBJECT SELECTION

The following eligibility criteria are designed to select participants for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular participant.

4.1 Study Population

This study proposes to obtain consent from 195 potential participants, to yield 156 randomized 1:1 across the CKT and QG arms (the ITT sample) and aims to enroll equal numbers of men and women. Pregnant females will not be explicitly excluded from participation, as pregnant females are encouraged to quit smoking and the app interventions

are not expected to confer significant side effects or adverse events related to pregnancy. The racial and ethnic breakdown of the target population is as follows:

	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	**Total**
American Indian/Alaska Native	2	2	0	0	4
Asian	10	10	0	0	24
Native Hawaiian or Other Pacific Islander	2	2	0	0	4
Black or African American	11	11	7	7	48
White	39	38	9	9	115
Other / More than One Race	14	14	4	4	36
Total	78	77	20	20	**195**

Half of the potential subjects will be recruited via social media advertising, while the other half will be recruited via mail to individuals covered by Magellan's value-based care program. Both advertisements will seek smokers who are ready to set a quit date in the next 30 days with assistance from a study comparing smartphone apps that may help them quit. Proposed advertisement content is included in Appendix 15.18 for approval.

4.2 Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before participants are included in the study. There must be evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study prior to any study procedure being performed. Participants must be willing and able to comply with study procedures such as the outcome survey and exhaled CO assessment.

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male or female age 18 to 65.
2. Fluent in written and spoken English (confirmed by ability to read and comprehend Informed Consent Form).
3. Lives in the United States.

4. Smokes at least 5 cigarettes daily.
5. Is interested in quitting smoking in the next 30 days.
6. The participant owns and has access to an iPhone with iOS 9 or greater capabilities, or an Android with OS 7 or greater capabilities.
7. The participant is willing and able to receive SMS text messages on their smartphone.
8. The participant is willing and able to receive email messages.
9. Ability to confirm download of installed treatment arm app via telephone on randomization date.
10. One half of the study sample will be recruited from the general population of smokers via social media advertisements.
11. One half of the study sample will be recruited via mail from a Magellan Behavioral Health value-based care network.

4.3 Exclusion Criteria

1. Prior use of Clickotine or QuitGuide.
2. Current use of pharmacotherapy for smoking cessation or nicotine replacement therapy (NRT).

4.4 Replacement of Subjects

Drop-outs will not be replaced.

5. STUDY TREAMENTS

5.1 Clickotine

The intervention regimen around Clickotine® is almost entirely user-directed. When a person has a craving, a series of options are available to ease the craving and resist the urge to smoke. The user will also engage with Clickotine® leading up to their quit date to complete a program of 21 Missions, daily activities which help prepare them to quit and keep them off cigarettes. Ideally, the user will open and use Clickotine® several times a day.

5.2 National Cancer Institute's QuitGuide

The QuitGuide (QG) app is operated by the National Cancer Institute to provide education and support to smokers seeking to quit. The QG regimen is entirely user-directed. When a user has a craving or wants support or education, they can log into the QG app. The QG app also provides lessons relevant for preparing to quit and beginning to quit.

5.3 Allocation to Treatment

Eligible participants will be randomized, 1:1 ratio, to receive Clickotine or QuitGuide. Randomization will occur during the randomization call at which time of successful installation of the assigned application will be confirmed. The participate user ID is assigned prior to randomization.

5.4 Maintaining the Blind

Subjects will be blinded to group assignment and will be hypothesis blind along with site investigators, as they will be informed that the study is investigating 2 different apps to treat smoking cessation that could both be effective. The study team will be blinded to participant group assignment, including the PI, biostatistician, and medical monitor, with the exception of the research coordinator who will need to be aware of group assignment in order to assign unique study IDs and offer technical assistance appropriate to the app assigned to participants.

5.5 Measures to Minimize Bias: Randomization and Blinding

In order to minimize bias with randomization and blinding, the study sponsor "Click Therapeutics" will be masked and will not be revealed until after study completion of protocol # CT-101-002. This decision was made by the sponsor "Click Therapeutics" to avoid potential unblinding and study bias that could be caused by Click's software "Clickotine" being used as the primary experimental arm for the CT-101-002 protocol. "My Digital Study" will be listed as the study sponsor at the start of the trial for all participants to properly ensure blinding is maintained. The sponsor will disclose "Click Therapeutics" as the study sponsor after study completion. Upon study completion, all study participants that were randomized into the clinical trial will be emailed or mailed documentation revealing the study sponsor as "Click Therapeutics" along with a brief explanation of the sponsor's masking rationale. (See Appendix **12.7**).

6. DEVICE SUPPLY

6.1 Software Provision

Once the participant is randomized, the investigator will make sure that the participant has properly downloaded the mobile applications necessary for their assigned treatment group. This will consist of the interventional applications, Clickotine or QuitGuide, and the iCO Smokerlyzer application. The participants are instructed to have their device fully charged and are encouraged to have wifi accessibility during the randomization phone call.

6.2 iCO Smokerlyzer

Participants will receive an iCO Smokerlyzer to be used at the user's discretion periodically throughout the trial regardless of treatment group. At Week 4 (Day 28), participants will be asked to submit an exhaled CO assessment to ensure the Smokerlyzer works properly, to identify any issues and as an adherence check. At the time of the Outcome Survey, participants will be required to submit another exhaled CO assessment, which be recorded as a study endpoint.

Upon completion of the Outcome Survey, participants will be invited to submit the CO assessment over a live video feed to confirm identity, until videos are received from 25 CKT users and 25 QG users. After 25 videos are received from each treatment group, participants will no longer be invited to submit the CO assessment over live video feed and will instead receive a reminder to remotely submit an exhaled CO assessment.

In order to conduct the CO assessment via live video monitoring, participants must have access to another device with video capabilities, such as another mobile device or computer. Participants that are invited to conduct the CO assessment via live video monitoring will consent to participate in live video monitoring at the end of the outcome survey by answering "Yes" or "No". Study participants that answer "Yes" and will then be linked to schedule a video call via Calendly with the research coordinator. Participants will have the option to select their preference of video platform on Calendly.

During the live video monitoring participants will be required to provide a personal ID to confirm identity. Participants who consent to participate in the live video CO assessment will receive an additional $50 Amazon gift card for their participation.

Those who do not consent to participate in the live video monitoring CO assessment will receive a reminder to submit the end of study CO assessment.

6.3 Participant Follow-up Procedure

In the event a participant does not complete a scheduled activity/assessment on the projected target date or within the protocol specific window (see protocol section 6.5: schedule of activities), the research coordinator will initiate 3 follow-up attempts via- SMS, email, or telephone. The follow-up SMS messages & Phone Call Voicemail dialogue can be found in appendix 15.11-15.12.

Baseline follow-up
Day 1: 24 hours post baseline survey email: SMS Message & Email
Day 3: 24 hours post baseline survey email: SMS Message & Email
Day 5: Phone Call follow-up
Day 8: Lost to Follow-up Letter (if baseline survey not completed by day)

Randomization follow-up (3 day window to schedule)
Day 1- Phone Call follow-up
Day 4: Lost to follow-up letter

Smokerlyzer Confirmation Assessment Follow-up
Day 29: SMS Message & Email
Day 30: SMS Message & Email
Day 31: Phone Call follow-up

End of Study follow-up
Day 56: SMS Message & Email
Day 57: SMS Message & Email
Day 58: Phone Call follow-up

6.4 Permitted Concomitant Treatments

To control for medication or NRT use, participants will not be eligible to enroll if they are currently using a medication or NRT at study enrollment.

Starting at Day 0 of the study, study participants will be allowed to choose to begin using a smoking cessation medication or NRT. Participants will be asked about medication or NRT use during the study in outcome survey.

6.5 Excluded Concomitant Treatments

None.

6.6 Subject Completion and End of the Study

Participants who continue with the study through its completion will spend a total of 8 weeks using CKT or QG. They will be declared officially finished with the study following an outcome

survey at the end of this period but can continue to use CKT or QG even after the study's official completion.

7. STUDY PROCEDURES

An overview of the procedures and time points for each procedure is depicted by the schedule of activities on Pages 19.

7.1 Recruitment, Screening and Baseline Period

Advertisements (See Appendix 15.18) will be placed on social media and sent to 11,000 participants in a Magellan Behavioral Health value-based care network. Respondents to the advertisements will be directed to a website that asks several questions to determine their eligibility to participate in the study (See Appendix 15.2). If answers indicate eligibility, the user will be prompted to review and sign the informed consent. Participants are instructed to contact the study coordinator via telephone or email to answer any questions that the participant has, and/or to further discuss the study prior to completing the online Informed Consent form. Upon completion of the online Informed Consent, a copy of the signed ICF will be provided to the participant.

After the informed consent is signed, each participant will be assigned a unique participant user ID that will be used for the duration of the study. Once participant user ID numbers have been assigned, they cannot be reassigned or reused for any reason. The investigator and research coordinator must maintain a log linking the participant user ID to the participant's name. The investigator and study coordinator must follow all applicable privacy laws in order to protect a participant's privacy and confidentiality.

After signing the online informed consent, participants will automatically receive the Baseline Survey via email. The online Baseline survey (See Appendix 15.7) must be completed within 7 days (*Ex. Criteria #3*) as the participant's personal Baseline survey link expires 1 week after the automated email is generated to the study participant. Please see Section 6.3 for the baseline follow-up attempt procedure. Participants who do no complete the Baseline Survey during the 7-day baseline period window will be considered a screen fail and discontinued from the study. Participants that are discontinued from the study will not be eligible for rescreening.

This questionnaire was constructed from several standard surveys measuring smoking and addiction behavior (Modified Cigarette Evaluation Questionnaire, Capelleri et. al 2007; Mood and Physical Symptom Scale, West and Hajek, 2004; Morisky Medication Adherence Scale, MMAS-4,

Morisky et. al 1986), as well as basic medical history and demographic questions for data purposes (Cappelleri, et. al, 2007)

Upon completion of the online informed consent and Baseline Survey, participants will be directed to schedule a telephone call via Calendly with the study coordinator for Randomization. Participants will be given a three-day window to schedule the date for the Randomization phone call with the research coordinator., Participants who are not able schedule the randomization call within the protocol window will be considered a screen failure and not included in the ITT sample.

7.2 Randomization

Randomization to treatment arm will utilize a predetermined sequence for up to 195 participant enrolled in the study, balanced 1:1 CKT:QG, balanced in blocks of 4. The research coordinator will be the only study staff member with access to the randomization sequence and will assign participants to CKT or QG based on their position in the randomization sequence.

Randomization procedures will occur via telephone with the research coordinator to verify participant eligibility and confirm download of installed treatment arm application on the randomization date. In the case of technical error during the scheduled call or other need to reschedule, participants will have **1** business day to reschedule the randomization call with the research coordinator. If calls are not conducted within the protocol window, the participant will be considered a screen failure and not included in the ITT sample.

Participant study eligibility will be verified prior to randomization on the day of the scheduled telephone contact with the research coordinator. Once eligibility is confirmed, the research coordinator will facilitate randomization assignment into a treatment group of CKT or QG. The assigned treatment arm and Smokerlyzer application links will be emailed to the participant for downloading of CKT or QG.

The study intervention start **date/ day 0** will be on same day of randomization and confirmed installed treatment application of activated Clickotine or QuitGuide. Only randomized participants that are able to confirm download of assigned treatment arm will be included in the ITT sample.

In the event participants are randomized to a treatment group and unable to confirm successful download of assigned treatment application, they will be **excluded** from the study by *(Incl # 10)* and will **NOT** be included in the study ITT sample.

7.3 Treatment Period

Participants are expected to use the CKT or QG apps for 8 weeks after randomization. During a period of 8 weeks, the user will be able to use all of the features of CKT or QG to help them quit smoking. Participants will have an adherence check at Week 4 (Day 28) to encourage user engagement adherence and to confirm the Smokerlyzer is in proper working condition. Participants will be notified via SMS and email at Week 4 (Day 28) to submit their CO assessment.

Failure CO assessment submission at the 4-week compliance check will not be considered a protocol deviation, but only recorded as a study data point. However, if the CO assessment submission for adherence is not received at Week 4 (Day 28), the research coordinator will begin the follow-up procedure (Section 6.3) on Day 29 (Day 1: Text; Day 2: Text 2; Day 3: F/U Phone Call). Day 53: Participants will be sent a link to complete the end of study assessments (outcome survey +CO assessment) via SMS and email. A link to the Smokerlyzer video instructions will also be provided on Day 53. At the end of treatment on Day 56, a reminder SMS and email will be submitted to the participants who have not completed the EOS assessments. A link to the outcome survey will also be provided for the participants that have not submitted prior to Day 56.

7.4 Study Completion

Study termination letters will be emailed or mailed to participants upon loss to follow up or upon study completion (completion of the Outcome Survey).

Additionally, all participants that were randomized into the clinical trial will be emailed or mailed documentation revealing the study sponsor as “Click Therapeutics” along with a brief explanation of the sponsor’s masking rationale. (See Appendix **15.14**).

There will be no long-term follow-up of users after the 8-week outcome survey is completed.

7.5 Schedule of Assessments

The study schedule of activities is as follows:

Protocol Activity	Screening	Baseline	Randomization	Treatment	
Study Treatment Day	-28 — -7	-7 — -1	0	28	56
End of Week	Weeks -4 to -1	Week 0	Week 1	Week 4	Week 8
Informed Consent	X				
Eligibility Criteria	X	X	X		
Baseline Survey		X			
Randomization			X		
Adherence Check				X	
Primary Endpoints					
Outcome Survey					X
Exhaled CO Assessment					X

7.6 Screening Period

Screening procedures will occur online where individuals will be asked several basic questions to determine study eligibility for participation. (See Appendix 15.2) If answers indicate eligibility, the user will be prompted to complete the informed consent. Upon consent, the user will be emailed a personalized link to complete the baseline survey.

The below information/assessments will be collected during the screening period:

- Eligibility Questionnaire via Magellan / social media advertisement
- Informed Consent must be digitally signed and dated by the participant prior to any baseline assessments or any study-related assessments (participants should contact the study coordinator via phone or email with any questions about the study or consent prior to signing the consent form). Upon completion of the online Informed Consent, a copy of the signed ICF will be provided to the participant.
- Assign participant unique user ID number
- A personalized link that can be traced back to the user ID will be sent to the participant to complete the baseline survey.

7.7 Baseline Period (0-10 days prior to Randomization)

Once the personalized link to the baseline survey is sent to the participant, the participant has a 7-day window to complete the baseline survey and a 3-day window to complete a phone call with the research coordinator that is contingent upon completion of the baseline survey. This phone call serves as a secondary measure to confirm eligibility once more before participant can be randomized. Completion of the baseline survey will prompt the participant to schedule the randomization phone call with the study coordinator via Calendly.

7.8 Randomization (Day 0 of treatment period)

Once the baseline survey has been completed and the phone call between the participant and study coordinator has been scheduled, the next step is randomizing the participant over the phone call. During this phone call, the participant is randomly assigned to an application by receiving a link to download the application via email from the research coordinator. Those who are not able to complete the study procedures by confirming successful download of the application over the phone call with the study coordinator will be considered a screen failure and not included in the ITT sample.

<u>The following information/assessments will be collected at the randomization phone call:</u>

Step 1: Research coordinator confirms eligibility and randomizes

- Study coordinator reviews baseline questionnaire answers with participant to confirm eligibility

- After study eligibility is confirmed, the study coordinator will randomize the participant into one of the two treatment groups (Clickotine or QuitGuide)

- The assigned treatment and iCO Smokerlyzer application links will be emailed to the participant for download. The study coordinator will provide step-by-step application download instructions for the participants over the phone call and explicitly written out in the email. The participants who are randomly assigned to Clickotine will receive an access code in the email that contains the application download instructions because Clickotine requires a valid access code for the user to partake in the program.

Step 2: Participant confirms success or failure of application download

- Participant confirms or denies successful installation of both the treatment application and iCO Smokerlyzer application. Successful application download initiates Day 0 of the treatment (intervention) period.

Step 3: Site Investigator or Site Staff mails CO assessment device

- Research coordinator confirms participant address to mail the iCO Smokerlyzer device after study start date/successful app installation is confirmed. The participant may use the Smokerlyzer at their own discretion but are encouraged to use the devise throughout the study.
- Participant "Welcome Letter" via SMS & email including a link to the Smokerlyzer video instructions

7.9 Smokerlyzer Confirmation Assessment (Week 4/ Day 28)

Participants will be notified to submit Smokerlyzer assessment via SMS & email at Week 4 (Day 28). A link to the Smokerlyzer Instruction video will also be provided. Smokerlyzer receipt and functioning will be confirmed by having the participant submit an exhaled CO assessment via their iCO Smokerlyzer and recorded in the study database as "Yes" or "No"

The following information/assessments will be collected at Day 28:

Compliance check:

- Participants will submit exhaled CO assessment via their iCO Smokerlyzer
- Verify Participant received Smokerlyzer
- Verify Smokerlyzer is in working condition

Participants will:

- Continue to use Clickotine® or QuitGuide as instructed
- Continue their smoking cessation medication or NRT, if applicable
- Complete and submit exhaled CO assessment

7.10 Study Outcome Assessment (Day 53 – 59)

Participants will be notified at Day 53 via SMS and email to complete the 8-Week Study Outcome Survey + iCO Smokerlyzer CO assessment. The target completion date for the study outcome survey is at Day 56; however, the participants will be sent a link to the Outcome Survey via SMS and email at Day 53.

Study participants will have 7 days from Day 53 to complete the EOS assessments. An additional SMS and email reminder (SMS and & email) to complete EOS assessments will be sent to the participants who have not submitted the EOS assessments on Day 56. In the event that the study

outcome assessments are not submitted by Day 56, the research coordinator will intervene per the protocol outlined end of study follow-up attempts procedure (Section 6.3)

The following information/assessments will be collected at the participant end of study (Day 53-59):

Outcome Survey:

- Link to survey will be sent via email and SMS
- After a participate completes the outcome survey a linked CO assessment reminder will be automated.
- Participants will report any smoking cessation medication or NRT use

Exhaled CO assessment:

- Participants will submit exhaled CO assessment via their iCO Smokerlyzer
- Participants will have the opportunity to conduct the CO assessment via live video monitoring to confirm identity
- The assessment will be used to compare CO measurement with self-report data

At Day 56, if the participant has already completed the Outcome Survey and submitted their exhaled CO assessment, they will receive an EOS: Thank you letter *(Appendix 15.13.)* via SMS and email. If the participant has not completed the Survey or CO assessment the study coordinator will then intervene as per the protocol outline follow-up attempts procedure *(Section 6.3)*.
On Day 59, the trial period ends, and the Outcome Survey link will expire at the end of the day. Participants who have not completed the Survey or CO assessment after the follow-up attempts procedure will be considered as a Lost to Follow-up participant.

7.11 Withdrawal Criteria/ Participant Withdrawal

Participants will be instructed that they are free to withdraw from the study at any time without penalty or implications for any healthcare they receive. Participants who terminate the study early for any reason will be considered withdrawn.

Participants who were randomly assigned and withdraw from the study will not be replaced, regardless of the reason for withdrawal. If a participant does not complete a scheduled or required assessment or survey, every effort should be made to contact the participant. In any circumstance, every effort should be made to document participant outcome, if possible.

Reasonable efforts will be made by the research coordinator to retain participants in the study and to complete study assessments within protocol specified timeline. In the event a participant misses a required activity or assessment, follow-up efforts will include outreach via SMS, email, and phone-per the protocol follow-up procedure (Section 6.3).

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Subjects who do not complete the final outcome survey at 8 weeks will be considered Lost to Follow-Up and will not receive any compensation for participation. Subjects will receive payment for all completed study assessments after submission of the outcome survey at week 8.

8. ASSESSMENTS

8.1 Smokerlyzer Confirmation Assessment (Week 4 / Day 28)

SMS messages are delivered to promote participant adherence and regular app use. Both treatment conditions will receive messages with links to required surveys and assessments as they become available.

The Smokerlyzer confirmation assessment will take place at Week 4 (Day 28). Adherence will be assessed by having the participant submit an exhaled CO assessment via their iCO Smokerlyzer recorded as a study data point of "**Yes" or "No"** for the participant adherence check. The research coordinator will be able to monitor participant receipt of the iCO Smokerlyzer and also verify the Smokerlyzer device is in proper working condition prior to the EOS.
At the time of the Outcome Survey, participants will be asked to submit another exhaled CO assessment to compare value with self-report data.

8.2 Outcome Assessment

At the end of the 8-week period users will be contacted to complete the web-based 8-week outcome survey and submit the remote CO assessment (See Appendix 15.4). The link for the outcome survey will be sent via SMS & email at Day 53. After the outcome survey is submitted, the participant will be reminded to complete the exhaled CO assessment.

At Day 56, if the participant has completed the Outcome Survey and submitted their exhaled CO assessment, they will receive an end of study thank you letter via SMS & email (Appendix 15.13).

An additional EOS reminder will be sent on Day 56 to participants via SMS and email.
The EOS reminder will include a survey link for the participants that have not submitted the outcome survey. If the outcome survey or CO assessment is not submitted by Day 56, protocol EOS follow-up procedure (Section 6.3) will start. Participants will receive a phone call follow-up at Day 58 for the last reminder to complete the EOS assessments.

After Day 59, the Outcome Survey link will close and the trial period ends. Participants who have not completed the Survey or CO assessment will be considered Lost to Follow-up. Participants that are deemed lost to follow-up will also receive a separate EOS: Thank-You / Lost to follow-up Letter (Section 15.15).

Participants will receive EOS: Thank you letter upon completion of outcome assessments or after the trial period ends / outcome survey link is expired.

A portion of the study populations that completes the outcome survey will be invited to conduct the CO assessment via live video monitoring to confirm identity. Participants that are invited to conduct the CO assessment via live video monitoring will consent to participate in live video monitoring at the end of the outcome survey by answering "Yes" or "No". Study participants that answer "Yes" will then select their preference of video platform and will then be linked to schedule a video call via Calendly with the research coordinator.

Those who do not consent to participate in the live video monitoring CO assessment will then receive the automated reminder to submit the end of study remote CO assessment. After 25 videos are received from each group, participants will no longer be invited to submit the CO assessment over live video feed.

Study participants will have the opportunity to receive up to $150 (Amazon Gift Certificate) at the end of study completion / Week 8. The participant will be rewarded a $50 Amazon gift certificate in return for completing each of the following activities/assessments:

$50- Outcome Survey

$50- CO Assessment Submission

$50- CO Assessment via Live Video Monitoring

Subjects will receive a separate $50.00 Amazon Gift Certificate payment for each completed study activity/assessment that is submitted. The clinical research coordinator will provide the $50.00 Amazon gift certificates via email after submission.

8.3 Assessment of Efficacy

To assess 30-Day Sustained Abstinence from Smoking (NACQ, 2016) participants are asked the following questions in the Outcome Survey to determine Russell Standard Self- Reported 4-Week Quitter status (West et al., 2005):

1. Have you smoked (even a puff) in the last 30 days?

a. Yes
b. No

2. (If yes, this question will appear) Have you smoked (even a puff) in the last 14 days?
    a. Yes
    b. No
3. (If yes, this question will appear) Have you smoked (even a puff) in the last 7 days?
    a. Yes
    b. No

The Outcome Survey will instruct subjects to submit an exhaled carbon monoxide (CO) reading with the iCO Smokerlyzer they were mailed after participant randomization. iCO Smokerlyzer devices will be programmed to email the exhaled carbon monoxide measurement results to the research coordinator directly.

The primary outcome, 30-day abstinence from smoking, will be assessed via self-report on the outcome survey. Confirmation with the remote CO assessment will be conducted to assess concordance between self-report and remote CO assessment results. Abstinence as per the CO assessment will be defined as an iCO reading of fewer than 7ppm exhaled CO.

Fagerstrom Test for Nicotine Dependence

The Fagerstrom Test for Nicotine Dependence is used to quantify the severity of nicotine dependence in smokers. This test is also used to determine if a participant may need additional assistance in quitting smoking with a Nicotine Replacement Therapy (NRT) or medication.

The Fagerstrom score is used to determine nicotine replacement therapy recommendations based on the participants nicotine dependence total score. In scoring the Fagerstrom Nicotine Dependency Test, yes/no items are scored from 0 to 1 and multiple-choice items are scored from 0 to 3. The items are added to yield a total score of 0-10. The higher total Fagerstrom score indicates a more intense/ higher dependency to nicotine (Heatherton, et. al, 1991). The test is administered at both the Baseline Survey and at the 8-week Outcome Survey (FTND only administered at the 8-week Outcome survey based on the participants self-report smoking status)

To evaluate nicotine dependence, participants are asked the following questions from the Fagerstrom Test for Nicotine Dependence (Heatherton, et. al, 1991):

1. How soon after you wake do you smoke your first cigarette?

❒ Within 5 minutes ❒ 31 to 60 minutes
❒ 6 to 30 minutes ❒ After 60 minutes

2. **Do you find it difficult to refrain from smoking in places where it is forbidden?** (e.g., in church, at the library, in the cinema)?

   ❒ YES
   ❒ NO

3. **Which cigarette would you hate to give up?**

   ❒ The first in the morning
   ❒ Any other

4. **How many cigarettes per day do you smoke?**

   ❒ 10 or less ❒ 21 to 30
   ❒ 11 to 20 ❒ 31 or more

5. **Do you smoke more frequently during the first hours after waking than during the rest of the day?**

   ❒ YES
   ❒ NO

6. **Do you smoke when you are so ill that you are in bed most of the day?**

   ❒ YES
   ❒ NO

8.4 Assessment of Level of Risk

This study presents minimal risk, as the interventions do not involve any invasive or risky medical procedures and can be considered no greater risk than ordinarily encountered in daily life. The potential benefit of study participation includes successful smoking cessation. Although documented risks of smoking cessation apps have rarely if ever been demonstrated, potential risks may be considered minimal and no greater than those associated with standard of care behavioral therapies for smoking cessation. In this context, the benefit-risk balance for study participation is considered highly favorable. Furthermore, this trial will ascertain potential adverse events via medical monitoring procedures and will be conducted in compliance with the protocol, good clinical practice (GCP), and the applicable regulatory requirements.

Both Clickotine and QuitGuide were developed to follow US Clinical Practice Guidelines for smoking cessation interventions. Use of either app may produce risks caused by the nicotine withdrawal associated with any attempt to quit smoking, including irritability and insomnia. Both QuitGuide and Clickotine are commercially available apps. Neither includes manufacturer's safety warnings nor involves any medical recommendations regarding use of prescription or over the counter quit aids.

9. DATA SAFETY AND MONITORING PLAN

This Data and Safety Monitoring Plan has been approved by NIDA for grant 1R43DA045395- 01 "Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification."

9.1 Oversight

Medical monitoring of this study will be provided by Joseph A. Ladapo, M.D., Ph.D. The Study PI (Brian Iacoviello, PhD) will have the primary responsibility for data and safety/confidentiality monitoring during the trial.

9.2 Plan for Monitoring for Safety/Confidentiality

The Study PI (Brian Iacoviello, PhD) will have the primary responsibility for monitoring the trial. Dr. Iacoviello will meet monthly with the research coordinator to monitor data entry and completeness, as well as to ensure appropriate safety data monitoring and reporting. Dr. Iacoviello will regularly monitor potential risks and procedures for protecting against risks and will monitor the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk, and other factors that can affect study outcome. The PI will also consider factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Data and Safety Monitoring Board: National Institute of Drug Abuse (NIDA; funding this study) determined that a Data and Safety Monitoring Board (DSMB) was not necessary and will not be created for this trial.

Frequency of Data and Safety Monitoring: Dr. Iacoviello will meet monthly with the research coordinator to monitor data entry and completeness, as well as to ensure appropriate safety data monitoring and reporting.

Monitoring of Safety Data: For the purpose of monitoring the safety of the study, the PI will review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, reasons for drop-out, physical and emotional discomforts associated with being in the study, and side effects. In the event that differences between groups are apparent, the PI will consult with NIDA to determine further evaluation of safety.

Serious Adverse Events: Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event,

permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the IRB and NIDA, regardless of any judgment of their relatedness to the study intervention. All relevant information will be reported including information about the event and its outcome, the subject's medical history and current conditions, and any relevant laboratory data. Information will be reviewed and a determination made of whether there was any possible relevance to the study intervention. Reporting to Western IRB and NIDA will be done within 72 hours of detection of the SAE.

Non-Serious Adverse Events: In monthly data review meetings, the PI will review summaries of the numbers and rates of adverse events by treatment group compiled by the research coordinator. These reports will include types of events, severity, and outcome if available. At the same intervals, the PI will also receive summary reports of treatment retention and reasons for drop-out, by treatment arm. In the event that differences in AE or retention rates between groups are apparent, the PI will consult with NIDA to determine further evaluation of safety.

Study Stopping Rules: If at any time during the course of the study, the PI or NIDA judges that risk to subjects outweighs the potential benefits, either shall have the discretion and responsibility to recommend that the study be terminated.

Monitoring of Data Quality: In the monthly Data and Safety monitoring meeting the PI will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with surveys and CO monitoring as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients and their primary and secondary outcomes.

Data and Safety Monitoring Reports: After the monthly meetings, the PI and research coordinator will prepare a summary report of their findings regarding safety and data quality based on data received to that point in the study. This report will include a brief description of the trial; baseline sample characteristics as available; summary of all safety findings; as well as an assessment of protocol compliance and data quality.

9.3 Adverse Events

If an adverse event experienced by a participant, and the participant or their physician determines they should cease use of the study app, the participant will be withdrawn from the study. Participants will have access to the e-mail and phone number of a study coordinator in case they experience any adverse event during the study.

If an adverse event is reported and evaluated by the study physician and is deemed to be severe enough to require withdrawal from the study, the participant will be withdrawn. Participants will have access to the e-mail and phone number of a study coordinator in case they are experiencing discomfort with Clickotine®.

All Adverse Events that occur during study participation will be solicited from study participants in both groups via an email-based system for reporting AE/SAEs. Participants are made aware of the email system during the informed consent and study enrollment process. Reports are reviewed by the research coordinator and the PI within 24 hours of the report and conveyed to the Medical Monitor (MM) for review and follow-up if appropriate. A Medical Monitoring form (See Appendix 12.6) is completed for each AE reported to the MM, to include: a description of the event; onset/offset dates; treatment required and/or condition resolution; designation as AE/SAE; and judgment of association with study intervention.

Expedited review will occur for all events reported by study participants that meet the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life- threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. Reporting to NIH will be done according to NIH regulations governing SAE reporting: the PI will contact NIDA within 72 hours after the detection of a SAE. Reporting of Suspected Unexpected Serious Adverse Reactions (defined by WIRB as "unanticipated adverse device effects") to Western IRB will be done within 5 days of the report in accordance with WIRB policy.

10. STATISTICAL CONSIDERATIONS

10.1 General Considerations

All study analyses will be conducted after the study database is locked. All analyses will be performed on the intent-to-treat (ITT) population.

10.2 Analysis Populations

Intent to Treat (ITT) population

All participants randomized to a study app that are able to confirm download of installed treatment arm app via telephone on the randomization date will be included in the ITT cohort.

10.3 Primary Endpoint

The primary endpoint will be self-reported 30-day abstinence from smoking on the outcome survey as per Russell Standard Self- Reported 4-Week Quitter status.

30-day smoking cessation status (dichotomous variable: yes/no) will be compared between the CKT and QuitGuide groups utilizing logistic regression. Two-sided p-values will be calculated from logistic regression models, with adjustments to the models by: race, education, nicotine dependence, and living with a partner who smokes, consistent with previous studies' models.

10.4 Secondary Endpoint

Concordance rates between self-reported 30-day abstinence and the remote CO monitoring result will be estimated, with concordance > 85% considered evidence of a valid reporting process by Magellan Behavioral Health. Concordance rates will be compared between users that submit the CO measurement under video monitoring and those that do not. Upon completion of the Outcome Survey, participants will be invited to submit the CO assessment over a live video feed to confirm identity, until videos are received from 25 CKT users and 25 QG users. After 25 videos are received from each group, participants will no longer be invited to submit the CO assessment over live video feed.

Secondary analysis of the subgroup of NRT/pharmacotherapy users will be conducted to compare cessation rates between the CKT+NRT group and the CKT-only group, to confirm the initial trial result that CKT+NRT is not superior to CKT-alone.

10.5 Sample Size

Power analysis: Estimated ITT 30-day cessation rates after 8-weeks of use for CKT and QG are based on published reports: CKT 26.2%, QG 8.3%. A power analysis for logistic regression using g*Power 3.1 software was conducted with the following parameters: 85% power to detect a group difference with $\alpha = 0.05$ two-sided significance level, and estimated Group 1 proportion, p1, of 0.262 and a Group 2 proportion, p2, of 0.083. A sample size of 78 subjects in each group will yield 85% power to detect such a difference. To obtain this sample size, we plan to obtain consent from 195 subjects and enroll 156 into the study by downloading the assigned app, which reflects a conservative approach to the retention rate observed in our pilot data.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Collection

Data collection during the 8-week study will occur through the Baseline Survey, Smokerlyzer Confirmation (Day 28), the Outcome Survey at 8 weeks and the iCO Smokerlyzer assessment**.**

Primary outcome data, including covariates to be included in regression analyses, are acquired via the web-based baseline survey and outcome survey. Data are conveyed via an automated process from the web-based survey into a format matching the study database. Research coordinator is responsible for entering the survey data into the study database within 72 hours of survey completion.

Secondary outcome data: 1) CO readings are automatically conveyed via email by the iCO Smokerlyzer App to the study coordinator, who will enter the result into the database (a numerical value in parts-per-million (ppm; <7 ppm is defined as evidence of cigarette abstinence); 2) self-reported NRT and smoking cessation pharmacotherapy use (including e- cigarette use) will be acquired via the outcome survey.

11.2 Audit and Inspection of the Study

No audit or formal Inspection of the study is planned.

12. ETHICS

12.1 Regulatory Considerations

As this study utilizes solely commercially available Apple iPhone and Google Play Store devices, and does not involve any medical recommendations regarding use of prescription or over the counter quit aids, this study is subject to Investigational Device Exemption (IDE).

This study is funded by a National Institute of Health, National Institute of Drug Abuse grant 1 R43 DA045395-01 “Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification” to Brian M. Iacoviello, Ph.D. The PI will seek NIDA prior approval for any significant changes proposed to the protocol. All Western IRB actions relevant to the study, including changes or amendments to the study protocol, will be communicated to NIDA.

12.2 Institutional Review Board or Independent Ethics Committee

Before this study begins, the protocol will be submitted for IRB review. IRB approval will be obtained prior to any screening or recruitment activity.

12.3 Informed Consent

The sponsor and delegates will fully inform potential participants of pertinent aspects of the study, via the “Informed Consent Form” (See Appendix 14.1). This informed consent will be obtained by electronic communication prior to the conduct of any study-specific procedures. Opportunities to

ask questions by email or telephone are provided prior to signing informed consent. The participant will receive a copy of the signed informed consent.

12.4 Withdrawal of Consent for Continued Study Participation

Participants will be instructed that they are free to withdraw from the study at any time without penalty or implications for any healthcare they receive. Participants who terminate the study early for any reason.

13. FINANCING AND INSURANCE

Funding for this study is provided by the National Institutes of Health / National Institute of Drug Abuse grant 1 R43 DA045395-01 “Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification” (PI: Brian M. Iacoviello, Ph.D.).

Click Therapeutics shall maintain, at all times, the following insurance coverages:

a) Commercial general liability insurance for bodily injury and property damages of $2 million for each occurrence and $4 million in the aggregate for policy year;
b) Errors and omissions including coverage for data breach and cyber liability of$1 million per occurrence and $3 million in the aggregate for policy year;
c) Workers compensation insurance as required by law;
d) All policies shall be written using at least A- carriers falling within a “Secure rating” by the A.M. Best Company or its replacement

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15. APPENDIX

15.1 Informed Consent

PARTICIPANT INFORMATION & INFORMED CONSENT FOR CT-101-002 STUDY

TITLE: Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification

PROTOCOL NO.: CT-101-002
WIRB® Protocol #20180920

SPONSOR: **My Digital Study**

INVESTIGATOR: Brian M. Iacoviello, PhD
860-879-2855
Email: pi@mydigitalstudy.com

STUDY RELATED PHONE NUMBER(S): Ashlea Chandler
860-879-2855
Email: study@mydigitalstudy.com

RESEARCH COORDINATOR: Ashlea Chandler

You can expect to find the following information in this document

Participate or not? This will help you decide

First of all, please read all this information carefully

Thank you for your interest in this clinical study. To help you decide if you'd like to take part in this smoking cessation study, this form will tell you about the trial and what it will involve.

Before you make your decision, it is important for you to understand the study and get detailed information about the study
Please take as much time as you need to read through this information. If you have any questions, please discuss them with the investigator or research coordinator prior to consent.

Anything else you would like to clarify or discuss? Then please ask the study doctor/study team to explain any words or information that you do not clearly understand.

Of course, you can discuss your participation with anyone you choose in order to better understand this study and your options. If you understand the information contained herein and decide to participate in the study, please sign and date the consent form at the end of this document.

Your participation is voluntary. If you do not wish to participate or wish to withdraw from the study, this will not place you at any disadvantage. Whether you choose to participate or not, you can ask your study doctor about alternative treatments and medications.

Part A: Participant information

1. General information about the study

You are being asked to participate in this research study because you are a current smoker that is motivated to quit smoking with assistance of a mobile solution in the next 30 days.

As an adult proficient in the English language and willing and able to test methods intended to help you quit smoking, you may qualify for this study. If you'd like you may proceed with the sign-up process. This study could benefit participants by helping them smoke less and eventually quit smoking. We hope that the information we learn from the study will guide our future work designing effective digital smoking quit aids.

This study will involve use of mobile-based technology to aid attempts to reduce and quit smoking. If you agree to participate and have confirmed your informed consent to participate in the study, you will be directed to an initial survey to measure your smoking behavior and associated characteristics and will then be asked to provide an email address, so you can receive instructions to download the application for your smartphone.

1.1. Who is the sponsor of this study?

The study is managed and sponsored by My Digital Study. Further information about the company is available through the internet at www.mydigitalstudy.com.

1.2. What kind of study is this?

This study involves the use of two commercially-available smoking cessation applications ("apps") designed for your smartphone. Study procedures will be conducted in a digital-only environment

"Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical *verification" is a Phase I, randomized controlled trial (RCT), single-blind, study to evaluating the efficacy of two separate smoking cessation applications for short-term smoking cessation in a fully remote, single-blind, randomized controlled trial (RCT) .*

Since you may not *be familiar with all of the terms in the study title or study name, here are a few common definitions:*

Randomized: Study participants are randomly assigned (by chance alone, like drawing a straw) to receive one of the treatments or treatment regimens that are being studied.

Single-Blind: Single-blind means that you do not know which treatment group that you have been assigned. Additionally, the study team will be blinded to participant group assignment, with the exception of the research coordinator who will need to be aware of group assignment in order to assign unique study IDs and offer technical assistance appropriate to the app assigned to participants.

The reason for this blinding is to avoid introducing potential bias or otherwise skew the results introduced by the partial unblinding of the investigator team.

Two-arm Comparator: This means that the study involves the assignment of two effective study treatment applications: Experimental arm and Active Control arm. An active comparator was selected as placebo interventions cannot be implemented in digital interventions of this type. When starting the treatment, you will be randomly assigned to 1 of the 2 treatment arms.

Phase: Clinical studies are conducted in a series of steps, called phases – each phase is designed to find out different things about the study treatment that is being studied. If a treatment successfully passes through Phases I, II, and III, it might be approved for use in the general population.

1.3. What is the purpose of this study?

The purpose of this research study is to compare the effectiveness of two commercially-available smoking cessation applications ("apps") designed for your smartphone. Each app is intended to help users smoke less and eventually quit. establish the feasibility of biochemical verification of smoking cessation in a fully remote, digital clinical trial.

The overarching study aim is to recruit a population of current smokers who are motivated to quit with the assistance of a mobile solution, enroll them into a study testing apps to help them quit, and randomize them into one of two arms.

1.4. What are my other options to quit smoking?

Even if you decide not to participate in this study, there are other ways you can access help for quitting smoking. The National Cancer Institute offers help on their website (www.smokefree.gov),and quit-lines can be reached throughout the United States by calling 1-800-QUIT-NOW (1-800-784-8669).

1.5. How long will the study last, and how long will I be involved in it?

If you decide to join, your participation in this study will last at least ***8 weeks***, in which you will not be required study visits to a study center. After the 8-week treatment period, you will have the option to continue using the application on your smartphone.

The study will last approx. 8 weeks

This study will use competitive enrollment. This means that when a target number of subjects begins the study, all further enrollment will be closed. Therefore, it is possible that you could be in the screening phase, ready to begin the study, and be discontinued without your consent if the target number of subjects has already begun the study.

1.6. How do I potentially benefit from being in the study?

A benefit of the study is that you could successfully quit smoking. Even if you do not make it to a point where you are completely smoke-free, you may reduce your dependence on nicotine, or at the very least you may learn strategies to help you cope with cravings going forward. You will still have access to the mobile application after the 8-week study is complete, so you can continue to work towards your goal of quitting or reducing smoking.

Your participation will also help researchers learn more about effective ways to manage nicotine addiction and quitting smoking. Your data and feedback will help improve the app, which has the potential to help other

smokers who wish to quit. You may personally benefit from the feeling that you have helped this research succeed.

You may benefit as a result of your participation in this study. There is, however, no guarantee that you will benefit from your participation in this study. Results from this study may benefit others in the future

1.7. How much will I be paid for compensation in the study?

All participants in the study will be eligible to receive $100, paid in two (2) Amazon gift cards of $50 value, for completion of the following activities below:

8 Week Survey x1 = $50
8 Week CO Monitor Test x1 = $50

In addition, a subset of participants will be eligible on a first-come first-serve basis for an additional $50 Amazon gift card, for conducting their 8 Week CO Monitor Test via live video. These participants, upon completion of the 8 week survey and the 8 week CO monitor test conducted via a live video with the research coordinator, will receive an Amazon gift card with a total value of $150.

Once all of the end of study assessments have been submitted, the clinical research coordinator will provide the Amazon gift certificate(s) to the participant via email.

How much will this study cost me?
There are no costs for being in this study

1.8. Can I leave the study early?

You can end your participation in the Smoking Cessation study at any time without giving reasons.

You can cancel your participation in the study at any time. You are not required to provide a reason.

Your decision whether or not to take part in this research study is completely voluntary. If you agree to take part in the study but then change your mind, you are free to withdraw your consent and stop your participation at any time. There will not be any penalty or loss of benefits to you if you decide not to take part. Should you decide to end your participation in this study, you must notify the research coordinator that you wish to stop. If you choose to leave the study early, you will not be able to withdraw any data that was collected about you prior to leaving the study. This data will remain in the study.

1.9. Where will study information be made available?

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

A description of this clinical study may also be available in other publicly available clinical study databases, which will also not include information that can identify you.

Please note that the study results will only become available after the study has finished. Depending on when you leave the study, it may be a long time before the study results are available. This could take months or even years.

1.10. Who can I speak to if I have questions?

If you have any questions about this study (including requests for more information, information about your rights as a participant, concerns, complaints, or general questions), or if at any time you feel you have had a research-related injury please contact the Research Coordinator at study@mydigitalstudy.com or call 860-879-2855. If you have had a negative health event as a result of the study, please report this by sending an email to study@mydigitalstudy.com. A Medical Monitor may then reach out for more information about the event. We aim to get back to you within 48 hours.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@WIRB.com

WIRB® is a group of people who perform independent review of research.

WIRB® will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB® if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

You have the right to ask questions concerning the possible risks of this study at any time. You will be told of any safety information related to the

study or study treatments. If you have any questions, concerns or complaints about this research study, its procedures, its risks and benefits, or alternative types of treatment, or if you have any research-related injury, you should contact the investigator or research coordinator at the phone number listed on page 1 of this document.

2. Study Treatment Information

The purpose of this research study is to compare the effectiveness of two commercially-available smoking cessation applications ("apps") designed for your smartphone.

You will be randomly assigned to one of these 2 smoking cessation apps. You will have an equal chance to get either app. Each app is intended to help users smoke less and eventually quit. If you decide to join, your involvement in the study will last 8 weeks. After 8 weeks, you will have the option to continue using the application on your smartphone.

2.1. What are the risks of participating in the study?

As with any medicine, you may experience unwanted side effects. For more information, see Section 5 ("Information about possible side effects"). This study is based within a mobile application and health questionnaires, and the risk of participating is deemed minimal. There is a very small risk that your survey information will be viewed online by an unauthorized party, though we have protected against this risk (see Section IV).

Additionally, when a person tries to quit smoking, she/he may experience short-term negative side effects of nicotine withdrawal. Though the app will suggest non-invasive, therapeutic ways to manage these symptoms (e.g. deep breathing), feel free to consult your doctor if you have any questions or serious concerns regarding nicotine withdrawal symptoms or other adverse health consequences. If you believe you are experiencing an adverse health event during the study, please let us know by sending an email to study@mydigitalstudy.com; we may then follow-up with you to collect additional information about the health event.

3. Course of the study

3.1. What does my participation in this study involve?

After providing informed consent, your experience will include:

(1) Completing an initial survey online to measure your smoking behavior and associated characteristics,
(2) Being randomly assigned to 1 of 2 smoking cessation apps,

(3) Using your smartphone to download the app and participating in the smoking cessation program for that app during the 8-week study period,
(4) Completing an adherence check at Week 4 (Day 28) by submitting an exhaled CO assessment at Day 28.
(5) Completing an outcome survey online to measure your smoking behavior and associated characteristics
(6) Submitting an exhaled carbon monoxide (CO) Assessment using an iCO Smokerlyzer which will be mailed to you; you may be requested to complete the CO assessment on a video feed to confirm your identity.

It is important to note that medication will not be provided in the study - the apps can act alongside other nicotine-replacement therapies or medications you may be using. It is not necessary to be using any other form of quit aid to participate in this study.

3.2. What information will I be asked to provide?

Once you give your consent, you will be directed to an initial online survey to collect data about yourself and your smoking habits. The survey should take no longer than 15 minutes. Data provided in the initial survey are collected for study purposes only and may include personally identifiable information (PII) such as full legal name, date of birth, and mailing address. Your mailing address is used solely for payment purposes to receive your compensation upon completion of the 8-week study and will be kept secure and confidential. You will have one week (7 days) from when you give your consent to fill out this initial survey. Only upon completion of this survey will you be deemed eligible to participate in the study and receive the link via email to download the smoking cessation app.

At the end of the study, you will be asked to complete the 8-week outcome survey online to assess your cessation progress before you receive your compensation. This survey will take no longer than 15 minutes and will ask questions to learn how your motivation to quit and your ability to resist smoking urges have changed over the 8-week study.

All of the surveys will be conducted via the web, reaching you through links sent to your e-mail or via SMS (text message).

3.3. iCO Smokerlyzer Assessment

A Smokerlyzer is a handheld device used to measure the amount of carbon monoxide in your breath. Carbon monoxide is inhaled and exhaled while smoking, so it is a great way to measure cigarette intake.

Carbon Monoxide Reading: Users will be provided with a commercially available mobile device, the iCO Smokerlyzer, and asked to install its associated smartphone app. All users will be instructed at the end of the post-trial form to use the iCO Smokerlyzer monitor by following the app instructions (hold breath for 15 seconds before exhaling into the monitor

tube) and set it to email the results to the project manager. Participants will also receive an additional incentive if they use the Internet to send the project manager a video of themselves performing the CO reading in which their face and the digital readout are clearly visible.

Why are CO assessments collected in this study?
You are requested to submit an exhaled carbon monoxide measurement for validity of self-reported smoking cessation of the remote CO monitoring.

Live Video Monitoring CO Assessment

To ensure the validity of the remote CO monitoring, approximately half of the study population will be invited to complete the CO monitoring assessment on a live video feed to confirm identity. Participants will be asked for consent to conduct the Smokerlyzer assessment via live video monitoring after the end of study Outcome Survey.

Participants will also receive an additional $50 Amazon gift card for submitting the exhaled CO assessment via live video monitoring after submission of the outcome survey for the EOS assessments.

3.4. Electronic Data Collected

This fully-remote study will rely on digital procedures for data collection (e.g., web-based surveys; auto-emailed results of the CO assessment).

Research Material: The following electronic data will be obtained from living individuals who are participating in the study:

Trial participant forms: recruitment eligibility and enrollment survey responses

Email: results of the analysis of exhaled CO sent by the iCO Smokerlyzer to the study email address

Administrative forms: adverse medical events, early termination, protocol violations, and results of the video conference to verify the exhaled CO procedure in subjects randomized to that subgroup SMS, call, and email logs including only the date and time of a sent or received communication (text, phone, or email) between a participant and the study team

4. Confidentiality

We will do our best to ensure that the information you provide is kept confidential, although information may be disclosed to governmental, judiciary, or public health authorities, or any other authorities or agencies as permitted by law. Such cases are rare and not expected.

Privacy of study participants is respected, and participants will only be contacted at email addresses and phone numbers provided for that purpose. Participants will only be emailed study-related information and voice messages will not be left unless the participant provides permission to do so.

4.1. How will my personal data be protected when transferred and stored?

Various security measures are utilized to ensure that PHI and other associated personal data are protected from unauthorized access, alteration, disclosure, destruction, and other malicious activity. Data associated with the study is protected in transit over computer networks using secure socket layer (SSL) and transport layer security (TLS) encryption. Information stored in databases are safeguarded by deidentification, automated network and software monitoring, automated patching and penetration testing, and strict physical security measures. Areas of the study that are accessible by multiple study participants are password protected for each user.

4.2. How will my personal data remain confidential?

If you participate in the study, you will be given an identification number. Your study-related data will be stored and analyzed under this number and not your name. This is what is referred to as coded data.

4.3. What will happen to my coded data?

By signing the informed consent form, you give your permission for your coded data to be collected, recorded, stored, checked, transferred or otherwise processed under the responsibility of the sponsor. All study-related documents and electronically processed data will be held confidential so far as permitted by law. The results of the study will only be published anonymously, and you will not be identifiable using the study data. This data will never include your name, initials, or your exact date of birth.

4.4. Who has access to my coded data?

Your PII is accessible to certain people working for or on behalf of My Digital Study to ensure the correct documentation and integrity of the data for study purposes, and PII is protected from unauthorized access.

4.5. Who can access my coded data?

Your coded data (i.e., data which does not identify you by name) may be accessed by persons who are working for or on behalf of My Digital Study, its affiliates, outside academic researchers, representatives of the Institutional Review Board who reviewed and approved this study, and regulatory authorities in other countries. These persons and authorities may be located in countries outside the USA that may not have an appropriate level of data protection. My Digital Study will, however, take reasonable measures to protect your coded data.

CO assessments that are submitted to the research coordinator will be analyzed under your coded identification number for purposes of the study. Participant carbon monoxide values can only be accessed by My Digital Study, its business partners and collaborators, their group companies and their contract service providers (e.g., laboratories).

4.6. How will my data be collected?

Data Integrity

Use of web-based surveys for primary data collection enables us to ensure the completion of data collected (forms cannot be submitted unless complete, and incomplete fields will be highlighted to inform participants of missing data). These remote and digital data collection procedures also ensures the integrity of data collected.

You are not obligated, by clicking on the link that led you to this page, to be in this study. Your alternative is not to participate. You are free to say yes or no, or drop out during the study. There is no penalty if you say no or drop out mid-study, though you will not receive the compensation.

CONTACT INFORMATION:

Please list some good ways for us to contact you. All contact information is kept completely confidential. Your information will be kept separately in a password protected file on a secure server.

Legal Name: _____

Cell Phone Number: (__ __ __) __ __ __-__ __ __ __

E-Mail Address: _____

Street Address:_____

City:_____, State_____ ZIP _____

What's the best way to contact you? Please circle all that apply
a. Cell c. Work
b. Home d. Email

What is the best time of day to contact you?
a. Morning Hours_____
b. Afternoon Hours_____
c. Evening Hours_____

Part B: Your consent

CONSENT TO PARTICIPATE:

I have read this consent form. All my questions about the study and my part in it have been answered.

☐ I consent to participate in this study.

☐ I **do not** consent to participate in this study.

_____

Digital Signature of Subject

My Digital Study Research Volunteer Registry Informed Consent:

At My Digital Study, our mission is to help individuals make behavior and lifestyle changes to manage and treat their medical conditions by a digital treatment through mobile app. In pursuit of this mission, we conduct several research studies each year. Your participation in these studies brings us closer to our dream of perfecting digital therapeutics that enable more personalized, convenient and effective medical treatment.

To conduct these research studies, we need help from volunteers like you helping to support further digital treatment development. You can help by volunteering to join our research registry. Anyone can join our registry.

This research volunteer registry is a database of individuals who are interested in hearing about, and perhaps participating in, the various research studies that are conducted by My Digital Study each year. In joining this registry, you will be the first to hear about our research – we will periodically send you brief emails with information on our current research studies. Directly from your inbox, you can request more information or join the studies that interest you.

Enrolling in this research volunteer registry is voluntary and confidential. You do not have to enroll unless you want to, and we will not share any of your information with outside entities. If you sign up to be included in the research volunteer registry, t**his does not automatically enroll you in any research study**, nor does it obligate you to participate in any research study. You may only agree to participate in a particular research study after learning about the benefits and risks associated with that particular study. Participation in any My Digital Study research trial is always voluntary and confidential.

If you have any questions about this form or the research volunteer registry, feel free to call 860-879-2855 or email study@mydigitalstudy.com.

By signing up to be included in the research volunteer registry, you are agreeing to receive email notifications, SMS (text) messages, or phone calls about research studies that are actively recruiting participants. All of the data that you provide will be stored indefinitely on secure, password protected servers at My Digital Study.

WHAT IF I CHANGE MY MIND?

You have the right to withdraw from the research volunteer registry at any time without giving any reason, and without penalty. You may withdraw from the research volunteer registry by:

1) Opting out of any of the email notifications that you receive by being on this registry or
2) Contacting the research volunteer registry coordinator at 860-879-2855 or by emailing Study@mydigitalstudy.com and asking to be removed from the registry.

WOULD YOU LIKE TO JOIN THE RESEARCH VOLUNTEER REGISTRY?

If you click "AGREE" below, it means that you have read all of the information on this page (or have had it read to you) and you would like to enroll in the My Digital Study volunteer registry.

Do you agree to enroll in the Research Volunteer Registry?

☐ I **agree to enroll in the** My Digital Study Research Volunteer Registry

☐ I **do not agree to enroll in the** My Digital Study Research Volunteer Registry

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

During your participation in this research study, the Investigator and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations or procedures you undergo while in the study) and record it on study documents. The Investigator will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the Investigator may obtain, and include in your records, information regarding your past, present and/or future physical or mental health and/or condition. Your Investigator may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called Protected Health Information (or "PHI").

Under federal law (the "Privacy Rule"), your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission. This permission is called an "Authorization". Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the Investigator and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the Investigator to disclose PHI as described below:

• The sponsor of this study and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your records for deidentification. This means that you will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your complete study records that identify you. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your PHI during these visits to make sure the information is correct.

• The Institutional Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

☐ The Investigator or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries as permitted by law.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with the federal law, your PHI will no longer be protected by this law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your records.

This Authorization will never expire unless you revoke (cancel or withdraw) it. You have a right to revoke your Authorization at any time. If you revoke the Authorization, your PHI will no longer be used

for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research.

To revoke your Authorization, you must submit a request in writing to the Investigator stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a PDF copy of this Authorization after your digital signature

Digital Signature of Subject	Date

15.2 Eligibility Questionnaire

"If the answer to any of questions 2 -8 is "no" or if question 9-10 is "yes", the user is not eligible for the study"

My Digital Study Eligibility Survey

This survey will determine if you are eligible to participate in the study and includes basic questions about your smoking history. Your answers to the eligibility survey questions will be entered in this secured website and kept confidential by the My Digital Study Team.

1. **Please enter your:**

   Full name: _____ Email address: _____

2. **Do you smoke at least 5 cigarettes a day?**

   ❒ YES
   ❒ NO

3. **Are you interested in quitting in the next 30 days?**

   ❒ YES
   ❒ NO

4. **Do you have access to an iPhone with iOS 9 or greater capabilities, or an Android with OS 7 or great capabilities?**

   ❒ YES
   ❒ NO

5. **Are you between 18- 65 years old?**

   ❒ YES
   ❒ NO

6. **Do you currently live in the United States?**

   ❒ YES
   ❒ NO

7. **Are you willing and able to receive email & SMS (text messages)?**

   ❒ YES
   ❒ NO

8. **Do you have internet access to download treatment while on the phone with the research coordinator?**

   ❒ YES
   ❒ NO

9. **Are you currently using a mobile phone-based smoking cessation intervention?**

   ❒ YES
   ❒ NO

10. Are you currently using a nicotine replacement therapy (nicotine patch, gum, inhaler, nasal spray, or lozenge)?

- ❒ YES
- ❒ NO

11. What time of mobile do you have?

- ❒ iPhone
- ❒ Android

12. If you have an iPhone, what model do you have?

- ❒ iPhone 7 or above
- ❒ iPhone 6, iPhone 6+, iPhone 6s, iPhone 6S Plus
- ❒ iPhone 5, iPhone 5c, iPhone 5s
- ❒ iPhone 4s

13. What is your current mobile provider?

- ❒ Verizon Wireless
- ❒ AT&T
- ❒ T-Mobile USA
- ❒ Sprint Nextel
- ❒ U.S. Cellular
- ❒ Other: _____

You have reached the end of the survey. Please click "Finish" to submit your survey responses.

15.3 Baseline Survey

My Digital Study Baseline Survey

We want you to consider the information collected on this form to be private. We will keep it confidential and only use it to contact for this study.

In order to ensure that the data collected is useful and complies with the Western Institutional Review Board (WIRB) guidelines, all study participants must meet certain requirements.

Welcome to the Baseline Survey!

7. What is your birth date (MM/DD/YYYY)?

DOB: __ __ / __ __ / __ __ __ __

8. Please specify your gender:

- ❒ MALE
- ❒ FEMALE

9. Please specify your race / ethnicity:

- ❒ White
- ❒ Hispanic/Latino
- ❒ Black or African American
- ❒ Native American or American Indian
- ❒ Asian / Pacific Islander
- ❒ Other: _____
- ❒ Prefer not to answer (?)

10. A family may be described as "adults and children who live together most of the time and share their income." Using this definition, how many people (including yourself) are in your family?

❒ 1 ❒ 2 ❒ 3 ❒ 4 ❒ 5 ❒ 6 ❒ 7 ❒ 8 ❒ 9 ❒ 10

11. Please describe your family's annual income level:

- ❒ Less than $20,000
- ❒ $20,000 to $55,000
- ❒ $55,000 - $100,000
- ❒ Over $100,000

12. If you have a spouse or romantic partner who lives with you, does he/she smoke cigarettes regularly?

- ❒ No
- ❒ Yes
- ❒ I have no spouse or romantic
- ❒ My spouse or romantic partner does not live with me

13. What is the highest level of education that you completed?

- ❒ Did not graduate from high school and did not get GED
- ❒ Graduated high school
- ❒ Received a GED
- ❒ Some college
- ❒ Associate degree
- ❒ Bachelor's degree
- ❒ Some graduate school
- ❒ Master's degree
- ❒ Professional degree (e.g., PhD, MD or JD)

14. How old were you when you started smoking?

Smoking onset age: _____

15. How long have you been a regular smoker?

- ❒ Less than 2 years
- ❒ 2-5 years
- ❒ 6-10 years
- ❒ More than 10 years

16. Have you previously tried to quit smoking?

- ❒ YES
- ❒ NO

17. If Yes, how many times have you previously tried to quit smoking?

- ❒ YES
- ❒ NO

18. What was your longest duration without smoking?

- ❒ Less than a week
- ❒ 1 week – 1 month
- ❒ 1 month – 6 months
- ❒ 6 months – 1 year
- ❒ More than 1 year

19. How soon after you wake do you smoke your first cigarette?

- ❒ Within 5 minutes
- ❒ 6 to 30 minutes
- ❒ 31 to 60 minutes
- ❒ After 60 minutes

20. Do you find it difficult to refrain from smoking in places where it is forbidden? (e.g., in church, at the library, in the cinema)**?**

- ❒ YES
- ❒ NO

21. Which cigarette would you hate to give up?

- ❒ The first in the morning
- ❒ Any other

22. How many cigarettes per day do you smoke?

- ❒ 10 or less
- ❒ 11 to 20
- ❒ 21 to 30
- ❒ 31 or more

23. Do you smoke more frequently during the first hours after waking than during the rest of the day?

- ❒ YES
- ❒ NO

24. Do you smoke when you are so ill that you are in bed most of the day?

- ❒ YES
- ❒ NO

25. In the last week, approximately how much money have you spent buying cigarettes?

- ❒ Less than $15
- ❒ $16-$30
- ❒ $31-$50
- ❒ More than $50

26. Within the past 30 days about how often do you use the internet?

- ❒ At least several times per day
- ❒ At least once per day but less than several times per day
- ❒ At least once per week but less than once per day
- ❒ At least once in past month but less than once per week

Medical History:

27. Please enter your height and weight:

Height: _____ Weight: _____

28. Please indicate how strongly you agree with this statement: "I generally feel sad or depressed".

❒ *Never* ❒ *Rarely* ❒ *Sometimes* ❒ *Often* ❒ *Very often* ❒ *Always*

29. Please indicate if you have ever been diagnosed by a doctor with any of the following conditions:

Pulmonary:

	YES	NO	Not sure
Emphysema / Chronic Obstructive Pulmonary Disease			
Asthma			
Other lung or breathing condition			

Cardiac:

	YES	NO	Not sure
Coronary artery disease (blockade of heart arteries)			
Heart attack			
High blood pressure			
Congestive heart failure			
Other heart conditions			

Neurologic:

	YES	NO	Not sure
Stroke			
Epilepsy			
Migraine or chronic headaches			
Multiple sclerosis			
Traumatic Brain Injury			
Chronic pain			
Other brain or spinal cord condition			

Metabolic:

	YES	NO	Not sure
Diabetes			
High cholesterol or triglycerides			
Thyroid condition			
Other metabolic condition			

Cancer:

	YES	NO	Not sure
Lung Cancer			
Breast Cancer			
Colon Cancer			
Other Malignant Cancer			

Mental Health:

	YES	NO	Not sure
Depression			
Anxiety disorder			
Schizophrenia			
Hospitalization for mental or emotional problems			
Other mental or emotional disorder			

30. Please answer these smoking-related questions to the best of your ability

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
Do you find cigarettes satisfying?	1	2	3	4	5	6	7
Do cigarettes taste good to you?	1	2	3	4	5	6	7

Do you enjoy smoking cigarettes?	1	2	3	4	5	6	7
	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Does smoking cigarettes calm you down?	1	2	3	4	5	6	7
Does smoking cigarettes make you feel more awake?	1	2	3	4	5	6	7
Does smoking cigarettes make you feel more irritable?	1	2	3	4	5	6	7
Does smoking cigarettes help you concentrate?	1	2	3	4	5	6	7
Does smoking cigarettes reduce your hunger for food?	1	2	3	4	5	6	7

	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Does smoking cigarettes make you less dizzy?	1	2	3	4	5	6	7
Does smoking cigarettes make you nauseous?	1	2	3	4	5	6	7

	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Do you enjoy the sensation in your throat and chest when you smoke cigarettes?	1	2	3	4	5	6	7
	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**

Does smoking cigarettes immediately relieve your craving for a cigarette?	1	2	3	4	5	6	7

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
I believe a mobile solution will help me to achieve my goal of becoming smoke-free	1	2	3	4	5	6	7
I am extremely confident that I will be able to quit this time.	1	2	3	4	5	6	7
I would be attempting to quit even without participating in this study.	1	2	3	4	5	6	7
I believe that a financial reward would help me quit smoking.	1	2	3	4	5	6	7

31. Please indicate how strongly you agree with these statements

Please show for each of the items below how you have been feeling over the past week?

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
Depressed	1	2	3	4	5	6	7
Anxious	1	2	3	4	5	6	7
Irritable	1	2	3	4	5	6	7
Restless	1	2	3	4	5	6	7
Hungry	1	2	3	4	5	6	7
Poor Concentration	1	2	3	4	5	6	7

Poor Sleep at Night	1	2	3	4	5	6	7

How much of the time have you felt the urge to smoke in the past week? *(Circle one number)*

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All of the time
0	1	2	3	4	5

How strong have the urges been? *(Circle one number)*

No urges	Slight	Moderate	Strong	Very Strong	Extremely Strong
0	1	2	3	4	5

Have you experienced any of the following over the past week? *(Circle one number for each item)*

	No	Slight	Moderate	Severe	Very Severe
Sores in the mouth	1	2	3	4	5
Constipation	1	2	3	4	5
Cough / Sore Throat	1	2	3	4	5

You have reached the end of the survey. Please click "Finish" to submit your survey responses.

15.4 Outcome Survey

My Digital Study Outcome Survey

We want you to consider the information collected on this form to be private. We will keep it confidential and only use it to contact for this study.

Welcome to the Outcome Survey! Please answer these questions to the best of your ability.

1. Have you smoked (even a puff) in the last 30 days?

- ❒ YES
- ❒ NO

2. If YES, have you smoked (even a puff) in the last 14 days?

- ❒ YES
- ❒ NO

3. If YES, have you smoked (even a puff) in the last 7 days?

- ❒ YES
- ❒ NO

~~ If the answer is "YES" to any of the questions 1-3, users will be prompted to Fagerstrom Test (Questions 4-9) for Nicotine Dependence

4. How soon after you wake do you smoke your first cigarette?

- ❒ Within 5 minutes
- ❒ 6 to 30 minutes
- ❒ 31 to 60 minutes
- ❒ After 60 minutes

5. Do you find it difficult to refrain from smoking in places where it is forbidden? (e.g., in church, at the library, in the cinema)**?**

- ❒ YES
- ❒ NO

6. Which cigarette would you hate to give up?

- ❒ The first in the morning
- ❒ Any other

7. How many cigarettes per day do you smoke?

- ❒ 10 or less
- ❒ 21 to 30

❒ 11 to 20 ❒ 31 or more

8. Do you smoke more frequently during the first hours after waking than during the rest of the day?

❒ YES
❒ NO

9. Do you smoke when you are so ill that you are in bed most of the day?

❒ YES
❒ NO

10. Are you currently taking any quit aids (ex. Nicotine Replacement Therapies (NRT) like nicotine gum, nicotine lozenges, nicotine patches, nicotine nasal spray / inhalers, or something similar) or medication (ex. Chantix, Zyban, or something similar) to help you quit smoking? *~~ If the answer is "YES", users will be prompted to complete Questions 11-16*

❒ YES
❒ NO

11. Please check which quit aid(s) you are currently using:

❒ Nicotine gum
❒ Nicotine lozenge
❒ Nicotine patch
❒ Nicotine nasal spray
❒ Nicotine inhaler
❒ Chantix® (Varenicline)
❒ Zyban® or Wellbutrin® (Bupropion)
❒ Other (please specify): _____

12. Do you ever forget to use your medicine / NRT?

❒ YES
❒ NO

13. Are you sometimes careless about using your medicine / NRT?

❒ YES
❒ NO

14. Sometimes when you feel worse about your medicine / NRT, do you stop using it?

❒ YES
❒ NO

15. When you feel better do you sometimes stop using your medicine / NRT?

❒ YES
❒ NO

16. How helpful was the app with staying adherent to your cessation medication or NRT?

❒ *Not at all* ❒ *A Little* ❒ *Somewhat* ❒ *Very* ❒ *Extremely*

17. Please answer the user experience / satisfaction questions to the best of your ability.

	Not at all	**A Little**	**Somewhat**	**Very**	**Extremely**
How satisfied were you with the app experience?	1	3	4	6	7
How easy was the app to use for your quit attempt?	1	3	4	6	7
How helpful was the app as part of your quit attempt?	1	3	4	6	7

18. Please answer these smoking-related questions to the best of your ability

	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Do you find cigarettes satisfying?	1	2	3	4	5	6	7
Do cigarettes taste good to you?	1	2	3	4	5	6	7
Do you enjoy smoking cigarettes?	1	2	3	4	5	6	7
	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Does smoking cigarettes calm you down?	1	2	3	4	5	6	7

Does smoking cigarettes make you feel more awake?	1	2	3	4	5	6	7
Does smoking cigarettes make you feel more irritable?	1	2	3	4	5	6	7
Does smoking cigarettes help you concentrate?	1	2	3	4	5	6	7
Does smoking cigarettes reduce your hunger for food?	1	2	3	4	5	6	7

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
Does smoking cigarettes make you less dizzy?	1	2	3	4	5	6	7
Does smoking cigarettes make you nauseous?	1	2	3	4	5	6	7

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
Do you enjoy the sensation in your throat and chest when you smoke cigarettes?	1	2	3	4	5	6	7
	Not at all	**Very Little**	**A Little**	**Moderately**	**A lot**	**Quite a lot**	**Extremely**
Does smoking cigarettes immediately relieve your craving for a cigarette?	1	2	3	4	5	6	7

19. How much of the time have you felt the urge to smoke in the past week? ***(Circle one number)***

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All of the time
0	1	2	3	4	5

20. How strong have the urges been? ***(Circle one number)***

No urges	Slight	Moderate	Strong	Very Strong	Extremely Strong
0	1	2	3	4	5

21. Please show for each of the items below how you have been feeling over the past week?

	Not at all	Very Little	A Little	Moderately	A lot	Quite a lot	Extremely
Depressed	1	2	3	4	5	6	7
Anxious	1	2	3	4	5	6	7
Irritable	1	2	3	4	5	6	7
Restless	1	2	3	4	5	6	7
Hungry	1	2	3	4	5	6	7
Poor Concentration	1	2	3	4	5	6	7
Poor Sleep at Night	1	2	3	4	5	6	7

22. Have you experienced any of the following over the past week? ***(Circle one number for each item)***

	No	Slight	Moderate	Severe	Very Severe
Sores in the mouth	1	2	3	4	5
Constipation	1	2	3	4	5
Cough / Sore Throat	1	2	3	4	5

23. At any point during the study did you experience a negative health event?

- No
- Yes - please describe the negative health event you experienced:

[The following questions will only be presented to user if answers "Yes" to the previous question]

What negative health event did you experience? _____

When did the negative health event occur mm/dd/yyyy

If you experienced a negative health event, did it impact your ability to carry out your typical daily functions?

- No
- Yes - please describe how your daily life was affected by the negative health event:

If you experienced a negative health event, did you seek any professional care to address the negative health event you experienced?

- No
- Yes - please describe the professional care you received:

What was the outcome of this negative health event?

- resolved completely
- partially resolved
- ongoing

During the study did you experience any other negative health event?

- No
- Yes

[A portion of the study populations that completes the outcome survey will be invited to conduct the CO assessment via livevideo monitoring to confirm identity. Participants that are invited to conduct the CO assessment via live video monitoring will consent to participate in live video monitoring at the end of the outcome survey by answering "Yes" or "No". Study participants that answer "Yes" will then select their preference of video platform and will then be linked to schedule a video call via Calendly with the research coordinator. Those who do not consent to participate in the live video monitoring CO assessment will receive a reminder to submit the end of study CO assessment.]

24. Would you like to participate in completing the CO assessment via live video-monitoring- you'll receive an additional $50 Amazon gift certificate?? (you will need another device: computer or phone with video capabilities in order to submit the assessment)

- ☐ If NO, remote CO assessment reminder
- ☐ If YES, Video monitoring preference, link to Calendly schedule

You have reached the end of the survey. Please click "Finish" to submit your survey responses

15.5 My Digital Study Welcome Card

Welcome to the Digital Smoking Cessation study!

Congratulations on beginning your journey to a smoke free life!

As part of the study, and to show our gratitude, you are receiving a Smokerlyzer. Please test it at your earliest convenience and submit the CO value to ensure it works properly. We highly encourage you to use it throughout the study to track your progress and motivate you. Not only will regularly using your Smokerlyzer push you to keep seeing your CO values drop, it will also ensure that your Smokerlyzer is working properly.

While not required, we would really appreciate it if you submitted your values throughout the study. Doing so allows us to better support you throughout your journey.

As you prepare to begin this new experience, remember to stay strong and that you're not alone. We're here with you every step of the way!

Sincerely,
My Digital Study Team

To get started:

1. Download the Smokerlyzer app on the AppStore or Google play store
2. Enter the pin code on your Smokerlyzer and the prompted information into the app

Smokerlyzer instructions for use:

1. Plug the white cord into the Smokerlyzer and into your phone's headphone jack
2. Take a deep breath and hold it for 15 seconds
3. Exhale into the Smokerlyzer
4. Readings will appear on your phone instantly
5. Results will be explained and charted

Go to this **[LINK]** for the iCO Smokerlyzer device video instructions ☺

15.6 Participant Eligibility, Informed Consent, and Calendly Messages

Message prompt for Eligible Participants :

Thank you for your interest in the Digital Smoking Cessation Study! You may be eligible to enroll in the study. To help you decide if you'd like to take part in this smoking cessation study, this form will tell you about the trial and what it will involve. Before you make your decision, it is important for you to understand the study and get detailed information about the study. Please take as much time as you need to read through this information. If you have any questions, please discuss them with the investigator or research coordinator prior to consent.

****PLEASE BE AWARE** that you will not be able to return to the Participant Information & Informed Consent form after closing the document from your internet browser. Please **DO NOT** exit from the informed consent form link until your questions about the study or consent (if you have any) have been discussed with the research coordinator.

Here is the **[LINK]** for the Digital Smoking Cessation Study: Participant Information & Informed Consent

If you have any questions, please contact the research coordinator at study@mydigitalstudy.com or 860-879-2855.

Message prompt for Ineligible Participants :

Thank you for your interest in the Digital Smoking Cessation Study! Unfortunately, **you are not eligible** [to participate]. For help with quitting smoking, please go to www.smokefree.gov or call 1-800-QUIT-NOW.

Baseline Survey + Participant ICF Reminder Message :

Thanks again for your time and willingness to participate in our study! Please check your email as we just sent you the link to complete the baseline survey + your signed copy of the consent. You only have 1 week to complete the baseline survey before the link expires.

If you have trouble viewing the baseline survey link from your personal email or have any questions, please contact the research coordinator at 860-879-2855 or email study@mydigitalstudy.com

Baseline Survey + Participant ICF Reminder Message :

Thank you for your interest in the Digital Smoking Cessation Study! Please check your email for a copy of your signed informed consent. If you are unable to review your signed informed consent or have any additional questions - please contact the research coordinator at 860-879-2855 or email study@mydigitalstudy.com

Calendly Schedule Message :

Thank you for submitting the Baseline Survey/Outcome Survey!

Please click the Calendly link below to schedule the Randomization Call/Live Video Monitoring Call with the research coordinator. If you have any questions regarding scheduling

the randomization phone call/live video call, please contact the research coordinator at 860-879-2855 or email study@mydigitalstudy.com

Tap this **[LINK]** to schedule the Randomization Call/Live Video Monitoring Call via Calendly

15.7 Baseline Survey + Participant ICF Email

Baseline survey link + Participant ICF copy email

Subject Line: Digital Smoking Cessation Study- Next steps to enroll

Thank you for your interest in the Digital Smoking Cessation Study! You may be eligible to enroll. The next steps in the enrollment process are in the Baseline Survey and Randomization phone call with the research coordinator. You will have 7 days from now to submit the Baseline survey + schedule the randomization call to complete your eligibility for the study.

Tap this **[LINK]** to get started on the baseline survey!

Attached is your signed copy of the informed consent. If you have any questions, please contact me at 860-879-2855 or email study@mydigitalstudy.com

Thank you!

Participant ICF copy email

Subject line: Digital Smoking Cessation Study- Participant signed informed consent

Thank you for your interest in the Digital Smoking Cessation Study. Attached is your signed copy of the informed consent.

We wish you all the best,

My Digital Study Team

15.8 Randomization Email

Hi [Name],

It was so nice speaking with you today. Thanks again for your time and willingness to participate in our study. This code will allow installation on one iOS or Android device only and may not be shared with other individuals.

1.) **Here is the link for the assigned treatment application: [LINK]**

2.) **The link to download the iCO Smokerlyzer application can be found here: [LINK]**

Please don't hesitate to contact me should you have any questions after our phone call at 860-879-2855 or email study@mydigitalstudy.com

Thank you**!**

15.9 Welcome Email & SMS

Congratulations! You are now enrolled in the Digital Smoking Cessation Study. The purpose of this research study is to compare the effectiveness of two commercially-available smoking cessation applications ("apps") designed for your smartphone. Each app is intended to help users smoke less and eventually quit. We thank you for choosing to be a part of this study and helping to support further development of this digital treatment option for smoking cessation.

You will be in the study for at least 8 weeks. During the study, you will be required to complete an 8-Week Outcome Survey and submit an exhaled carbon monoxide assessment via your iCO Smokerlyzer device. The Smokerlyzer device will be a part of the welcome package that will be mailed to you after the randomization phone call. If you do not receive the My Digital Study Welcome Package within 2 weeks, please contact the research coordinator.

All participants in the study will be eligible to receive $100, paid in Amazon gift cards (gift cards will be paid to the participant in $50.00 increments), for completion of the 8-week Outcome Survey, and the 8-week Carbon Monoxide Assessment. A subset of participants will be invited to conduct the 8-week carbon monoxide assessment via live video monitoring at the end of the outcome survey. Participants will also receive an additional $50 Amazon gift card for submitting the exhaled CO assessment via live video monitoring.

Be sure to contact the research coordinator with any additional questions you may have at 860-879-2855 or email study@mydigitalstudy.com

Tap this **[LINK]** for the iCO Smokerlyzer device video instructions ☺

Sincerely,

The My Digital Study Team

Welcome SMS: Welcome!! You are now enrolled in the Digital Smoking Cessation Study. If you have any questions, please contact the research coordinator at

study@mydigitalstudy.com or 860-879-2855. Tap this **[LINK]** for the iCO Smokerlyzer device video instructions ☺

15.10 Participant SMS & Email Messages: Baseline, Week 4, Day 53, Day 56, F/U

a. Baseline Survey SMS

Thank you for your interest in the Digital Smoking Cessation Study! You may be eligible to enroll by completing the next steps in the enrollment process: baseline survey and randomization phone call.

You will have 7 days from now to submit the Baseline survey to complete your eligibility for the study. Tap this **[LINK]** to get started on the baseline survey!

b. Smokerlyzer Check Week 4 (Day 28) Email and SMS

Subject Line: Digital Smoking Cessation Study- Week 4 (Day 28) Smokerlyzer Check

Congratulations [name]! You're halfway there! By submitting the Smokerlyzer CO assessment, you are helping us confirm that the device works! Please submit your Smokerlyzer assessment now. If you have any questions or have not received your Smokerlyzer please contact Ashlea at 860-879-2855 or email study@mydigital.com. Keep up the good work!

Tap this **[LINK]** for the Smokerlyzer video instructions ☺

Sincerely,

The My Digital Study Team

Week 4 SMS: Congratulations [name]! You're halfway there! By submitting the Smokerlyzer CO assessment, you are helping us confirm that the device works! Please submit your Smokerlyzer assessment now. Tap this **[LINK]** for the Smokerlyzer video instructions ☺

3. Day 53 EOS Assessment Email

Subject Line: Digital Smoking Cessation Study- 8-week Outcome Survey

You're almost there! Whether you were able to quit or not, make sure to complete the outcome survey and Smokerlyzer CO assessment. Don't forget that everyone who finishes the study can earn up to $150 in Amazon gift cards regardless of current quit status.

Tap this **[LINK]** to get started on the outcome survey!
Tap this **[LINK]** for the Smokerlyzer video instructions ☺

Sincerely,

The My Digital Study Team

4. EOS Thank you SMS

    a. Congrats, [name]! You've completed the smoking cessation study at My Digital Study! You've worked hard on this journey. Feel free to continue using [CKT or QG] or even after the study's official completion. Don't give up on your goal to quit, Great work!!
    b. ***Our team would like to thank you for completing the smoking cessation study. We wish you the best of luck and hope that you enjoyed your experience!!

15.11 User SMS & Email Reminders: Baseline, Week 4, CO prompt, Day 56, F/U

Baseline Survey Reminder

a. Hi [name], this is Ashlea from My Digital Study… Don't forget to fill out the baseline survey by [deadline]! Remember, you are eligible for up to $150 for completing the study! Pretty cool, right? Tap this link to get started:

b. Hi [name], this is Ashlea from My Digital Study for your 2nd follow-up reminder to complete the baseline survey by [deadline date]!.. Did you know you have only 7 days to complete the baseline survey before the link expires?!? Start the baseline survey before it expires! Tap this link to get started:

Smokerlyzer Check Week 4 (Day 28) Reminder

a. Don't forget [name]! You're Smokerlyzer Test is waiting for you! Please submit your Smokerlyzer CO assessment now to receive up to $150 in Amazon gift cards at the end of the study. Keep up the good work!

b. Hi [Name]! This is your final reminder to complete your Smokerlyzer Assessment. We appreciate your participation with submitting your results, regardless of the outcome! If you have not received your Smokerlyzer or are experiencing technical difficulties, please contact Ashlea at 860-879-2855 or study@mydigitalstudy.com

Submitted Outcome Survey prompt reminder for the EOS CO Assessment

Thank you for submitting the 8-week Outcome Survey!

Please remember to submit your Smokerlyzer CO assessment if you have not done so already. If you have any questions, please contact the research coordinator at 860-879-2855 or email study@mydigitalstudy.com

Thank you!

Day 53/56 EOS Assessment Reminder

a. You're almost there! Whether you were able to quit or not, make sure to complete outcome survey and CO assessment. Start the outcome survey before it expires! Don't forget that everyone who finishes the study is guaranteed $150 in Amazon gift cards!

b. Whether you were able to quit or not, everyone in our study is now eligible to make up to $150 in amazon gift cards for completing the study. Pretty amazing, right?? All you need to do is finish the outcome survey plus the CO assessment and those Amazon gift cards are all yours!! Tap this link to get started:

c. ***Whether you were able to quit or not, everyone in our study is now eligible to make up to $150 in Amazon gift cards! All you need to do is finish the [outcome survey and /or the CO assessment] and those Amazon gift cards are all yours.

d. Hi- this is Ashlea with my Digital Study. Don't forget to fill out the (outcome survey + Smokerlyzer) so you can receive up to $150 in amazon gift cards! Did you know you have only 7 days to complete the outcome survey before the link expires?!? Here's the link to start the outcome survey before it expires on [date]!

Day 1 & Day 2 Follow-up SMS & Email

a. Hi Click or QuitGuide User! Don't forget to submit your [Baseline survey, Week 4-CO submission, EOS Outcome survey, EOS CO Assessment].Thank you for participating in our study! Remember all of the reasons you decided to start your quit journey and stay strong! Here's the link again [no link for week 4 adherence check]

b. Hi [name]! Please don't forget to complete the [Baseline survey, Week 4 CO assessment submission, EOS Outcome Survey, EOS CO Assessment]. This is a great way to track your progress and important for our study. Thanks for all of your hard work! Here's the link:

15.12 Voicemail Script

Baseline Survey Voicemail Script: Hi [name], this is Ashlea from My Digital Study! I was just calling to follow-up your submitted baseline survey. Remember you only have 7 days to complete the baseline survey before the link expires. Start the baseline survey by [date] to be included in the study- participants can earn up to $150 at Week 8- End of Study Completion.

Smokerlyzer Assessment Check (Day 28) Voicemail Script: Hi [name], this is Ashlea from My Digital Study! I was just calling to remind you to submit your Day 28 Smokerlyzer assessment. By submitting the Smokerlyzer CO assessment, you are helping us confirm that the device works! We appreciate your participation with submitting your results, regardless of

the outcome! If you have not received your Smokerlyzer or are experiencing technical difficulties, please contact me Ashlea at 860-879-2855 or email study@mydigitalstudy.com.

End of Study Voicemail Script: Hi- this is Ashlea with my Digital Study. Whether you were able to quit or not, make sure to complete the outcome survey and Smokerlyzer assessment. Don't forget that everyone who finishes the study can earn up to $150 in Amazon gift cards regardless of current quit status. Don't forget to fill out the (outcome survey + Smokerlyzer) before the link survey link expires on [date]!

15.13 End of Study: Thank you Letter SMS & Email

Dear [Name],

On behalf of My Digital Study, we want to again thank you sincerely for your completed participation in the My Digital Study Smoking Cessation Study: Clinical Trial of an Innovative Digital Therapeutic for Smoking Cessation with Biochemical Verification.

We realize that participating in this study was time consuming and may have asked a lot of you. We value the time you committed to our research efforts. Your contributions will help others as a result of the medical and scientific knowledge gained from your participation. It is only with the help of volunteers like you that we can perform the essential research to find a new and effective treatment for smoking cessation.

If at any time you wish to access a public record of the study, you may locate this information on {clinicaltrials.gov/other registry domain} using the {NCT ID/registry identifier} {XXXX}.

Thank you very much again for your participation and for your contribution to medicine and to science!

Best Regards,

My Digital Study

SMS:
Congratulations! You have now completed the Smoking Cessation Study. Thank you very much again for your participation and for your contribution to medicine and to science! If you have any questions, please contact the research coordinator at study@mydigitalstudy.com or 860-879-2855.

15.14 Participant Letter: EOS / Sponsor Reveal Letter

Dear [Name],

Thank you for completing our smoking cessation study. Now that your participation in the study is complete, we wanted to disclose some additional information about the study. The sponsor of this study was Click Therapeutics, Inc., rather than "My Digital Study". The purpose of blinding the name of the study's sponsor was to avoid bias in your responses. Participants may have responded differently to surveys had they known that the developer of one of the apps being tested in the study, Clickotine, was sponsoring the study. We appreciate your honest answers and we hope that you continue on your quitting journey!

Thank you,

Click Therapeutics

15.15 Participant Letter: Lost to Follow up

[Insert date]
Subject Line: Research Lost to Follow-up

Dear [Name],

This letter is being sent to you as a participant in the Digital Smoking Cessation Study. The Digital Study team has attempted to contact you in regard to a missing study activity/assessment that is required for the study. Our attempts to reach you by telephone, SMS, and email at [Insert telephone number(s)] on three separate occasions have been unsuccessful.

Participants who have not completed required activities or assessments after follow-up efforts per the protocol follow-up procedure will be considered as a lost to follow-up participant. Unfortunately, the My Digital Study team must discontinue your study participation, as reasonable efforts have been made by the research coordinator to retain your participation in the study and to complete study assessments within protocol specified timeline.

We realize that participating in this study was time consuming and may have asked a lot of you, but we value the time you committed to our research efforts.

Sincerely,

My Digital Study Team

15.16 How to use a Smokerlyzer Video Script

Hi, I'm Hari from My Digital Study and today I'll be showing you how to use your new Smokerlyzer for the digital smoking cessation study. A Smokerlyzer is a handheld device used to measure the amount of carbon monoxide in your breath. We highly encourage you to use your Smokerlyzer throughout the study to track your progress and motivate you. Regular use of your Smokerlyzer will push you to see your carbon monoxide values drop and ensure that your Smokerlyzer is working properly. While not required, we would really appreciate it if you

submitted your values throughout the study. Doing so allows us to better support you throughout your journey and personalize your experience.

Your kit should come with an ICO Smokerlyzer, a white stereo cord, and a small visual diagram for further instructions.

Start by downloading the free Smokerlyzer app. This can be done by first opening the apple store or google play store on your mobile device. Go to the "search" tab of the store and tap the search bar. Type in "Smokerlyzer." The Smokerlyzer app should be one the first results. Proceed to download the app.

[cut scene of Hari doing that]

When you open the app, the app will first ask for you preferred language. On the following the app will request a pin code. Your pin code will be on the back of your new Smokerlyzer. Input this pin code to proceed to the next page. Next, the app will ask for your Clinician's name and email address. Enter "Ashlea" for the Clinician and "study@mydigitalstudy.com" for the email.

The next page will for your name and email address. Please enter your full name and your preferred email address.

[does that]

Now, you're ready to use your Smokerlyzer. Plug the white cable cord into the Smokerlyzer and then into your phone's headphone jack.

For those with an iPhone 7 or later, use an adapter to plug the smokerlyzer into your iPhone. One end of the adapter should plug into the other end of the white cable cord and the other end of the adapter should plug directly into the bottom of your iPhone. This adapter should have come with in the box when you purchased your iPhone.

[attaches wires]

With the app open and ready, select "new breath test." Turn the volume on your mobile device to the maximum setting. On the top of your screen, you should see "device status: connected" in white font. Wait a few seconds for the program to load. Once loaded, the gray bar on the bottom will turn blue, stating "begin test."

The program will first ask to take a deep inhalation and hold your breath for 15 seconds. After 15 seconds, the program will instruct you to exhale into the Smokerlyzer. Be sure to completely exhale all the air in your lungs. Readings will appear on your phone instantly.

[Hari holds breath]

After complete exhalation, wait a couple seconds for the program to load. Once loaded, the gray bar on the bottom will turn blue, stating "press to continue." On the following page, the program will ask two questions about the number of cigarettes you smoke per day and how long you wait

until you smoke your first cigarette of the day. After filling out this information, press "continue." The next page will provide a brief qualitative analysis of your smoking habits. On the following page, the program ask for a name and email address to share your results with. The name "Ashlea" and email address "study@mydigitalstudy.com" should already be appear in this section. If that content does not appear, enter that information manually. Next, select "send email." A page will slide up displaying your email draft. Select "send" in the top right corner of the page. It is very important that you complete these instructions exactly so that information from your breath tests can be shared with my digital study.

[finish demonstration]

Congratulations, you've completed your first Smokerlyzer test.

15.17 Advertisement Script

Advertisement content to be posted on Facebook, LinkedIn, Google+, and Instagram, and mailed to potential participants in a Magellan Health Care value-based care network.

Ads will include reference to a web link [LINK] that will bring participants to the Eligibility Questionnaire (see Appendix 15.2).

Sample Ad 1: Want to quit smoking? Want to earn money in the process? Sign up to join an 8-week research study evaluating 2 different smoking cessation apps that could help you break up with nicotine for good! Developed by doctors, scientists, and engineers, these apps will help you develop a smoking cessation plan complete with strategies for overcoming cravings and helpful ways to deal with withdrawal symptoms. You can earn up to $150 for using your iPhone or Android to quit smoking, and you'll never be asked to visit a study site. Join now! Go to [LINK] to see if you are eligible.

Sample Ad 2: Want to quit smoking and earn up to $150 doing it? We are looking for smokers to join a research study evaluating 2 different smoking cessation apps to help you quit. Developed by doctors, scientists and engineers, these apps have helped many quit smoking already. Space is limited. Visit [LINK] to see if you are eligible and to sign up now.

Sample Ad 3: Want to quit smoking? Want to earn $150 in the process? We are evaluating 2 different smoking cessation apps that could help you break up with nicotine for good! Developed by doctors, scientists, and engineers, these apps will help you develop a customized smoking cessation plan, complete with strategies for overcoming cravings and helpful ways to deal with withdrawal symptoms. Sign up today to join a remote (you'll never be asked to visit a study site!) 8-week, IRB-approved research study! Go to [LINK] to see if you are eligible.

Sample Ad 4: Sign up to join an 8-week, IRB-approved research study of 2 different smoking cessation apps that you can download on your iPhone or Android. Based on scientific research

and developed by doctors, scientists, and engineers, these apps will help you develop a smoking cessation plan, complete with strategies for overcoming cravings and helpful ways to deal with withdrawal symptoms. Join this 8-week, remote (you'll never be asked to visit a study site!) study today to quit smoking and earn up to $150 in the process. Go to [LINK] to see if you are eligible.

Sample Ad 5: Want to quit smoking? Want to earn $150 in the process? Join this 8-week, remote research study evaluating 2 different smoking cessation apps to help you break up with nicotine for good. Go to [LINK] to see if you are eligible.

15.18 Advertisements

15.19 Welcome Card

My Digital Study Welcome Card

Welcome to the Digital Smoking Cessation study!

Congratulations on beginning your journey to a smoke free life!

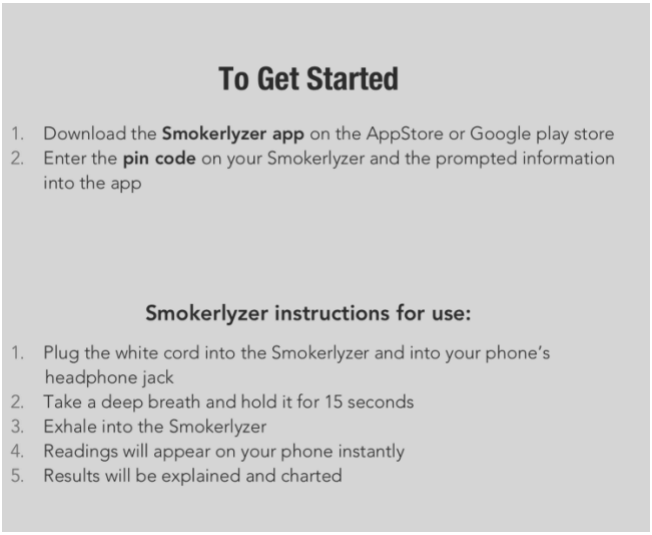
As part of the study, and to show our gratitude, you are receiving a Smokerlyzer. Please test it at your earliest convenience and submit the CO value to ensure it works properly. We highly encourage you to use it throughout the study to track your progress and motivate you. Not only will regularly using your Smokerlyzer push you to keep seeing your CO values drop, it will also ensure that your Smokerlyzer is working properly.

While not required, we would really appreciate it if you submitted your values throughout the study. Doing so allows us to better support you throughout your journey.

As you prepare to begin this new experience, remember to stay strong and that you're not alone. We're here with you every step of the way!

Sincerely,

Ashlea, Brian, Hari
My Digital Study Team



To Get Started

1. Download the **Smokerlyzer app** on the AppStore or Google play store
2. Enter the **pin code** on your Smokerlyzer and the prompted information into the app

Smokerlyzer instructions for use:

1. Plug the white cord into the Smokerlyzer and into your phone's headphone jack
2. Take a deep breath and hold it for 15 seconds
3. Exhale into the Smokerlyzer
4. Readings will appear on your phone instantly
5. Results will be explained and charted

16. MEDICAL MONITORING

Medical Monitoring Form

To be completed by the Medical Monitor upon participant report of an adverse event via the email reporting system.

Participant ID:

Description of the event:

Onset date:

Offset date:

Treatment required:

Resolution (select one):

Resolved completely

Partially resolved

Ongoing

Medical Monitor Designation (select one from each section):

Adverse Event

Serious Adverse Event

Suspected Unexpected Serious Adverse Reaction

None of the above

Associated/related to study intervention

OR

Not associated/related to study intervention