Document Title: CT-101-002 Statistical Considerations and Data Safety Monitoring Plan

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

NCT Number: NCT03694327

Date: 10Mar2022

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.

Data and Safety Monitoring Plan

"Clinical trial of an innovative digital therapeutic for smoking cessation with biochemical verification" (NIH Grant#: 1 R43 DA045395-01)

PI: Brian M. Iacoviello, Ph.D.
Medical Monitor: Joseph A. Ladapo, M.D., Ph.D.

Summary of the protocol

The purpose of this SBIR Phase 1 project is to demonstrate the efficacy of Clickotine (CKT) in producing long-term cigarette abstinence in a value-based care population served by Click Therapeutics, Inc.'s commercial partner Magellan Behavioral Health, and to demonstrate the ability to base reimbursement from CKT on remote biochemical verification of successful cigarette abstinence. To do so, this SBIR Phase 1 project will support a pilot blinded, randomized, controlled trial of CKT versus the NCI QuitGuide (QG) app to test the hypothesis that CKT will produce greater 30-day abstinence rates than QG after 8 weeks of use. To demonstrate the feasibility of evaluating CKT in a Magellan value-based care population, half the study sample will be recruited from a Magellan value-based care population. To demonstrate the ability to base reimbursement on remote biochemical verification of successful cigarette abstinence, concordance rates between self-reported cessation on the outcome survey and the exhaled CO monitor result will be investigated; video monitoring of a subset of the first 50 study completers (first 25 completers in both CKT and QG groups) submitting the exhaled CO assessment will be conducted to validate the remote CO monitoring process. Smokers that are currently using a pharmacotherapy or Nicotine Replacement Therapy (NRT, including e-cigarette use) at study enrollment will not be eligible to participate. However, since 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. 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 address expected med/NRT use during the trial and to confirm the initial trial result that CKT+NRT is not superior to CKT-alone.

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. In a fully-remote study design, a pre-screening phone call for advertisement respondents will be conducted to assess eligibility and answer participant questions prior to obtaining informed consent. Informed consent will be obtained from participants via a web portal provided after the pre-screening call, and baseline demographic and smoking characteristic data will be collected via an online survey. Participants are then randomly assigned to download either CKT or QG. All participants who complete the initial survey and are enrolled into the study will be mailed a mobile CO monitor, the iCO+ Smokerlyzer (coVita, Santa Barbara, CA), with instructions on how to install its linked smartphone app and set the study email as the address to which CO results are to be sent. A final

online follow-up survey will be administered eight weeks after initial enrollment. A $50 Amazon gift certificate will be provided in return for completing the online survey. The post-intervention survey will instruct subjects to obtain a CO reading with the iCO Smokerlyzer, to be transmitted to the study coordinator.

Primary outcome measure: self-reported 30-day abstinence from smoking on the outcome survey. Secondary outcome measures: iCO Smokerlyzer exhaled CO reading to confirm cigarette abstinence and assess concordance with self-reported abstinence; self-reported smoking cessation pharmacotherapy or nicotine replacement therapy (NRT) use.

Inclusion Criteria: (1) ages 18 to 65; (2) smoke at least five cigarettes daily; (3) want to quit in the next 30 days; (4) own an iPhone with iOS 9 or higher or Android with OS 4.1 or higher; (5) be willing and able to receive SMS text messages; (6) be able to comprehend the English language; (7) live in the US; (8) one half of the study sample will be recruited from the general population of smokers via social media advertisements; (9) one half of the study sample will be recruited via mail from a Magellan-managed value-based care network . Exclusion criterion: (1) prior use of Clickotine or QuitGuide; (2) current use of pharmacotherapy for smoking cessation or nicotine replacement therapy (NRT) including e-cigarette use.

Power analysis: Estimated ITT 30-day cessation rates 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. All participants enrolling in the study and downloading CKT or QuitGuide will be included in the ITT sample for analysis.

Trial Management

This is a single-site trial in which Click Therapeutics, Inc. will be the center, located at 101 Avenue of the Americas, 8th Floor, New York, NY 10013.

Projected Timetable:

3/18-4/18	5/18 - 8/18	7/18 - 10/18	11/18 – 2/19
Study startup	Advertising for recruitment; enrolled subjects randomized to study arms.	Participants complete 8 week trial; data collection complete in 10/18.	Data analysis; study wrap-up; SBIR Phase 2 application submitted; publication of Phase 1 results.

Target Population Distribution:

	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**

Data Management and Analysis

Data Acquisition:

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; <8 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.

Data Analysis Plan:

Gary Cutter, PhD, will conduct all study analyses after the study database is locked. All analyses will be performed on the intent-to-treat (ITT) population, with non-response imputed as continued smoking. 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.

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 between the video-monitored and unmonitored groups will be compared to determine the value of video monitoring the CO assessment.

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.

Quality Assurance
This fully-remote study will rely on digital procedures for data collection (e.g., web-based surveys; auto-emailed results of the CO assessment). Use of web-based surveys for primary data collection enables us to ensure the completion of data collected (forms can not be submitted unless complete and incomplete fields can be highlighted for participants). Survey data are conveyed in a format matching the study database for ease of entry into the study database by the research coordinator. The research coordinator will be responsible for entering all survey data into the study database within 72 hours of survey completion. Using these remote, digital procedures nature of the study results in data collection procedures that ensure the integrity of data collected. Validity of self-reported smoking cessation has been established in previous trials. To ensure the validity of the remote CO monitoring, a subsample of the first 50 study completers will be invited to complete the CO monitoring assessment on a live video feed to confirm identity.

Regulatory Issues
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 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 (SUSARs; defined by WIRB as "unanticipated adverse device effects") to Western IRB will be done within 5 days of the SUSAR report in accordance with WIRB policy.

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.

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

Disclosure of any conflict of interest in the DSM: There is currently no conflict to disclose in the DSMB membership. As noted below, the DSMB membership includes consultants with expertise in statistics, clinical trials and smoking cessation, who have been named on the grant as

consultants for these roles. These consultants are not employees of the sponsor nor do they have a financial interest in the outcome of the study. They will be compensated for their time consulting on the design and execution of the trial, including time spent serving on the DSMB.

Trial Safety

Potential risks and benefits for participants: 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.

Preliminary data related to the safety of Clickotine were obtained in a clinical trial of 416 smokers. Negative health events were ascertained via spontaneous report by users in-app, and via proactive ascertainment by a focused question in the Week 8 questionnaire: "At any point during the study did you experience a negative health event?" All negative health events reported were sent to the Medical Monitor for evaluation. The medical monitor assessed each event, and, when needed in order to comprehensively assess and document reported events, requested additional information via study team members in contact with the participant. All events judged clinically significant by the medical monitor were considered adverse events (AEs). The medical monitor also made a determination of relatedness to Clickotine (possibly related, not related) based on all available information and clinical judgment. Four negative health events were reported spontaneously, and an additional 32 were reported in response to the focused safety question in the 8-week questionnaire. Of these 36 negative health events, 19 were considered clinically significant and documented as AEs. Of the 19 AEs, 2 were considered possibly related to Clickotine use in the judgment of the Medical Monitor (nightmare, depressed mood). The most common AE was fatigue (reported in 3 participants), mood change was reported in 2 participants, and no additional AE occurred in more than one participant.

No manufacturer safety warnings are associated with the iCO Smokerlyzer device and the minimal risk associated with its use is related to the potential loss of privacy stemming from accidental disclosure of the data produced by the reading of carbon monoxide.

Collection, reporting and management of AEs and SAEs:

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 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 (SUSARs; defined by WIRB as "unanticipated adverse device effects") to Western IRB will be done within 5 days of the SUSAR report in accordance with WIRB policy.

Trial Efficacy

No interim analyses of efficacy data will be conducted as this is a brief, feasibility study. Efficacy analyses will be conducted after data collection only.

DSM Plan Administration

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: a Data and Safety Monitoring Board (DSMB) was not deemed 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.