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Study design

Effectiveness of a mHealth App as an add-on for Smoking Cessation in One year: A multicenter and randomized Trial (The MASCOT study)

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ABSTRACT:

Introduction: Smoking accounts for 480,000 deaths per year in the United States. Traditional pharmacotherapeutic interventions for smoking cessation continue to fail, urging the implementation of new therapies to prevent further harm. Mobile Health apps have appeared to support smoking cessation; their low cost, wide availability, absence of side effects, and drug-to-drug interaction make them useful adjuncts in some populations. Despite promising results, only a small number of smoking cessation apps have been formally researched as an add-on therapy. Therefore, we hypothesize that using a mobile health app (PIVOT) as add-on to the current standard therapy (varenicline plus cognitive-behavioral therapy) could increase the smoking cessation rate.

Methods: We propose a Phase III, multicenter, randomized, parallel-group, open-label, superiority trial. The control group will receive varenicline 1mg/daily for three months plus ten sessions of cognitive-behavioral therapies. The intervention group will receive the same treatment plus the addition of the PIVOT® app for one year. Participants will be 21 to 60 years old and meet the Tobacco Use Disorder criteria. The primary outcome will be smoking abstinence at one year of follow-up. Secondary outcomes will be lapses and relapses, cotinine hair drug testing at the end of follow-up, and the impact on Quality of Life measured through the WHO Quality of Life Scale-Brief questionnaire.

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Discussion: mobile Health Apps are widely available and extensively used by smokers to aid smoking cessation; however, their effectiveness as an add-on is unproven. This study will provide evidence to advise future clinical practice guidelines and decrease the morbidity and mortality attributable to tobacco use.

Keywords: Smoking cessation, Tobacco, mHealth App, Cognitive-behavioral therapy (CBT), Varenicline, Tobacco Use Disorder.

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Introduction

Within substance use disorders, nicotine dependence due to tobacco products has been a global problem for decades (Cornelius, 2019). The annual smoking-related death rate outlined over 8 million deaths worldwide (WHO, 2021). Cigarette smoking accounts for more than 480,000 deaths annually in the US, including 41,000 deaths from secondhand smoke exposure (CDC, 2021).

Nicotine, the principal constituent of tobacco, stimulates nicotine receptors in the brain to release the neurotransmitter dopamine in the GABAergic and dopaminergic pathways. This aids the nicotine-induced maladaptive behavior in drug-induced reward and reinforcement. The continued use of nicotine leads to addiction via the upregulation of Nicotinic Acetylcholine Receptors (nAChRs). Nicotine replacement therapy and non-nicotine replacement therapy (Bupropion and Varenicline) shape the cornerstone of smoking cessation therapy by downregulating neurotransmitter pathways. However, behavioral therapy and counseling are required to address addiction's psychological and behavioral components (USPSTF, 2015). Current guidelines for smoking cessation recommend eight sessions of cognitive-behavioral therapy (CBT) for 12 months along with the pharmacotherapy treatment. Nevertheless, the smoking cessation threshold is at least one year of abstinence, making long-term adherence a burden for patients and leading to a high rate of relapses. Moreover, the rise in stress levels during the COVID-19 pandemic has increased the number of smokers and restricted access to in-person programs and follow-ups (Xie, J., 2021). Therefore technology-driven approaches can be helpful in mitigating these limitations by diminishing the impact of social distance and lockdown measures.

Recently, state-of-the-art technology contributed to developing interventions to support smoking cessation, such as automatic text messaging, mobile devices, and social media (NIDA, 2021). Compared to traditional care, mobile health apps (mHealth) offer personalized information and could support adherence to smoking cessation treatment. Additionally, they serve as a monitoring tool beyond conventional clinical settings for patients in drug addiction therapy, where aftercare with ongoing treatment monitoring is not usually offered. Although these mHealth apps show promising results, few have been researched as smoking cessation apps, even less as an add-on to pharmacologic therapies (Haskins, 2017).

The MASCOT study (mHealth, App, Smoking, Cessation, One year, Trial) hypothesizes using a mHealth app as an add-on to the current standard therapy (varenicline and CBT) would increase the smoking cessation rates while also improving the quality of life of the patients.

Materials and Methods

Trial Design

This study is a multicenter, randomized, parallel-group, open-label, superiority trial. The control group will receive a smoking cessation standard of care (varenicline plus CBT), and the intervention group will receive the standard of care plus a subscription to a mHealth app (PIVOT app). Patients will be recruited at outpatient primary care practices (community, municipal, or general health clinics), pneumology, psychiatry, public hospital-based facilities, and/or healthcare institutions specialized in addiction treatment from California, New York, and Texas.

Randomization

The randomization schedule will be performed through the automated, central, online randomization system REDCap tool (Harris, 2009), which will also assure the concealment. The allocation between control and experimental groups will be 1:1, stratified by site and age groups using permuted blocks of random sizes. The randomization list will be identified by a numerical code and performed by 'quality assurance personnel' external to the study.

Blinding

This will be an open-label study. Neither the participants nor the treatment providers (psychologist/psychiatrist providing the CBT treatment to the patients) will be blinded to the intervention. However, third-party assessors in charge of evaluating the patient's reported outcomes will remain blinded throughout the study. Data analysts will be fully blinded as well.

Eligibility Criteria

Inclusion criteria: Patients between 21 and 60 years old who meet Tobacco Use Disorder criteria (Baker, T. B., 2021) motivated to stop smoking, considered suitable for smoking cessation attempts using PIVOT App, and able to provide informed consent.

Exclusion criteria: Patient already enrolled in smoking cessation treatment (including mHealth apps); e-cigarettes users; severe or uncontrolled concomitant hypertension, renal impairment, psychiatric disease, or severe laboratory abnormalities; contraindication or hypersensitive reaction to varenicline; pregnancy, breastfeeding, or childbearing potential without effective birth control method; history of other substance abuse disorder; considered by the investigator unsuitable for receiving the investigational drug according to varenicline label or unstable condition to comply with study assessments.

Recruitment Strategy

Subjects will be recruited during smoking cessation visits at outpatient clinics and specialized smoking cessation clinics in New York, Texas, and California states of the USA. The trial will be publicly advertised in handouts and leaflets distributed in smoking cessation support groups, online on patients' community websites, and the respective state's National and State Tobacco Control Program (NTCP) website (Buller, 2012).

Adherence

At the initial intervention and during each study visit, the importance of adherence will be expounded to the study participants. Details provided will include reinforcing the adherence to taking varenicline pills and CBT sessions for both groups. Also, there will be verification of the varenicline pill count at each visit as well as stating the importance of contacting the site in the occurrence of any adverse events. For the intervention group, the purpose and use of the PIVOT app will be reiterated, including how to report difficulties in using the app.

At subsequent follow-ups, the participants will be asked about the reasons for missing doses. They will be empowered with simple strategies for enhancing adherence, e.g., setting phone alarms for taking pills and linking the app to check daily activity. The participants should bring the remaining varenicline tablets to the follow-up visits so that physicians can better manage the treatment.

Timeline and Interventions

After signing informed consent, volunteers will be included in a 3-day run-in phase where each individual will receive videos and quizzes daily to assess trial commitment. After the successfully completed the run-in period, the volunteers will be randomized into both arms. All the participants will receive a video about the study design and instructions on how to answer surveys. Additionally, participants in the intervention group will receive a video containing relevant information about the PIVOT app and how it will work throughout the study. Both arms will start with varenicline at a low dose for one week and participants will have a baseline WHO Quality of Life Scale-Brief (WHOQOL-BREF) questionnaire and a CBT session.

Then, varenicline will be administered at a standard dose for 12 weeks. CBT will be provided at baseline, followed by four sessions in the first two months, and then one session in the 3rd, 4th, 6th, 9th, and 12th months, for a total of 10 CBTs (Ebbert, J.O. 2017).

The intervention group will receive the PIVOT app along with a breath sensor in addition to the standard treatment of varenicline and CBT for one year. An access code will be given to activate the app after downloading it from the mobile store. Participants will choose a quit date and answer questions on their demographic and smoking characteristics. The application will collect data from the sessions with each login.

The intervention has 5 phases: Explore (samples collected with the Pivot Breath Sensor, log cigarettes, coaching), Build (motivate and encourage the participant to set a quit date and build a quit plan), Mobilize (put into practice the quit plan), Quit (from the selected quit-day, the participant continues through the first week of living smoke-free) and Secure (motivate users to stay smoke-free with the help of lessons, animations, games, and immersive activities included in the app bundle). The app features include around-the-clock community support, identifying milestones for each hour not smoked during the day, and fun activities to fight cravings. Furthermore, the program includes human coaching delivered through in-app text messaging. Coaches contact participants twice a week with increased frequency based on individual preferences.

During follow-up interviews, clinicians will record outcomes and confer the WHOQOL-BREF at weeks 4, 12, 24, 36, and 52 (Killen, 2008). A cotinine hair drug test will be collected, and a survey regarding the mHealth app usage will be provided to the intervention group at the end of the study. (**Figures 1 & 2**.).

Outcomes

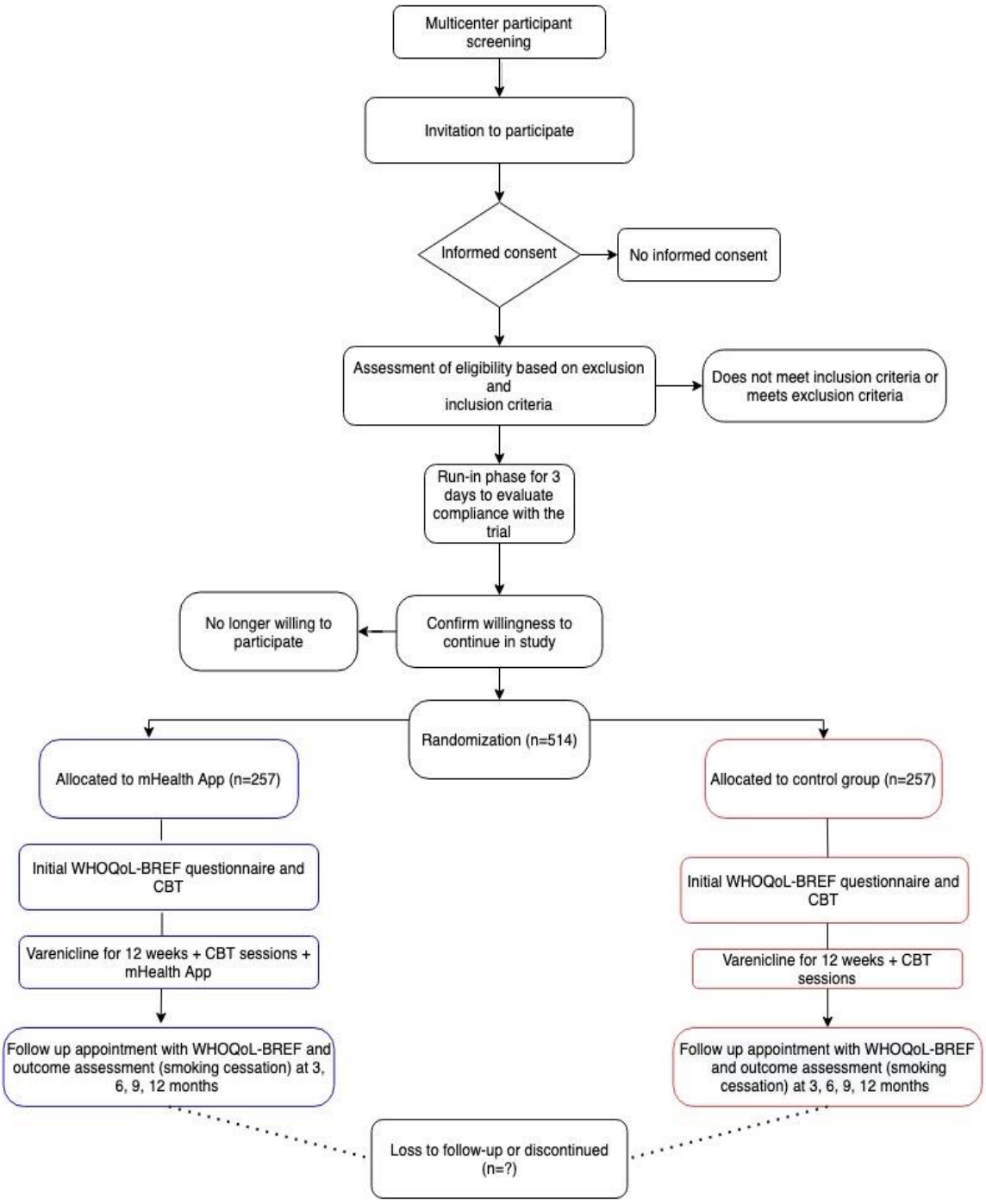

Figure 1. Flowchart of Study Timeline and Randomization.

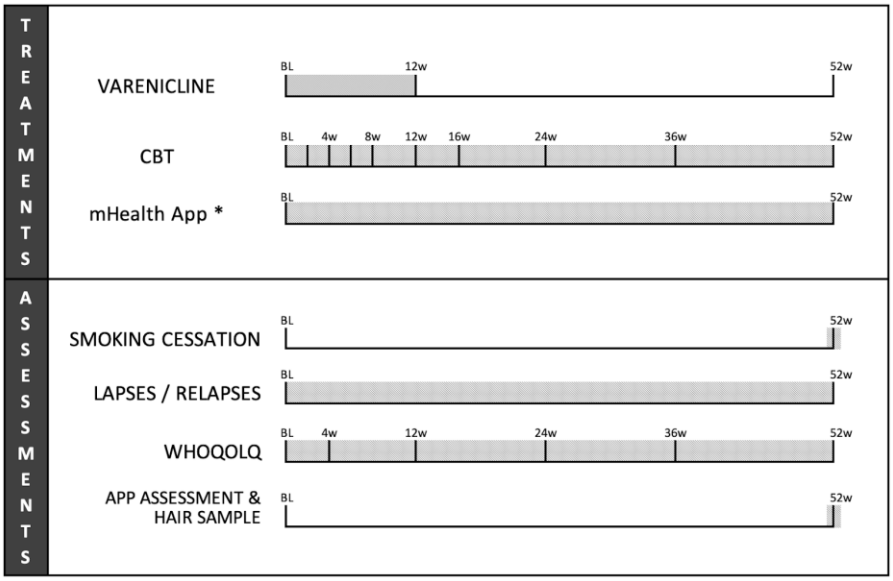

Figure 2. Distribution of Treatments and Assessment of Outcomes in the Follow-up Period. * Only the intervention group will receive the PIVOT app

The primary outcome will be smoking cessation at one year, with tolerance for lapses and relapses not exceeding 30 days of smoking annually. Through "yes" or "no," we will measure the difference between groups in relation to self-reported cigarette abstinence.

Secondary Outcomes

- Smoking lapses and relapses: Relapse: 3 or more consecutive days of smoking at any level. Lapse: any isolated tobacco usage for less than three days. Patients must self-report the number of cigarettes smoked and the number of days smoked during each follow-up visit. Lapses and relapses will be categorized according to the number of annual episodes (none, 1-4, ≥5) for the analysis.
- Cotinine Hair Drug Testing: At the end of the follow-up period, a biochemical test to detect Cotinine in a 4-centimeter hair sample will be performed.
- Impact on Quality of Life (QoL): The impact on quality of life will be measured through the WHO Quality of Life Scale- BREF (WHOQOL-BREF). The questionnaire will be completed at baseline and during the follow-up interviews at weeks 4, 12, 24, 36, and 52.
- Side Effects: We do not expect a difference in side effects between both groups related to varenicline treatment. Nonetheless, registration of side effects will be made during the follow-up interviews at weeks 4, 12, 24, 36, and 52.
- Qualitative app evaluation: after the follow-up period, the patient will be asked to answer a qualitative app evaluation questionnaire. They should answer on a 5-point scale, ranging from "completely disagree" to "completely agree."

Data Management

Data will be entered electronically at a Core Coordinating Center (DCC) by the investigator in the Case Report Form (CRF). An electronic copy of the CRF will be uploaded to the database, and a physical copy will be filed within locked cabinets in the participating site. The database will be retrievable for viewing through the data entry applications. A specialized software program designed to detect missing data will be used. The detected errors and their details will be summarized in the Data Query Reports and sent weekly to the Central Coordinating Centers responsible for carrying out the corrections. Each center will have access to the study data through a password-protected system, ensuring the data's security and restricted access. Twice a month, a complete backup of the primary DCC database will be executed. The clinical trial data will be stored for 15 years and then destroyed. The REDCap web application will manage the online surveys and the database.

Sample Size Calculation

The sample size was calculated according to the following parameters: Power of 80%, a significance level of 5%, and an effect of 12.5% difference between groups according to the results of a previous trial by Carrasco-Hernandez et al. (2020). We expect a drop-out rate of 35%. With these values, the sample size was calculated to be 514 subjects in total (257 subjects per group).

Statistical Analysis for primary and secondary outcomes

Volunteers in the case arm will be compared against the control for all primary analyses. The chi-squared test will assess the association between the intervention and smoking cessation at one year of follow-up. In addition, the chi-squared test will compare each category of lapses and relapses. Kaplan-Meier survival analysis and multivariable Cox proportional hazards analysis will be conducted to evaluate endpoints over time. We will perform linear mixed model analysis to assess the changes in time for the WHOQOL-BREF. We will analyze the Cotinine Hair Testing results with an unpaired T-test. For the subgroup analysis, binary and continuous outcomes will be analyzed using logistic and linear regression methods, respectively. We will perform subgroup analysis according to the age of participants, the number of cigarettes per day, and length of smoking habit, among others. We will also calculate relative risk and 95% confidence intervals for binary variables. P-values will be reported using four decimal places. All the analyzes will be performed using the last version of STATA. For all tests, we will consider alpha ≤ 0.05 as significant using 2-sided p-values.

Missing Data

Data will be analyzed by intention-to-treat, per-protocol, and restricted to high adherent (80%) patients to the trial visits. Data will be considered missed at random, expecting similar dropout rates in both groups, with similar causes, and imputed using multiple imputations from regression models (ten imputation datasets). Finally, sensitivity analysis will be performed with the worst/best-case scenario method.

Ethical aspects

The participant centers' IRBs will evaluate the regulatory and ethical aspects of this trial. The trial must be approved prior to its initiation. Participants will be informed about study methods and objectives in detail and will sign written informed consent but will be free to withdraw their consent at any time during the study.

Discussion

The greatest disease-producing product known to humankind is tobacco (Raja, 2016). Quitting smoking not only dramatically improves the life expectancy and quality of life of millions of smokers worldwide, but it also reduces the costs of healthcare systems. Technological advances have provided adjuvant therapies that can contribute to this goal, and some mHealth apps have been developed to help stop smoking. However, its effectiveness as an adjunct to standard therapy has not been well studied. We propose a study protocol for a phase III, randomized, multi-center, parallel-group superiority trial to provide evidence of its effectiveness. We aim to estimate the impact of adding a mHealth app (PIVOT) to standard care therapy (varenicline + CBT) in smoking cessation after one year.

We opted for a superiority trial design as the App is often used as an add-on to standard therapy, and there is no biological plausibility for its use as an exclusive therapy. In this way, it will be possible to test the potential gain of a combined virtual medical approach to achieve smoking cessation.

One of our study's strength is the standard 12-month follow-up period, a recognized criterion for smoking cessation. However, this criterion can lead to conflicting data with published studies with a shorter follow-up period, such as three months. However, we believe that periods of less than 12 months do not necessarily reflect the long-term reality, as participants can resume smoking within that year after the initial three months of follow-up.

The trial will be in a high-income country (United States), with well-established tobacco control policies and research subjects comfortable using mobile technologies. The study population can be criticized for presenting significant heterogeneity due to the broad age range and baseline covariates. On the one hand, what can reduce the statistical power and the probability of significant results can, on the other hand, increase the external validity with a robust sample.

The fact that the study population consists of patients who are highly motivated to quit smoking may raise concerns about selection bias. We consider that this setting might not impact the external generalizability of the study because it reflects the main characteristic of every patient who attempts to quit. The critical point in achieving smoking cessation is the willingness to stop. The reason behind the decision will be different depending on each person's motivations. Nonetheless, the patient must always be committed, otherwise, it would be impossible to achieve abstinence.

Our primary outcome will be self-reported abstinence from smoking at one year of follow-up. The Russell Standard recommends the abstinence definition as a self-report of smoking less than five cigarettes after the abstinence period begins (West, 2005). Nevertheless, lapses and relapses are usually accepted during treatment time. There has yet to be a consensus about how many lapses and relapses are acceptable during this period; therefore, we selected an arbitrary margin of 30 cigarettes (total) allowed during the year of follow-up before considering the participant as a failure to the treatment.

The measurement of secondary endpoints such as lapses, relapses, and quality of life will be self-reported by participants. At the 12-month follow-ups, a biochemical test for tobacco smoke exposure will be done using hair cotinine concentration. Hair cotinine characterizes tobacco exposure over a more extended period than blood or urine cotinine, with each centimeter length of hair representing approximately one month of exposure (Raja, 2016). However, this is not considered a bio-verified method to confirm abstinence, which is why we decided to use it only as a secondary outcome.

In conclusion, we hypothesize that adding a mHealth App to the standard care treatment will be superior to standard care treatment alone in achieving smoking cessation. If the data support this hypothesis, the mHealth App could become an excellent tool for public health due to its low cost, wide availability, and absence of side effects. It could be considered for the development of future smoking cessation guidelines.

Supplementary Materials: The trial will be registered on www.clinicaltrials.gov.

Author Contributions: T.G.G and I.P contributed equally to the work.

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Conflicts of Interest: The authors filled out the International Committee of Medical Journals Editors (ICMJE) form disclosure to declare no conflicts of interest. All listed authors agree with submitting the manuscript and approve the final version.

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