

TITLE: Coach2Quit TRIAL: Assessing a prototype personal carbon monoxide monitor for smoking cessation

NCT03142932

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Date: 05/15/2017

Dated: 15 May 2017

## 1. Abstract

Smoking is the leading preventable cause of morbidity and mortality in Maryland. Smokers are at increased risk of many cancers, heart disease and chronic obstructive pulmonary disease. Quitting smoking reduces the risk of these life-threatening conditions. In Maryland, annual expenditure on the treatment of cancer and smoking related diseases is approximately \$3.5 billion.<sup>1</sup> Therefore, continued prioritization of smoking cessation services is necessary to reduce the health and economic burden of smoking-related diseases.

While smoking cessation services such as nicotine replacement therapy and counseling are available, they are expensive and not easily accessible to everyone. Real-time biological feedback in clinic settings and mobile phone-based cessation support both independently show evidence of increasing a smoker's likelihood of quitting. The combination of these two strategies into a tailored system for smoking cessation is highly innovative and has the potential to provide an effective, inexpensive, and widely accessible tool for smokers attempting to quit. With smartphone use so widely prevalent, an interactive biofeedback and text message-based cessation program has great potential to decrease the heavy burden of tobacco use. We are currently working with partners to develop COach2Quit, a novel smartphone application that links to an individualized carbon monoxide (iCO) monitor and integrates biomarker feedback with appropriate motivational messaging.

The objective of this proposal is to conduct a randomized controlled trial to determine whether the use of the COach2Quit application reduces smoking more than brief advice for smoking cessation. We hypothesize that real time biomarker feedback and messaging support from the COach2Quit app will lead to greater smoking cessation rates than brief anti-smoking advice alone. If effective, the COach2Quit app could be an easily accessible and cost-effective tool to help smokers quit. The findings from this trial could have implications for the delivery of future outpatient smoking cessation programs.

## 2. Objectives (include all primary and secondary objectives)

1. To assess the efficacy of the COach2Quit smoking cessation application by comparing smoking cessation rates at 2-weeks and 1-month among participants using the COach2Quit app and participants receiving brief anti-smoking advice (primary outcome is 1- month). *We hypothesize that the 1-month quit rate will be 20% in the COach2Quit arm and 10% in the brief anti-smoking advice arm.*

2. To evaluate whether the treatments differentially influence cognitive and behavioral processes related to cessation outcomes. Although formal mediational analysis is precluded by the moderate sample size in this pilot investigation, we will examine how treatments affect various intermediate variables assessed during and at the end of treatment including; (1) Urges to smoke; (2) Withdrawal symptoms; (3) Reinforcing Smoking Decisional Balance; (4) Smoking Abstinence Self-Efficacy; and, (5) Satisfaction with the program. *We hypothesize these measures will all benefit with COach2Quit compared to brief advice alone.*

## 3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Tobacco is the leading cause of death in the world, contributing to 6 million deaths each year; nearly 500,000 of these deaths occur in the US with an additional 50,000 deaths due to exposure to second hand smoke.<sup>2</sup> Most recent estimates state that 19% of US adults smoke; although Maryland is under the

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national average at 16%, the prevalence in Baltimore City is 21%.<sup>3</sup> Smokers are at increased risk of many cancers, heart disease and chronic obstructive pulmonary disease. Quitting smoking reduces risk of these life-threatening conditions.<sup>2</sup>

In Maryland, approximately 149,600 residents are afflicted with at least one smoking induced chronic disease and smoking is responsible for 7,490 deaths each year on average.<sup>1</sup> Tobacco use is responsible for more deaths than homicide, suicide, HIV/AIDS and accidental injuries and overdoses collectively.<sup>1</sup> The economic burden of smoking is also high, with an annual expenditure of \$3.5 billion going towards the treatment of cancer and smoking-related diseases.<sup>1</sup> Therefore, continued prioritization of smoking cessation services is necessary to reduce the health and economic burden of smoking-related diseases.

### **Carbon Monoxide (CO) monitoring for smoking cessation**

CO in exhaled breath is a commonly used tool for measuring adherence to smoking cessation.<sup>4-9</sup> Exhaled CO (eCO) has also been considered as a cessation tool in primary care, however it has not been thoroughly studied.<sup>10-11</sup> Current evidence is only available for clinic-based use of eCO and suggests that cessation increases significantly following measurement, though the impact is short lived.<sup>12-14</sup> Pilot studies indicate that **more frequent and personal use of eCO may be an effective cessation tool.**<sup>15</sup> Beard and West report declining cigarette consumption after provision of a personal CO monitor over a 6-week period.<sup>16</sup>

Smartphone ownership has been steadily increasing and 64% of adults in America now own a smartphone.<sup>17</sup> This can be leveraged as an interactive modality through which smoking cessation interventions can be delivered. A smartphone application that combines biomarker feedback with message-based support offers the benefits of portability, accessibility and ease of use. There are several existing smoking cessation smartphone applications, but there have been no published studies to date that evaluate their impact on smoking cessation and this has been cited as an area that merits investigation.<sup>18</sup> **Combining brief cessation advice and relapse prevention strategies with daily personal CO monitoring may lead to increases in cessation and prolonged abstinence without the need for pharmaceutical interventions or nicotine replacement therapy.**

## **4. Study Procedures**

### **a. Study design**

**Overview:** The goal of this randomized controlled trial is to assess the efficacy of the novel COach2Quit smartphone application by determining whether the use of this app reduces smoking more than brief anti-smoking advice alone. This will be a two-arm individually randomized trial and participants who are currently smoking will be assigned 1:1 to either study arm. Smoking behavior will be measured through self-report at baseline, 2-week and 1-month follow up visits. Smoking behavior will also be verified by 2 biomarker measurements: carbon monoxide breath test and urine cotinine, collected at baseline, 2-week and 1-month follow-up visits. In addition, participants will receive weekly follow-up calls. **The primary outcome will be smoking cessation at the 1-month follow-up visit.**

### **Participant identification and recruitment**

A total of 150 adult smokers will be recruited to participate in this study through several channels, including:

- Patient will be recruited from clinics, inpatient and outpatient facilities within the Johns Hopkins Medical Institutions (JHMI) network in Baltimore. Posters advertising the study will be placed at these clinics and facilities. Recruitment cards with information about the study and contact information for study staff will be provided to physicians and nurses at inpatient and outpatient

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facilities to give to their patients and staff. However, inpatients will only be screened for enrollment once they have been discharged.

- JHMI staff will be recruited through the Human Resources office. Posters advertising the study will be placed in the office and recruitment cards will be given to JHMI staff.
- Posters advertising the study will be placed in several locations with high foot traffic around the JHMI East Baltimore campus.
- A Facebook COach2Quit page will be created for recruiting participants online. The page will have information about the study and contact information for study staff. The page will be promoted on a cost per click basis for the duration of the study recruitment period. Audience for the promotion will be limited by the location, interests and age filters provided by Facebook. Location will be limited to Baltimore city, interests will be limited to search terms such as smoking, quitting smoking, tobacco and nicotine, and age will be limited to people over the age of 18 years. **No Personal Health Information (PHI) will be collected online.** Interested participants will be able to contact study staff through the study contact information provided on the Facebook page.
- Center for AIDS Research (CFAR) at Johns Hopkins University: CFAR operates a study hotline, which is a service that pre-screens participants and provides referrals to research studies. CFAR will provide contact information for participants who have identified as smokers and we will contact these participants.

At initial contact with the participant, the study coordinator will discuss the study purpose and requirements and obtain informed consent from interested participants. Whenever possible, the initial assessment will be completed at this time. When this is not practical, the coordinator will schedule an appointment as soon as possible.

### **Initial Assessment**

After obtaining informed consent, an initial assessment will be conducted with participants. Participants will be asked to provide a baseline CO breath test and a urine sample to ascertain smoking status. If a candidate is deemed ineligible or chooses not to participate, they will be provided with information from the American Lung Association and referred to the Maryland Quit Line. Eligible participants will complete the baseline questionnaire which will include sociodemographic information, aspects of smoking history (e.g., years, quit attempts, etc), smoking urges, withdrawal symptoms and reinforcing effects of smoking, confidence to quit smoking, reasons to continue to smoke (pros) and barriers to quitting (cons), and perceived vulnerability to smoking-related illnesses, as well as other domains. A certified smoking cessation interventionist (SCI) will deliver standardized smoking cessation counseling using the National Cancer Institute's 5A's model (described below in section e). After brief counseling, all participants will set a quit date within the next 2 weeks and receive their randomized group assignment.

Participants in the COach2Quit arm will be provided with an individualized carbon monoxide (iCO) monitor along with instructions on the use of the monitor and the COach2Quit application. The SCI will help the participant install the COach2Quit app on their phone, guide them through completing an initial CO breath test using their iCO monitor connected to their smartphone, and answer any questions they may have. Participants will be requested to use their iCO monitor at least twice per day and answer a few questions about the amount smoked that day. The participant will be informed that their results will be sent to the study team through the application each time the participant uses their iCO monitor.

### **b. Study duration and number of study visits required of research participants.**

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Each participant will have a total of 3 study visits: baseline assessment, 2-week follow-up, and 1-month follow-up. The participant will also receive weekly follow-up phone calls. Thus, the participant will remain in the study for a total duration of approximately 1.5 months, depending on quit date. The complete schedule of study visits (for both groups) is detailed in Table 1. We anticipate a period of 4 months to complete this pilot trial.

**Table 1:** Visit schedule for pilot randomized controlled trial

Pilot RCT			
Visit #	Timeline	Schedule	Content
1	Day 0	Baseline, Counseling	CO breath test, urine sample; baseline assessment; study group assignment
2	2-weeks	Follow-up	CO breath test, urine sample, cognitive and behavioral processes questions
3	1-month	Follow-up	CO breath test, urine sample; cognitive and behavioral processes questions

**c. Blinding, including justification for blinding or not blinding the trial, if applicable.**

This will be an open-label trial in which neither the subjects nor the study coordinator will be blinded as to treatment assignment after randomization. However, the study interviewer conducting baseline breath CO and urine testing will be blinded as to treatment arm of the individual participants to decrease bias.

**d. Justification of why participants will not receive routine care or will have current therapy stopped.**

Participants will be excluded from the study if they are currently on NRT or other smoking cessation therapy. The care of patients at any Johns Hopkins facilities will not be affected in any way, regardless of whether they decline to participate in the study, remain in the study or drop out of the study.

**e. Justification for inclusion of a placebo or non-treatment group.**

Eligible participants will be randomized to receive one of two cessation strategies: (1) COach2Quit or (2) brief anti-smoking advice. All participants will receive advice to quit smoking and self-help materials in a standardized fashion. The advice to quit smoking message (3 min.) will follow the 5A's model for smoking cessation counseling.<sup>19-21</sup> This is a simple smoking cessation counseling strategy with 5 discrete components: (1) Ask about smoking at every opportunity; (2) Advise the patient to quit smoking; (3) Assess readiness to quit; (4) Assist the patient in quitting; and (5) Arrange follow-up. The 5A's model is endorsed by the World Health Organization in international settings as well as the US.

**f. Definition of treatment failure or participant removal criteria.**

Participants will be discontinued from the study if they (1) ask to be removed from the study (2) are found to be using other smoking cessation treatments (3) develop a medical condition precluding the use of the iCO monitor such as COPD (4) develop a serious adverse event (SAE).

**g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.**

The participant will continue to receive care at these facilities should he/she choose to leave the study for any reason. If a participant leaves the study prematurely due to an adverse event, text messages will stop being sent to them.

**5. Inclusion/Exclusion Criteria**

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Participants are eligible to take part in this trial if they meet the following **inclusion criteria**: (1)  $\geq 18$  years of age; (2) current, daily smokers, (3) agree to participate and anticipate to be living in Baltimore for at least 2 months, (4) own a phone that is compatible with the app, (5) be willing to set at baseline assessment a quit date within 2 weeks.

Participants will be **excluded** if they (1) are suffering from any unstable medical condition *precluding the use of the CO monitor* (e.g. severe COPD); (2) are currently using smokeless tobacco including e-cigarettes; (3) are currently using NRT or other smoking cessation treatment, (4) are pregnant, determined by participant self-report or (5) have a negative baseline result on both urine cotinine AND CO monitor.

## **6. Drugs/ Substances/ Devices**

### **COach2Quit smartphone application and iCO monitor**

Participants assigned to the COach2Quit arm will receive behavioral counseling (described above) and will download the COach2Quit app on their phone. They will be given an individualized carbon monoxide (iCO) monitor and instructed on how to use it with the COach2Quit app. Participants will receive 2 messages daily (1 in the morning and 1 in the evening) requesting them to use the iCO monitor. The iCO monitor has been developed by CoVita™ Bedfont®, and has been made available for the COach2Quit application. The iCO is a personal CO tester that connects to a smartphone via the headphone jack and provides an exhaled carbon monoxide (eCO) reading. Programmers have used the communication protocol supplied by coVita™ Bedfont® to read in data from the iCO monitor and integrate eCO readings with basic feedback messages. The data will be sent to a central data center, with a response message dependent upon CO result. **A measurement of  $\leq 10$  parts per million (ppm) will be a negative result** and will be followed with a message praising the participant's progress. If a positive result is read ( $>10$  ppm), a message of encouragement will follow, along with questions to be answered so that the result can be better understood and acted upon. Subsequent messages will be based on how the user's current CO reading compares to their previous reading. CO trends will be measured over time and the participant will be able to see a graphical display of their CO levels from initiation in to the study. Encouraging responses will also be received when declines in eCO are observed compared to prior results even if above the 10-ppm threshold. Users of the app will also have the option to request a call from a counselor.

### **Carbon Monoxide Breath Test**

When a smoker smokes a cigarette, or any tobacco product, he/she breathes in carbon monoxide, which competes with oxygen to combine with hemoglobin. Hemoglobin has a 200-250 times greater affinity for CO than for oxygen, thus greatly interfering with the necessary binding of oxygen to hemoglobin. Several machines are available to measure the COHb level in the blood of smokers, providing a means of measuring recent exposure to cigarette smoking. For our study, a point of care test for measuring carbon monoxide will be conducted via the piCO Smokerlyzer from OPS Medical, designed specifically for smoking cessation programs and tobacco control programs. Carbon monoxide will be measured in an exhaled breath in parts-per-million (ppm). **A reading of  $\leq 10$  ppm will indicate abstinence.** Participants will be asked about their smoking history since their last visit and on the day of the CO test. If the participant has a positive CO test, they will be further counseled for smoking cessation if enrolled in the clinical trial. If not in the clinical trial, they will be provided with information from the American Lung Association and referred to the Maryland Quit Line. Results will be recorded and labeled with the participant's study ID, and the participant will see their results immediately and the results will be explained to them.

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### **Urine Cotinine Test**

When a smoker smokes a cigarette or uses nicotine replacement therapy, his/her urine will have detectable levels of cotinine, a nicotine breakdown product. Cotinine is found in urine from 2 to 4 days after tobacco use, providing a means of measuring recent exposure to cigarette smoking. For our study, a point of care test for measuring cotinine levels will be conducted via SmokeScreen®, a rapid colorimetric assay from GFC Diagnostics Ltd. Cotinine levels will be semi-quantified according to the color chart included with the tests. A color change to red/orange indicates a positive sample, with a darker color indicating greater nicotine intake. If the participant has a positive urine cotinine test, they will be further counseled for smoking cessation if enrolled in the clinical trial. If not in the clinical trial, they will be provided with information from the American Lung Association and referred to the Maryland Quit Line. Results will be recorded and labeled with the participant's study ID, and the participant will see their results immediately and the results will be explained to them.

## **7. Study Statistics**

### **a. Primary outcome variable**

1. Smoking cessation rates at 1-month among participants using the COach2Quit application and participants only receiving anti-smoking advice.

### **b. Secondary outcome variables**

1. Intermediate variables assessed at the end of treatment including; (1) Urges to smoke; (2) Withdrawal symptoms; (3) Reinforcing Smoking Decisional Balance; (4) Smoking Abstinence Self-Efficacy; and, (5) Satisfaction with the program among all participants

### **c. Statistical plan including sample size justification and interim data analysis.**

#### **Data analysis plan**

**Overview** The primary outcome measure for the RCT is proportion of participants with biochemically verified smoking cessation as of 1-month; the primary exposure is study arm, brief-advice only vs. COach2Quit. We will compare proportions of smoking abstinence between study arms at 1-month.

Covariates of interest (e.g. sex, age, race, ethnicity, education, income, smoking history) will be assessed for relationship to prevalence of quitting. These comparisons will utilize the chi-square test for categorical variables and either the Student's t-test or the Wilcoxon signed rank test for continuous variables. Multivariate logistic models will be generated using forwards stepwise model selection, including study arm and all variables with  $p < 0.2$  or odds ratio  $< 0.5$  or  $> 2.0$  at the univariate level, ultimately generating the most parsimonious model.

We will conduct intent-to-treat analyses, providing the purest analysis for an RCT. For these analyses, participants who are lost to follow-up will be considered smokers from the date of last contact. This approach is conservative, as it will likely include participants who have not received either study intervention, but point estimates will be biased towards the null. This approach has been widely adopted in smoking cessation studies. We will compare rates of losses to follow up across the study arms, and look for differences in characteristics of those lost between the arms.

We will analyze number of smoke-free days obtained from questionnaires by comparing the proportions of smoke-free days between arms with a Wilcoxon signed rank test. We will estimate either the absolute difference in proportions, or after a  $\log(\text{days smoke-free}+1/\text{total days of follow up})$  transform if appropriate, with 95% confidence intervals. We will also measure durability of treatment effects using consecutive visits with biochemically verified smoking cessation.

### **Sample Size**

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This is a pilot RCT, thus our sample size is not powered to find significant differences between arms, but will provide estimates for future larger studies. We anticipate cessation rates of 20% in the COach2Quit arm and 10% in the brief-advice only arm at 1-month. We will enroll 150 participants into the study over 4 months, randomized 1:1.

#### **Interim analysis**

Due to the short duration of follow-up in this study, no interim analyses will be conducted.

#### **d. Early stopping rules.**

Due to the short duration of follow-up in this study, there will not be any early stopping rules.

#### **8. Risks**

##### **a. Medical risks, listing all procedures, their major and minor risks and expected frequency.**

Participation in this trial poses **minimal risk** to the participant's health.

There are no known medical contraindications for use of the exhaled breath CO machines for healthy individuals. These criteria are consistent with our previous research and have posed no undue risk or adverse events to participants.

Study procedures are anticipated to be associated with **minimal medical risk**, but if a participant develops any side effects, they will be referred for immediate care. A safety protocol will be written and closely adhered to for participants who experience serious adverse events.

Although privacy and confidentiality will be ensured throughout all study procedures, some questions may make the participant uncomfortable, such as questions about personal tobacco use or education. Should any breach in confidentiality occur, details of the breach will be fully investigated and documented and reported to the Johns Hopkins University IRB within seven days.

##### **b. Steps taken to minimize the risks.**

Risks to confidentiality will be minimized by the following procedures: participant interviews will be conducted in a private area of the clinic, study records will be stored in locked cabinets in secure locations, study records will be accessible only to authorized study staff, databases will be password-protected and accessible only to authorized study staff. Study records and databases will not be accessible by employers, and study participation will not affect employment status. All study personnel will complete a course in research subjects' protection. Protected Health Information (PHI) that will be collected from participants are name, age, and phone number. All PHI will be stored on paper, not electronically, in a locked cabinet in a secure location, and PHI will only be accessible to authorized study staff. **No PHI will be collected or stored online or within the smartphone application.** All participants will receive a unique user ID that will be used in the smartphone application. This ID will be linked to their PHI that will be recorded on paper and stored securely. The PHI will be owned by the Principal Investigator, Jonathan Golub, at JHU.

A detailed protocol will be established for all research staff to be trained to identify an Adverse Event (AE) or Serious Adverse Event (SAE) and to follow in the event of an AE or SAE. The research staff person identifying an AE or SAE will immediately report the event to Dr. Golub. The study staff will discuss the situation with Dr. Golub, and submit the appropriate paperwork to the IRB within 24 hours of becoming aware of the event. These events will also be documented during the IRB's yearly continuation review of the project.

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This study will use the NIDA's Common Adverse Events (AEs) and Serious Adverse Events (SAEs) definitions for clinical research. Adverse events are defined as any event or outcome that has resulted in harm to the participant, has affected the participant detrimentally, has worsened as a result of participation in the study, or that has resulted in increased risk to the participant or others whether or not the risk actually results in harm. Specific SAEs include:

- death;
- serious injury;
- a life-threatening experience;
- hospitalization;
- a persistent or significant disability or capacity;
- suicidal ideation/attempts;

In addition, all reactions to the study device that are not considered an SAE will be documented as an AE. The PI will be available by phone for any study issues.

Any AE that occurs between the time a participant signs the informed consent form and the time he or she departs the study at the end of the final follow-up visit will be captured and recorded. In the event that the participant is withdrawn from the study due to an AE, it will be recorded on the case report forms as such. The participant will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the SAE is either resolved, or that it has reached a stable state, after which no further follow-up is necessary. There will be documentation to support that determination.

Once an AE or SAE is known, research team members at the study site should ensure that participants receive appropriate care. All actions taken by the study staff after observing an AE or SAE should be documented, including increased monitoring of the participant, suspension of the treatment, etc.

**c. Plan for reporting unanticipated problems or study deviations.**

Should any breach in confidentiality occur, details of the breach will be fully investigated and documents and reported to the Johns Hopkins University IRB within seven days. The PI, Jonathan Golub, will have primary responsibility for monitoring and oversight of problem/events for this research, including adverse events as well as breaches to confidentiality. The study coordinator will be responsible for immediately reporting any such events or breaches to the PI, and the PI will provide continuous oversight to identify incidents and appropriate address them if they are to occur.

**d. Legal risks such as the risks that would be associated with breach of confidentiality.**

There are no anticipated legal risks other than breaches of confidentiality. All study participants will provide written informed consent stating that we will minimize risk of breaching confidentiality by minimizing the following procedures: study records will be stored in locked cabinets in secure locations, study records will be accessible only to authorized study staff, databases will be password-protected and accessible only to authorized study staff. Study records and databases will not be accessible by employers, and study participation will not affect employment status.

**e. Financial risks to the participants.**

There are no anticipated financial risks to the participants for participating in the study.

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## **9. Benefits**

### **a. Description of the probable benefits for the participant and for society.**

The proposed research will have direct benefit to individual study subjects, as they will be offered methods for aiding smoking cessation, which has been shown to prolong life. The proposed research has potential benefits to the broader community, since the research will help to determine the effectiveness of COach2Quit and our results will help design smoking cessation programs in the future. A better knowledge of these issues is anticipated to inform public health and individual health activities to better educate smokers on effective methods for smoking cessation.

## **10. Payment and Remuneration**

### **a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.**

Participants will receive gift vouchers worth \$25 for each of their first 2 study visits and a \$50 gift voucher for their final visit, for a total of \$100. This covers compensation for their time as well as reimbursement for transportation, text message or data plan expenses and any other expenses they incur.

## **11. Costs**

### **Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.**

Study participants will not be asked to pay for any drugs or procedures as part of the study.

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