CARBON MONOXIDE BREATH SENSOR SYSTEM (COBSS) PERFORMANCE, HUMAN FACTORS, AND USABILITY STUDY PROTOCOL [redacted]

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CARBON MONOXIDE BREATH SENSOR SYSTEM (COBSS)
PERFORMANCE, HUMAN FACTORS, AND USABILITY STUDY PROTOCOL

Device Names	1) Carbon Monoxide Breath Sensor System (COBSS) 2) Bedfont Scientific Ltd. Micro+ Smokerlyzer
Protocol Title	Carbon Monoxide Breath Sensor System (COBSS) Performance, Human Factors, and Usability Study Protocol ([redacted])
Principal Investigators	[redacted]
Protocol Number	[redacted]
Protocol Version	[redacted]
Protocol Shorten Name	Performance, Human Factors, and Usability Study Protocol
Study Design	Prospective, open label, single center clinical study enrolling 70 subjects. No medical decisions will be made related to test results.
Objective	Performance: • Non-invasively measure carbon monoxide (CO) levels in the exhaled breath of study subjects using two different types of measurement devices. • We will assess the correlation between the measured CO levels (in parts per million, or ppm) of the study CO breath sensor (Carrot Sense) and the predicate CO breath sensor (Bedfont). Human Factors and Usability: • Ensure that representative intended users are able to operate the COBSS independently. • Validate appropriate mitigations of use related hazards identified in risk management documentation. • Uncover previously unforeseen use errors.
Potential Subjects	70 subjects who self-report smoking 2 or more cigarettes each day.
Inclusion Criteria	18-80 years of age English speaking Owns and uses a smartphone Willing to sign the Informed Consent Form
Exclusion Criteria	Pregnancy
Recruitment	Eligible subjects will be identified via clinical research recruiter and advertisement at outdoor locations (i.e. flea markets, outside of movie theaters, shopping malls, train stations, stores that sell cigarettes), print media (i.e., local newspapers, billboards), and web media (i.e., Craigslist, Facebook).
Study Session	Single day study collecting 1 paired breath sample from each subject using two non-invasive breath sampling devices (COBSS and Bedfont; Performance), as

	well as conducting user tasks, user documentation assessment, subjective feedback and rating scales (Human Factors and Usability).
Performance Variable	CO concentrations in parts per million (ppm) in exhaled breath from subjects.
Performance Endpoint and Analysis	CO concentrations from each sensor type will be plotted for comparison.
Human Factors and Usability	Assessment of intended user performance in use scenarios, user documentation assessment, subjective feedback and rating scales.

Contents

1.0 LIST OF ABBREVIATIONS

CO	Carbon Monoxide
COBSS	Carbon Monoxide Breath Sensor System
CRF	Case Report Form
BSA	Breath Sensor Application
USB	Universal Serial Bus
IRB	Institutional Review Board
ICF	Informed Consent Form
HCP	Health Care Provider
ppm	parts per million

2.0 INTRODUCTION

2.1 BACKGROUND

The smoking of tobacco products is a leading cause of preventable morbidity and mortality, excess health care expenditure, and lost work productivity. [redacted]

[redacted] We have developed the Carbon Monoxide Breath Sensor System (COBSS, Carrot Sense, Redwood City, CA, USA), which consists of a handheld breath sensor to measure CO in exhaled breath, with results displayed in a smartphone app. COBSS is intended to be used as a personal and mobile product and available 'over the counter'. This study will compare the performance of the COBSS to that of a clinic-based CO breath sensor (Micro+Smokelyzer; Bedfont; Kent, UK) in the measurement of CO in exhaled breath, and, will assess the human factors and usability of the COBSS.

2.2 STUDY RATIONALE

Performance: We aim to non-invasively measure carbon monoxide (CO) levels in the exhaled breath of study subjects using two different types of measurement devices. We will assess the correlation between the measured CO levels (in ppm) of the study CO breath sensor (COBSS; Carrot Sense) completed by a lay user with no personal instruction (using labeling only) and the predicate CO breath sensor (Micro+Smokelyzer; Bedfont) administered by a person trained to instruct users on submitting a sample with the device.

Human Factors and Usability: We aim to assess whether an untrained lay user group (representative of intended users) can operate the device and interpret the results correctly using only the instructions that will be provided with the marketed device.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

There are no anticipated risks or harms to the subject. No medical decisions are made based on study data.

2.3.2 Known Potential Benefits

While we do not anticipate that subjects will receive any benefit from their participation in this study, it is possible that some subjects may experience an increased awareness of their smoking behavior.

2.3.3 Risk Benefit Assessment

Given the non-invasive nature of the breath sampling and the data collection, there are no anticipated risks to subject safety. Study staff will be with subjects and monitoring their use of the study devices for the duration of the study. Subjects are not asked to change their smoking behavior or lack thereof. No medical decisions are made based on study data.

3.0 OBJECTIVES

3.1 PERFORMANCE

We aim to non-invasively measure carbon monoxide (CO) levels in the exhaled breath of study subjects using two different types of measurement devices. We will assess the correlation between the measured CO levels (in ppm) of the study CO breath sensor (COBSS, Carrot Sense) and the predicate CO breath sensor (EC50 Micro^{+}™ Smokerlyzer® – Bedfont (K082315)).

3.2 HUMAN FACTORS AND USABILITY

The objectives of the human factors and usability portion of the study are to:

- Ensure that representative intended users are able to operate the COBSS independently, focusing on the following:
  - Proper breath sample collection using the CO Breath Sensor by a user
  - User comprehension of how to navigate the Breath Sensor Application (BSA)
  - User interpretation and comprehension of their results
- Validate appropriate mitigations of use related hazards identified in risk management documentation
- Uncover previously unforeseen use errors

Overall, this human factors and usability validation testing is conducted to demonstrate that the COBSS can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions.

4.0 REFERENCES

- FDA Guidance Document Entitled, "Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Medical Devices," issued on February 3, 2016
- FDA Guidance Document Entitled, "Design Considerations for Devices Intended for Home Use, Guidance for Industry and Food and Drug Administration Staff" issued on November 24, 2014
- ISO/IEC 62366-1:2015, Medical devices – Application of usability engineering to medical devices. Geneva, International Electro technical Commission.
- AAMI/ANSI HE75:2009, Human Factors Engineering – Design of Medical Devices.
- https://www.bluetooth.com/what-is-bluetooth-technology/bluetooth-technology-basics

5.0 DEFINITIONS

Bluetooth Low Energy (BLE): a global wireless communication standard that connects devices together over a certain distance.

Breath Sensor Application (BSA): The smart phone application ("app") that is part of the subject system. The BSA displays exhaled breath carbon monoxide value to the user. The BSA is paired

to the CO Breath Sensor via Bluetooth Low Energy.

Carbon Monoxide Breath Sensor System (COBSS): the name of the subject system. This system comprises the CO Breath Sensor and the Breath Sensor Application (BSA), and is intended for single-user use in smoking cessation programs as an educational and motivational tool showing how breath carbon monoxide levels are affected by smoking behavior.

Close Call (a.k.a. "Near-Miss"): Instances in which a user has difficulty or makes a use error that could result in harm, but the user takes an action to "recover" and prevents the harm from occurring (FDA Guidance 2016).

CO Breath Sensor: a component of the subject system. It is a personal mobile breath sensor that is capable of measuring the level of carbon monoxide (CO) in exhaled breath. The CO Breath Sensor is a portable, battery-powered, rechargeable device slightly smaller than the palm of one's hand. This device pairs to the Breath Sensor Application (BSA) on a smartphone via Bluetooth Low Energy. The user submits a breath sample by exhaling (blowing) into the personal mobile breath sensor via a provided straw.

Critical Task: A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient, user, or instrument, where harm is defined to include compromised medical care.

Guided Breath Test (GBT): a function in the BSA wherein the BSA prompts the user through the steps of submitting a breath test. Based on the user's adherence to the proper technique, the user is provided with a pass or fail. They may repeat this GBT as often as they like if additional education and reinforcement of the technique is desired.

Objective Data: Data collected through direct observation.

Subjective Data: Data collected through user feedback via comments, ratings, and assessments provided by participants.

Task: Action or set of actions performed by a user to achieve a specific goal.

Use Error: User action or lack of action that was different from that expected by the manufacturer and caused a result that (1) was different from the result expected by the user and (2) was not caused solely by device failure and (3) did or could result in harm. (Section 3.9, FDA Guidance 2016).

User: Person who interacts with (i.e., operates or handles) the COBSS.

6.0 DEVICE DESCRIPTION

6.1 CARBON MONOXIDE BREATH SENSOR SYSTEM (COBSS)

The Carbon Monoxide (CO) Breath Sensor System (COBSS) comprises a personal mobile breath sensor (CO Breath Sensor) capable of measuring the level of CO in exhaled breath and a Breath Sensor App (BSA) for smartphones which displays the exhaled breath CO value to the user. The BSA is compatible with iOS based devices (iPhone 5 and above, operating system iOS 9.0 and above) and Android based devices that support Bluetooth Low Energy (Android 4.4 and above,

operating system Android 4.4 and above). Carrot Sense intends to market COBSS as a single-user over-the-counter (OTC) device indicated for use by smokers in smoking cessation programs as an educational and motivational tool showing how breath carbon monoxide levels are affected by smoking behavior.

6.1.1 Intended Use

The Carbon Monoxide Breath Sensor System (COBSS) is a breath carbon monoxide monitor intended for single-user use by smokers in smoking cessation programs as an educational and motivational tool showing how breath carbon monoxide levels are affected by smoking behavior.

6.2 MICRO+™ SMOKERLYZER®, PREDICATE DEVICE

The Micro+™ Smokerlyzer® (Bedfont Scientific Ltd; Harrietsham, UK; 510K number: K082315) is an FDA-cleared hand-held, battery powered instrument which uses electrochemical technology to sample the gas and a microprocessor to convert the output from the sensor to a carbon monoxide (CO) concentration. The result and menus are displayed on a color LCD and an accompanying buzzer sounds in response to the CO level. The instrument is controlled using a touch screen operation. The range of CO measurement is 0-500 ppm

6.2.1 Indications for Use

The Micro+™ Smokerlyzer® is a Breath Carbon Monoxide Monitor intended for multi-patient use by healthcare professionals in smoking cessation programs and as an indicator of Carbon Monoxide poisoning in healthcare environments.

7.0 CARBON MONOXIDE BREATH SENSOR SYSTEM (COBSS)

7.1 LABELING AND PACKAGING

The CO Breath Sensor package includes:

- CO Breath Sensor with straw inserted
- 7 straws in a bag
- Micro USB charging cable
- User Manual [redacted]
- Quick Start Guide [redacted]
- Reference Card [redacted]

The CO Breath Sensor packaging [redacted] The text to be included on the package exterior is finalized however the final design of the package (text colors, font, etc.) is in progress. The packaging used in the study will be the final designs.

Additional labeling includes the Guided Breath Test [redacted] and video tutorial [redacted] which are part of the BSA.

7.2 CO BREATH SENSOR

The CO Breath Sensor (Figure 1) is portable, battery-powered, and small enough to be conveniently carried by the user throughout the day (pocket, purse, backpack). The CO Breath Sensor is rechargeable using a micro-USB cable. The LED pulses orange while charging and then solid green when fully charged.

The CO Breath Sensor pairs to the BSA on the smartphone via low-energy Bluetooth. The user submits a breath sample by exhaling (blowing) into the CO Breath Sensor via a straw. The CO Breath Sensor comes packaged with a straw already inserted in the inlet. The straw, made of polypropylene, is reusable, and can be cleaned with soap and water or replaced as necessary. In addition, there is a pack of 7 straws (for 8 straws in total) included in the CO Breath Sensor package.

7.3 BREATH SENSOR APPLICATION (PAIRING)

The BSA, Quick Start Guide and User Manual guide the first-time user through the process of pairing their smartphone to the CO Breath Sensor. Once paired, the CO Breath Sensor communicates exclusively with the user's phone and is invisible to other smartphones and other Bluetooth Low Energy wireless devices.

7.4 BREATH SENSOR APPLICATION (GETTING STARTED)

After pairing, the BSA displays a Getting Started screen containing a brief video tutorial [redacted] on how to submit a breath sample. This video depicts the user steps to submit a breath sample, as described in the User Manual. The BSA software automatically advances to and requires the user to complete the video tutorial after pairing. The video tutorial must be completed to advance further in the set-up and use of the BSA (system requirement). The video tutorial can be paused and played again. It is also accessible to the user at any time through the Settings screen in the BSA.

Next, a Guided Breath Test (GBT) function is used by the user wherein the BSA prompts the user through the steps of submitting a breath test (interactive version of the user steps disclosed in the User Manual). Based on the user's adherence to the proper technique, the GBT provides the user with a pass or fail. Pass or fail status is communicated to the user by the CO Breath Sensor LED (flashing green indicates pass and flashing red indicates fail), as well as the screen on the BSA, which includes a smiley face, flashing green dot and descriptive text for pass, or, a sad face, flashing red dot and descriptive text for fail [redacted] The BSA software requires the user to complete three GBTs before advancing further in the set-up and use of the BSA.

The user may repeat the GBT as often as they like if additional education and reinforcement of the technique is desired. The GBT is also accessible to the user at any time through the device button in the upper left corner of the CO Log screen in the BSA.

7.5 SUBMITTING A BREATH SAMPLE (SPECIFIC STEPS)

Submitting a breath sample involves the following steps (instructions provided in the User

Manual, Reference Card, video tutorial, Guided Breath Test and Quick Start Guide).

1. If not already in place, user places provided straw in the CO Breath Sensor inlet
2. User presses and holds (~2 seconds) the (only) button on the CO Breath Sensor until the device beeps once and the LED flashes blue
3. User takes a deep breath in and holds their breath
4. After about 10 seconds, the device beeps 3 times and the flashing blue LED converts to solid blue LED
5. The user then gently blows into the straw for at least 6 seconds (goal is 12 seconds) or until they exhaust their entire breath (Figure 2)
6. The user then removes straw from their lips
7. After a few seconds, the solid blue LED switches to:

    a. Blinking green LED indicates adequate breath sample, data stored, or,
    b. Blinking red LED indicates inadequate breath sample, please repeat

A properly submitted breath sample is defined, by the system, as one that initiates after the third beep prompt and is of at least 6 seconds duration. Breath sensor hardware and firmware is capable of detecting when a breath sample submission starts and stops.

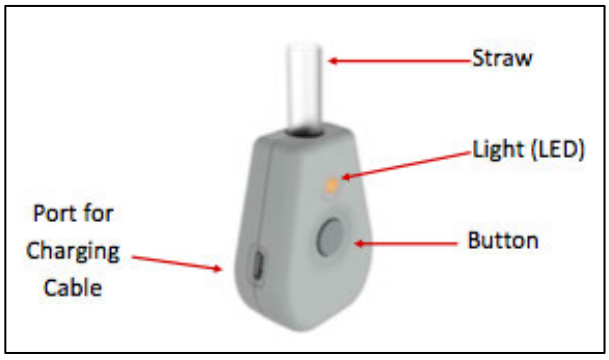


Figure 1. CO Breath Sensor

Figure 2. Submitting a Breath Sample

A properly submitted breath sample is indicated to the user through the CO Breath Sensor, with the LED flashing green for a proper submission and red for an improper submission. In addition, the CO Log screen in the BSA provides the CO (ppm) value for properly submitted breath samples, and provides a descriptive error message for improperly submitted breath samples (i.e. "Error: breath sample too late").

The computation of concentration of CO (ppm) is performed within the CO Breath Sensor firmware and the data (CO ppm concentration, time and date) are stored in the CO Breath Sensor memory. The measured values are transmitted via Bluetooth to the smartphone (when paired, in-range, and after synchronization) and are displayed on the primary screen of the Breath Sensor Application (CO Log) (Figure 3). The data is stored locally on the smartphone.

7.6 BREATH SENSOR APPLICATION (CO LOG)

The primary screen for the CO Breath Sensor is the CO Log screen in the Breath Sensor Application. In the CO Log, the most recent exhaled breath CO value in ppm is displayed at the top of the screen. The user can view previous values by scrolling within the log.

Values are color coded to align with the predicate device and scientific literature.

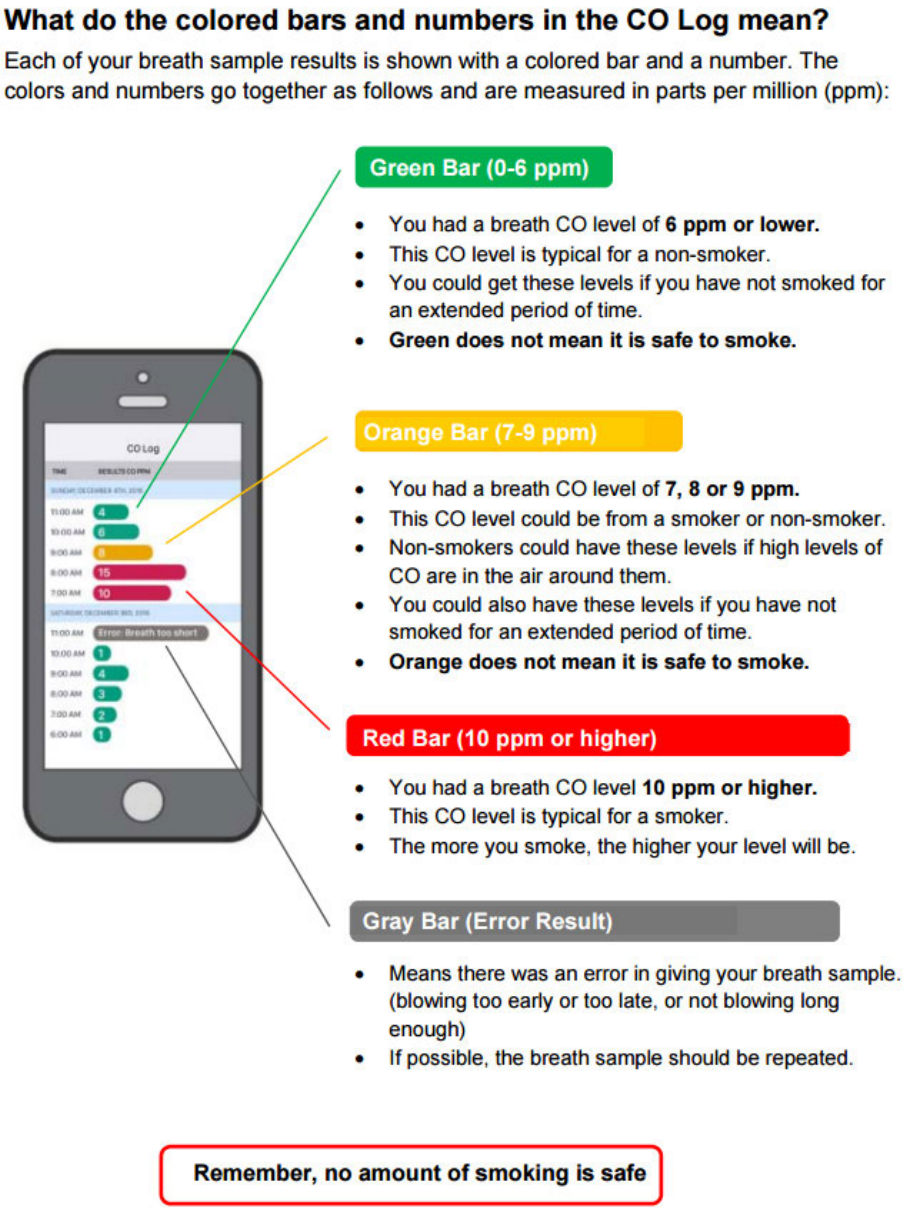


Figure 3. – Color coded bars according to CO breath levels (from User Manual)

Furthermore, the length of the bar is associated with the ppm value to graphically show the user

their relative levels of exhaled breath CO throughout the day and between days.

Maximum bar width = 50 ppm

Values above 50 ppm are annotated with a white arrow.

7.7 BREATH SENSOR APPLICATION (SYNCING WITH CO BREATH SENSOR)

Breath sample CO values, date and time are stored on the CO Breath Sensor until a sync occurs with the Breath Sensor App (BSA). Syncing occurs automatically when the app is open in the foreground or background. When a user submits a breath sample on the CO Breath Sensor, they will be able to view the results in the CO Log within one minute. If the most recent values are not in the CO Log, the time of last sync can be viewed in Settings and a manual sync can be performed in Utilities.

7.8 BREATH SENSOR APPLICATION (CO BREATH SENSOR SETTINGS)

In the BSA, when the user navigates to the Settings page by tapping on the gear icon in the upper right corner, the user sees device status (connected, not connected, syncing), last sync, and battery status.

A user may choose to use the Reminders function to help them remember to submit breath samples throughout their day. When reminders are toggled from off to on, the user may choose the time of the first and last reminder of the day, reminder time interval, type of reminder (vibration and/or beep), and the intensity (volume) of the reminder where applicable. Additionally, the user may set the volume of the breath test beeps described in the User Manual.

A utilities menu includes options to manually synchronize the CO Breath Sensor with the smartphone (in the event that auto sync is not working), ring the CO Breath Sensor (if misplaced), and forget the sensor (unpair).

Settings also provides access to the video tutorial on how to submit a breath sample, for those users who wish to obtain additional reinforcement and learning regarding breath sample submission.

7.9 BREATH SENSOR APPLICATION (GUIDED BREATH TEST, OR GBT)

In the BSA, the user may access the Guided Breath Test at any time using the device icon in the upper left corner. After completing device set-up and training (required 3 GBTs), the user may use the GBT for any and all subsequent breath samples.

8.0 TASK ANALYSIS AND IDENTIFICATION OF CRITICAL TASKS

For the human factors and usability portion of the study, a task analysis was performed to identify the tasks associated with the use of the COBSS. The task analysis is depicted in Figure 4.

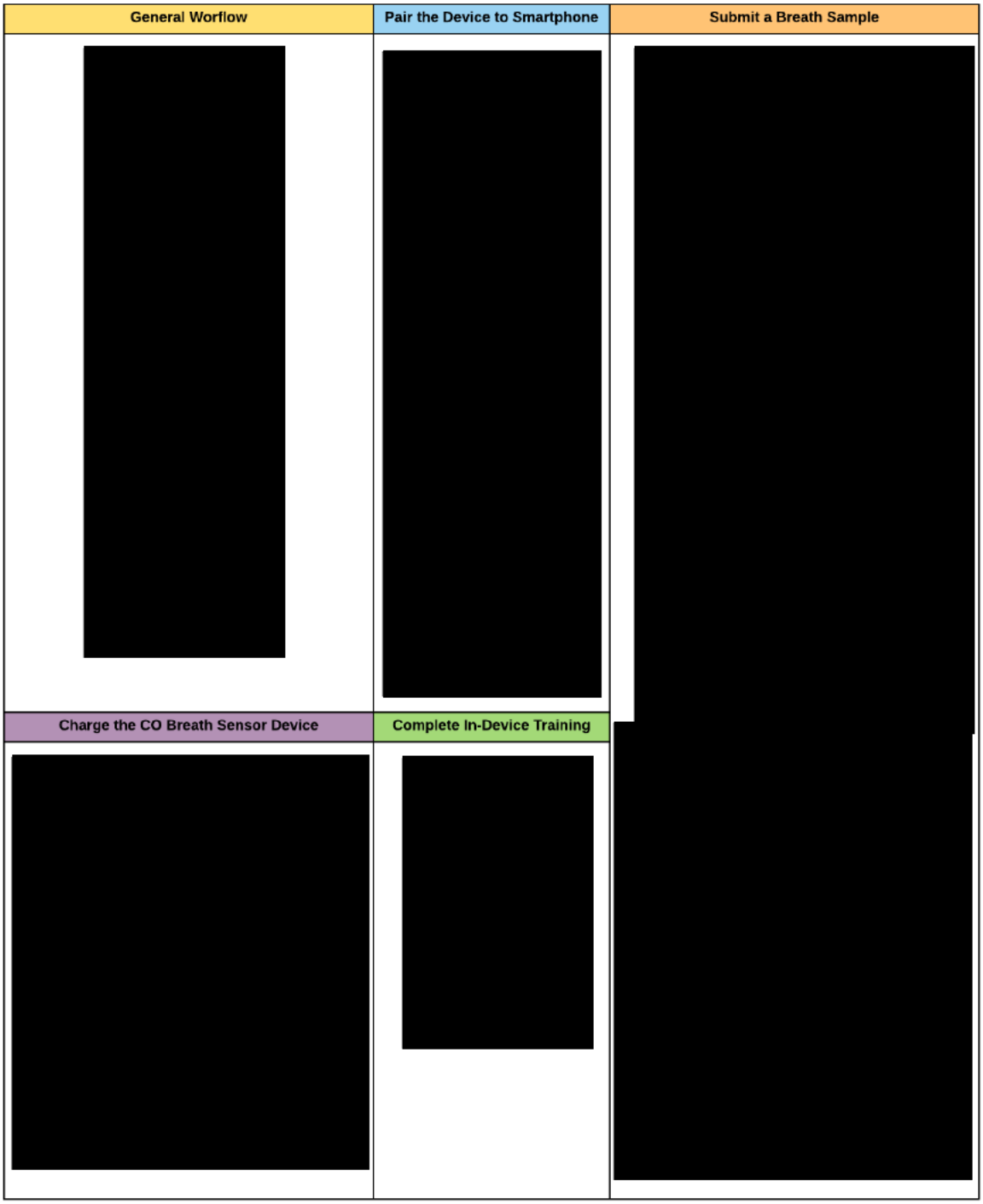


Figure 4. Task Analysis of Carbon Monoxide Breath Sensor System (COBSS)

As part of the product development process, a comprehensive use related failure mode and effect analysis (Use FMEA) was performed to identify and analyze the potential use-related failure modes (i.e., use errors) that might occur when the intended users interact with the CO Breath Sensor System.

The task analysis and the COBSS Use FMEA ([redacted]) were assessed for critical tasks. Based on the definition of a critical task provided in FDA "Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Medical Devices," issued on February 3, 2016 ("A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care"), it was identified that the COBSS does not have use related tasks that may result in serious harm or compromised medical care if the device is not operated properly by the user. [redacted] Carrot Sense chose to perform usability testing to assess user tasks and comprehension items that are essential to the effective operation of the device and user interpretation of breath sample results, and, to monitor for unforeseen use errors that could lead to serious harm.

Table 1. List of "Severity 2" Tasks

User Tasks and Comprehension Items	Severity
[redacted]	

9.0 STUDY DESIGN AND OVERVIEW

9.1 STUDY DESIGN

This is a prospective open-label clinical trial conducted with IRB approval in 70 subjects who report daily smoking at our research center in Redwood City or an equivalent location. Eligible subjects will be identified by a clinical research recruiter and via advertisement at outdoor locations (i.e. flea markets, outside of movie theaters, shopping malls, train stations, stores that sell cigarettes), print media (i.e., local newspapers, billboards), and web media (i.e., Craigslist, Facebook). Recruitment materials are reviewed by the IRB [redacted], along with the Informed Consent [redacted] Subject Stipend Schedule [redacted] Subject Stipend Form [redacted] and prompts used during the human factors and usability portion of the study [redacted] Eligible subjects who sign the informed consent form and participate will receive a nominal stipend. Subjects will have their exhaled breath non-invasively sampled for CO levels using two different CO breath sensors.

9.2 STUDY ENDPOINTS

9.2.1 Human Factors

Assessment of intended user performance in use scenarios, user documentation assessment, subjective feedback and rating scales.

9.2.2 Performance

Comparison of paired breath sample values from the study and predicate devices.

9.3 ELIGIBILITY CRITERIA

The intended user population for the CO Breath Sensor System are lay users who are smokers, ages 18 and above, capable of using a smartphone to track/monitor health-related data. The intended users range in age, degree of smoking, mental and physical capabilities, health literacy, experience using other CO analyzers or home use medical devices, and experience using smartphones.

The user population may be further classified into two age-based subgroups, 18-49yr and the 50-80yr age groups. The 18-49yr olds, in general, are believed to be more tech savvy and have better physical capabilities compared to the 50-80yr olds.

Study participants will consist of individuals who represent the intended COBSS user profile, current smokers. Participant inclusion criteria include all of the following:

- 18+ years of age
- Current daily cigarette smokers (at least 2 cigarettes per day with target distribution of individuals who smoke: 2-5 cigarettes per day, 6-10 cigarettes per day, 11-15 cigarettes per day and 16+ cigarettes per day)
- Resident of the United States
- Able to read and comprehend English
- Target a mix of male and female participants
- Target 35 participants in each of the two subgroups, the 18-49yr and the 50-80yr age groups, with at least 15 individuals in each group
- Currently own and use an Apple, Inc. iPhone iOS smartphone or an Android smartphone for at least one month (such that they are familiar with basic operations of the mobile platform)
- Willing to sign the Informed Consent Form

Exclusion Criteria

- Prior experience using the COBSS
- Not interested in quitting smoking
- Pregnancy

Study participants will be recruited in the United States. Each potential participant will be asked a standard series of questions to confirm study eligibility and to capture demographic data. Eligible participants who meet the inclusion/exclusion criteria will be entered into the study. An

Informed Consent Form [redacted] will be signed prior to participation.

9.4 SAMPLE SIZE AND JUSTIFICATION

This study will include 70 subjects. This sample size is expected to provide adequate data to compare CO measurements between the devices. Sample size needed was determined as described below.

Data from a formative study was used to develop the statistical methodology for the present study. We conducted a feasibility study titled [redacted], with approval by the Institutional Review Board [redacted] The study was conducted with signed informed consent. [redacted]

Figure 5. Plot of paired CO (ppm) levels for Carrot Sense (CS) vs. Bedfont (Predicate)

We performed power calculations based on the null hypothesis that the Pearson correlation coefficient of Predicate and CS was [redacted] and the alternative hypothesis that it was greater than [redacted]. Assuming a true Pearson correlation of [redacted] if we collect [redacted] samples from predicate and study devices, we will have [redacted] power to reach statistical significance assuming a 0.05 alpha level (red circle on graph, Figure 6). Further, assuming a true Pearson correlation of [redacted] if we collect [redacted] samples from predicate and study devices, we will have [redacted] power to reach statistical significance assuming a [redacted] alpha level (orange circle on graph, Figure 6). Based on this formative data analysis, our validation study will include 70 subjects (70 subjects who report daily smoking).

Figure 6. Sample Size power calculation scenarios

In a secondary analysis of this pilot data, [redacted] This resulted in no change to our power calculation to follow.

9.5 PERFORMANCE STUDY ENDPOINT ACCEPTANCE CRITERIA

Based on the null hypothesis that the Pearson correlation coefficient of Bedfont and CS [redacted] passing criterion is refuting the null hypothesis (confirming the alternative hypothesis) with a power of [redacted] or higher assuming a [redacted] alpha level.

9.6 STUDY ARTICLES

- Carbon Monoxide Breath Sensor System (COBSS) in representative packaging that includes:
    - CO Breath Sensor
    - Micro-USB charger
    - Pack of 7 straws for use with the CO Breath Sensor
    - User Manual [redacted]
    - Quick Start Guide [redacted]
    - Reference Card [redacted]
- The BSA, installed on an Apple, Inc. iOS and an Android smartphone
- Predicate device (Micro^{+}™ Smokerlyzer®, Bedfont Scientific Ltd; Harrietsham, UK; 510K number: K082315]

In addition, the testing room will be equipped with electrical outlets and a charging cube.

9.7 EQUIPMENT AND MATERIALS

- Apple, Inc. iPhone with the BSA installed on it
- An Android smartphone with the BSA installed on it
- CO Log Print Out
- Printed prompt cards for the participant to reference during each task
- Hydrogen breath sensor (Gastro+ Gastrolyzer ®, Bedfont Scientific Ltd.)
- Timer or clock
- Video recording equipment
- Camera
- Post-it notes
- Quick Start Guide for Observer/ Moderator
- User Manual for Observer/ Moderator
- Reference Card for Observer/Moderator

A full list of equipment and materials used during the study will be recorded in the report.

9.8 USER MANUAL AND TRAINING

The COBSS was designed to be as intuitive as possible, such that users are able to understand how to use the product on their own. No in-person training is formally offered to COBSS users. However, the User Manual, Quick Start Guide and Reference Card are included with the purchase of the device. Additionally, users are required by the COBSS software design to complete the COBSS video tutorial and 3 Guided Breath Tests. The video tutorial and Guided Breath Test provide in-app user training and reinforce the procedure of submitting a CO breath sample using the device.

Since in-person training will not be formally offered to all users who purchase the COBSS, in-person training will not be included in this study. Study participants will have access to the User Manual, Quick Start Guide and Reference Card in the device package, as will be the case for the marketed product. Any instance of participants referring to the User Manual, Quick Start Guide or Reference Card during the study will be recorded.

Additionally, the video tutorial and Guided Breath Test, offered by the COBSS user interface, as part of BSA start up, will help participants familiarize themselves with the device and understand how to use it. The BSA software requires completion of both the video tutorial and 3 Guided Breath Tests to advance through the COBSS set-up and start using the device.

During the usability validation, the participants will have the User Manual, Quick Start Guide, Reference Card, video tutorial and Guided Breath Test available to them at any point during the study. This mimics real-world use. However, they will not be asked to read instructions (except during the knowledge questions covered in the User Documentation Assessment – see Section 11.2) or use any of the forms of training available. At the beginning of the study, participants will have the opportunity to familiarize themselves with the product and instructions.

9.9 TEST ENVIRONMENT DESCRIPTION

9.9.1 Intended Use Environment

The COBSS has been designed as an over-the-counter device. The intended use environment is primarily the user's home, work, school, or similar environment.

The home environment can be characterized as a familiar environment with relatively dim (~150 lux) to relatively bright (~1000 lux) lighting; low to medium noise, medium level of activities, and some distraction (family, TV, radio).

- The work/school environment can be characterized as a familiar environment with low to medium noise, well illuminated, low level of activity, low level of traffic, and limited people interaction.

The user submits breath samples at their discretion, and will be able to factor environmental conditions (such as noise, light) into the decision of when to use the CO Breath Sensor.

9.9.2 Test Environment

The conditions under which simulated use testing is to be conducted will be sufficiently realistic to the expected use environment to enable the results of the testing to be generalized to anticipate

actual use. Environmental factors believed to affect user performance, such as lighting, noise, and space constraints, will be simulated.

The study will be performed indoors to assess use in the anticipated most common use environment. The study will be conducted in a conference room or office space, representative of the intended use environment, where the user is able to complete the assessment.

9.9.3 Dates testing will be performed:

Testing dates are anticipated to be in [redacted] Actual testing dates will be recorded in the study report.

9.9.4 Location testing will be performed:

The location of testing will [redacted]. For example, space may be rented to be nearer to test subjects.

9.10 STUDY PERSONNEL

The following roles will be fulfilled by Carrot Sense employees and consultants during the study:

- Study Moderator – Responsible for moderating the study, delivering instructions (as needed) and ensuring that participants progress from one use scenario to the next, and asking questions to probe about observed use errors and close calls.
- Study Facilitator – Responsible for organizing the simulated environment, study articles, equipment, and required documentation (e.g. informed consent form, non-disclosure agreements).
- Study Observer(s) – Responsible for taking notes during the study sessions and documenting key events of the study as they occur.
- Technical Support – Responsible for troubleshooting system issues and recording bugs in the case there is a system issue during the study session.

Individuals fulfilling the roles will be recorded in the final Usability Validation Study Report.

9.11 IRB OVERSIGHT

This study will be conducted under IRB oversight.

10.0 STUDY PROCEDURE AND SCHEDULE

For an overview of study session flow, see Figure 7. At the beginning of the study session, each subject will have ample time to read the Informed Consent Form (ICF) and the opportunity to ask questions. The subject will sign the ICF before participating in this study. Once signing the ICF, the subject will be given a unique identifier to protect subject privacy. Subjects may choose to exit the study at any time. They are not required to complete the study if they choose to stop.

Study personnel will collect information about the patient including

- Age
- Gender
- Eye sight
- Ethnicity
- Prior experience with Carbon Monoxide breath sensors
- Desire to quit smoking
- Smartphone experience
- When did you start smoking, how old were you?
- Number of cigarettes typically smoked per day
- Smoking history in the past 24 hours
    - Number of cigarettes smoked
    - Time of last cigarette
    - Use of any combustible, inhaled tobacco product other than cigarettes (pipes, cigars, cigarillos, etc.), any electronic cigarette product (e-cigs, vape, vapor), and any other inhaled combustible material.

Subject will self-train on how to use the study device using only the available study CO breath sensor device labeling, including product packaging, User Manual, Quick Start Guide, Reference Card, a technical support line provided in User Manual, and Breath Sensor App resources (video tutorial, guided breath test (GBT), Settings). These labeling materials will all be included in the future marketed product. To mimic real-world use, these labeling materials will be available to study subject at any point during the study. However, the study subject will not be asked to read instructions or use any of the forms of training available. Since in-person training will not be formally offered to all users who purchase the study device, in-person training on the study device will not be included in this study. Study personnel will refrain from answering questions on how to use the study device during the study.

As part of the process of setting up and learning to use the study device, the device software requires the user to complete the video tutorial and the GBT (the latter must be successfully passed three times); this is the case for the marketed device and therefore will be the case in this study as well.

Once the study subject has completed the system-required set-up and self-training on the study device, they will be asked if they feel ready to proceed with submitting another breath sample (continuing to the paired breath samples). If a subject indicates they do not feel ready, they will be asked to do what they would normally do at home to prepare to use the product and to let the test administrator know when they are ready to submit another sample.

When the subject indicates readiness to provide a breath sample, he/she will be instructed to proceed to provide one breath sample using the study device. After providing this breath sample, the subject will be asked to interpret his/her breath sample result followed by the first set of subjective questions.

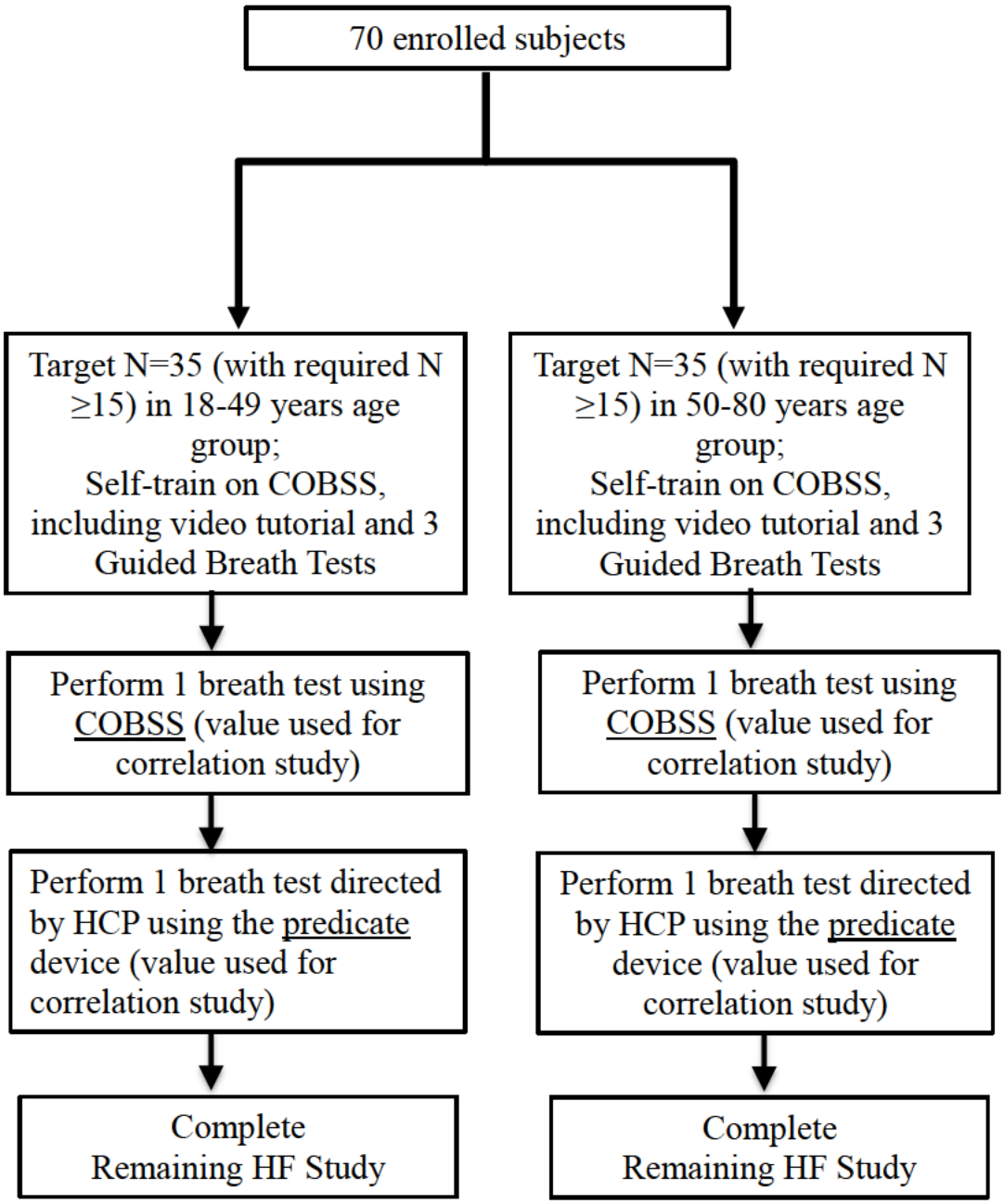
Within 3-5-minutes of the first breath sample and after completing the questions addressing interpretation of breath sample results and the 1st set of subjective questions, a health care professional (or test administrator) will guide subject through the submission of the second breath sample of the paired breath sample using the predicate device.

CO levels decrease gradually in the breath with time (half-life 4-5 hours), so it is not expected that the second sample in each paired sample will be substantially lower than the first sample.

A third breath sample to measure hydrogen (Gastro+ Gastrolyzer ®, Bedfont Scientific Ltd.) will be completed [redacted].

Upon completion of the paired breath sample and hydrogen breath sample, subjects complete the 2nd set of subjective questions and then do the user documentation assessment. During this time, ease of use and clarity of content are assessed for the product labeling, with focus on the User Manual. This is followed by rating scales.

Figure 7. Study session flow



11.0 TECHNICAL APPROACH AND STUDY DESIGN

Each study session will have the following format:

1. Introduction
2. Simulated Use
3. Performance Paired Breath Samples (performed during Use Scenarios; see section 11.1)
4. User Documentation Assessment
5. Subjective Feedback and Rating Scales

Following a brief introduction session, each participant will undergo a study session lasting about 90 minutes. The study session will comprise 8 individual use scenarios, comparative performance paired breath samples with the study device and predicate device, user documentation (User Manual, Quick Start Guide, and Reference Card) assessment, subjective feedback and rating scales. In addition to the subjective feedback obtained during the defined sections below, subjective feedback may be collected during the use scenarios and User Documentation assessment to inform root cause analysis.

The use scenarios included in the study consider inputs from risk management documentation (COBSS Use FMEA, [redacted] to test mitigations to device use (operation) related hazards. Each use scenario is expected to take up to 5 minutes (most will take 2-3 minutes). The use scenarios are listed in Table 2.

The study session will be conducted as a simulated use study where each participant will have access to the study article, a smartphone of their choice (Apple Inc. iPhone or Android smartphone), and will be monitored while performing the use scenarios. Each use scenario is monitored for difficulties, close calls and use errors. The use scenarios will allow for a detailed and focused assessment of the different components of the COBSS set-up and use.

Table 2 . Use Scenarios for Usability Validation

ID	Use Scenarios
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]

11.1 USE SCENARIOS

11.1.1 Use Scenario 1: Self-Selection

- Configuration:

The study moderator presents the participant with the Carbon Monoxide Breath Sensor device package.

- Prompt:

Take a moment to examine the package. Now I will ask you some questions about whether this product is appropriate for different types of people. (Note: [redacted]

1. [redacted]

2. [redacted]

3. [redacted]

11.1.2 Use Scenario 2: Start-up device and complete self-training

- Configuration:

The study moderator presents the participant with the Carbon Monoxide Breath Sensor device package and the smartphone of user's choice.

- Prompt:

Imagine you just bought this from the store. Given that you just bought this product, you can take as much time as you need to familiarize yourself with the product. Please start using the product when you are ready.

(If user does not begin using device after familiarization period) Please proceed with using the product.

- Tasks:
    - Open the Carbon Monoxide Breath Sensor packaging and remove contents
    - Open the installed BSA on the smartphone
    - Pair Breath Sensor with the smartphone
    - Complete [redacted] tutorial
    - Complete [redacted]
- Prompt:

How did that go for you?

11.1.3 Use Scenario 3: Interpret your results – Part 1

- Prompt:

Please walk me through your test results. What does each result mean?

➢ [redacted]

- Tasks:
    - Access the CO Log
    - Understand results from the breath tests

Note: This Use Scenario will be continued for interpreting results for Use Scenario 5. (See section 11.1.5 below.)

Expected Response:

For green value:

- [redacted]

  Or,

- [redacted]

  Or,

- [redacted]

For orange value:

- [redacted]

[redacted]

Or,

- [redacted]

Or,

- [redacted]

For red value:

- [redacted]

Or,

- [redacted]

Or,

- [redacted]

For grey bar (no value is provided in this instance):

- [redacted]

Or,

- [redacted]

Or,

- [redacted]

11.1.4 Use Scenario 4: Interpret more results

- Configuration:

The study moderator provides a CO log for the participant to interpret.

➢ Study moderator and/or observer to monitor participant [redacted].

- Prompt 1:

What does it mean if the result of a person's breath test looks like this? (Moderator points to a green, orange, red or gray result. An attempt will be made to evenly distribute the order the colors are presented across all groups by counterbalancing. Counterbalancing scheme will be provided in the final report. Moderator will only ask about results that were not previously

covered in Scenario 3)

Expected response: See 11.1.3 response

- Prompt 2:

What does it mean if the result of a person's breath test looks like this? (Moderator points to a green, orange, red or gray result, counterbalanced across participants. Moderator will only ask about results that were not previously covered in Scenario 3)

Expected response: See 11.1.3 response

- Prompt 3:

What does it mean if the result of a person's breath test looks like this? (Moderator points to a green, orange, red or gray result, counterbalanced across participants. Moderator will only ask about results that were not previously covered in Scenario 3) Note that Prompt 3 will be asked unless all result colors were previously covered.

Expected response: See 11.1.3 response

- Prompt 4:

[redacted]

- Prompt 5:

Are you ready to proceed with submitting another breath sample?

- Prompt 6 (if answer no to prompt above):

Do whatever you would normally do at home. Let me know when you are ready to submit the breath sample.

11.1.5 Use Scenario 5: Submit a breath sample with a new straw (this breath sample will be used as part of the paired breath sample for the Performance part of the study)

- Prompt:

Please use a new straw and submit a breath sample.

- Study moderator and/or observer to monitor for lightheadedness while providing a breath sample.
- Study moderator and/or observer to monitor and record the number of seconds of participant's breath hold starting from inhalation.

- Tasks:
    - Assemble the Carbon Monoxide Breath Sensor

- Submit a breath sample

- Study observer confirms breath sample taken 3 to 5 minutes from last Guided Breath Test breath sample, and records the time of the sample submission.

- Prompt:

How did that go for you?

(*Next prompt is a Continuation from Use Scenario 3 above*)

- Prompt:

Please walk me through your test result. What does this result mean?

➢ [redacted]

- Tasks:
  - Access the CO Log
  - Understand result from the breath test

Expected response: See 11.1.3 response

11.1.6 Subjective Feedback Part 1

- Prompt:

Were there any points during this portion of the study that you experienced difficulty or had concerns about the product?

- Prompt:

Did you experience any moments of hesitation while using the product?

- Prompt:

Do you have any safety concerns regarding the product or labeling?

11.1.7 Comparative Breath Sample with the Predicate Device followed by Breath Sample to Measure Hydrogen

Note this is NOT a Use Scenario but is included here to thoroughly represent the flow of this portion of the study.

- Prompt:

Now we are going to submit a sample using another Carbon Monoxide Sensor

- Subject provides a breath sample using the predicate CO breath sensor (Bedfont), submitted

with guidance by a trained test administrator.

- Study observer confirms breath sample taken 3 to 5 minutes after the previous breath sample (from section 11.1.5) and records the time of the sample submission.
- The Bedfont CO breath sensor result will be documented.
- Bedfont CO breath sensor result and COBSS result will be photographed side by side with participant number.

- Prompt:

[redacted]

- [redacted]

- [redacted]
- [redacted]

11.1.8 Use Scenario 6: Charge the Carbon Monoxide Breath Sensor

- Prompt:

Please proceed to charge the Carbon Monoxide breath sensor.

- Tasks:
    - Connect the micro-USB cable
    - Charge the device

11.1.9 Use Scenario 7: Set reminders for future breath tests

- Prompt:

Please set reminders to perform breath tests every 2 hours from 8am to 10pm.

- Tasks:
    - Access the BSA Settings Page
    - Set time limits and frequency for reminders

11.1.10 Use Scenario 8: Access the Frequently Asked Questions Page in the Application

- Prompt:

Please access the Carbon Monoxide Breath Sensor Frequently Asked Questions page in the application.

- Tasks:
    - Press Setting button
    - Press Frequently Asked Questions on Screen

11.1.11 Subjective Feedback Part 2

- Prompt:

  [redacted]

- [redacted].

Upon completion of the use scenarios and comparative performance paired breath samples, a user documentation assessment session and a subjective feedback session will be conducted to better inform the safety and efficacy of the COBSS.

11.2 USER DOCUMENTATION ASSESSMENT

Participants will never be asked to refer to the User Manual, Quick Start Guide, or Reference Card during simulated use scenarios. Any instance of participants referring to the instructions in the User Manual, Quick Start Guide, or Reference Card during the simulated use scenarios will be recorded and assessed.

After completion of the use scenarios and comparative performance paired breath samples, the user documentation (User Manual, Quick Start Guide, and Reference Card) will be tested for ease of use and clarity of content. Each user documentation assessment session will have test cases to assess the findability and the interpretation of knowledge task data found in the User Documentation. Participants will be asked to find and/or interpret 12 pieces of essential information. Participants will demonstrate understanding through verbal explanation. The questions and answers for the user documentation assessment are found in Table 3.

Table 3. Knowledge Tasks for User Documentation Assessment

Knowledge Task ID	Knowledge Tasks	Question	Participant Response
KT 1	[redacted]		

			[redacted]
KT 2	[redacted]	[redacted]	[redacted]
KT 3	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]
KT 4	[redacted]	[redacted]	[redacted]
KT 5	[redacted]	[redacted]	[redacted]

			[redacted]
Prompt: Please read these pages (*Provide User Manual with the Warnings, Precautions, Notes pages opened up*). I am going to ask you some questions about these pages.			
KT 6	[redacted]	[redacted]	[redacted]
KT 7	[redacted]	[redacted]).	[redacted]
KT 8	[redacted]	[redacted]	[redacted]

			[redacted]
KT 9	[redacted]	[redacted]	[redacted]
KT 10	[redacted]	[redacted]	[redacted]
KT 11	[redacted]	[redacted]	[redacted]
KT 11.1 (Ask only if participant did not state both	[redacted]	[redacted]	[redacted]

expected answers)			[redacted]
KT 12	[redacted]	[redacted]	[redacted]

11.3 SUBJECTIVE FEEDBACK AND RATING SCALES

In addition to the subjective feedback obtained periodically throughout the study session, subjective feedback may be collected during the use scenarios and user documentation assessment to inform root cause analysis. Following the user documentation assessment, the participants will be subjected to rating scale questions to rate the ease of use of the device, the clarity of the user documentation and their ability to understand and interpret the test results.

11.4 HUMAN FACTORS AND USABILITY ACCEPTANCE CRITERIA

Each use scenario and user documentation assessment test case will be attributed one of the following assessments for task success:

- Successful: User is able to complete the task safely and effectively.
- Difficulty: User is able to complete the task safely and effectively, but has significant hesitation or challenges while completing the task.
- Close Call: User is able to complete the task safely and effectively, but performs it in a way that presents the potential for user harm (i.e. near-miss).
- Unsuccessful (Use Error): User is unable to independently complete the task or does not complete the task safely and effectively. Includes instances in which users are unable to

complete the task and as a result require study moderator assistance are assessed as unsuccessful.

- Did Not Perform: User does not complete the task for safe and effective use of the device.

Any instance of study moderator assistance will be noted and assessed depending upon the extent of the assistance provided.

The COBSS Use FMEA ([redacted] governs Acceptance Criteria for the COBSS Usability Validation Study. Each hazard-related use scenario observed during usability validation testing will be documented and assessed for risk acceptability as defined in the Use FMEA.

In the case that a hazard-related use scenario is concluded to have an acceptable risk profile per the Use FMEA, its associated test case is considered to "pass." In the case that a hazard-related use scenario is concluded to have an unacceptable risk profile per the Use FMEA, its associated test case is considered to "fail." In the case of a failed test case, further risk mitigation and usability evaluation would be required. In the case that further risk mitigation is not possible, a risk-benefit analysis would be documented.

11.5 METHODS FOR CAPTURING USE ERRORS

During each study session, observer(s), and moderator(s) will observe for difficulties, use errors and close calls that could inform modifications to the COBSS Use FMEA. The study moderator will also ask probing questions, at the end of the session, to reveal close calls that were not conveyed through observation. All use errors and difficulties will be followed with questions to identify how and why the participant believes they occurred. New, unforeseen use-related hazards will be assessed for risk acceptability and added to the COBSS Use FMEA.

The study team will include subjective assessments by participants for any observed use-related issues that could potentially result in harm to the user.

Users will perform tasks independently and in a natural manner, without guidance, coaching, praise, or critique from the test facilitator or moderator. Users will not be allowed a "second chance" to perform a task correctly after a failure. That is, if an irreversible safety or efficacy issue is observed in which a user would not normally have a "second chance" to resolve the issue, then any subsequent attempts to compete the task will serve as input only for continuous usability improvement purposes.

The study team will ensure participant feedback is documented throughout the session, as well as any protocol deviations. Prior to the end of the test session, the study team will review all data sheets for completeness and pursue additional information or clarification as needed. The study team will then inform participants when the test session is complete.

The study team will scan the data sheets and save them to a secure study file. All members of the study team will be familiar with the device operation to be qualified to administer the test and assess participant performance with the device. The study team will write the summary report.

12.0 STUDY RESULTS

12.1 DATA COLLECTION AND CONFIDENTIALITY

Subjects will be assigned a unique subject ID which will be used for data collection. Data collection will take place on paper or electronic case report forms (CRF) completed by the study team and study subjects. CRFs will be reviewed by the study team prior to the end of the study session to ensure completeness and then stored in a secure filing cabinet at the end of the day with access limited to necessary study personnel. Study data will be kept in a secure database by the investigator. This database will be accessible only by necessary study personnel. The database will not contain personal identifying information; all subject data in the database will be associated with study identification numbers. The data will be kept for 5 years.

12.2 ANALYSIS

The study will utilize paper-based data entry procedures, subject to audit per Carrot Sense standard operating procedures.

12.2.1 Human Factors and Usability

The data sheets will be printed and used to facilitate note taking and the capture of close calls and use errors that are observed during each session. Data collection and analysis will include both objective data and subjective data collected via test cases that are provided to the user.

Objective data will include:

- Participant answers to use scenarios and user documentation assessment test case questions assessing user comprehension.
- Study team assessment by use scenario, based on pre-determined acceptance criteria (see sections 11.1 and 11.4)

Subjective data will include:

- Participant feedback on ease of use, understandability, and possible improvements.
- Study team feedback on any issues with participant comprehension or ability to complete user tasks.

In the case that a problem or a use error is observed, the study moderator will probe for root cause and record the participant's assessment of safety and risk acceptability. This subjective input of risk acceptability will inform the final assessment and conclusion of risk acceptability made by the study personnel during data analysis. Both observational data and subjective input will facilitate identification and understanding of the root causes of use errors or difficulties that occur.

As needed, photo and video recordings may be implemented during the study to facilitate post-study analysis of user-feedback, use errors, and close calls.

More than one study observer may record data using the data sheets. As a result, data may differ between note-takers. After the session is complete, the observer(s) and moderator(s) will meet to discuss any difficulties, use errors, or close calls. Data will be compiled in a spreadsheet, and

study team may re-assess ratings based on further analysis, video review, or discussion (e.g. a "Difficulty" may be re-assessed as a "Close Call" after the data sheets are complete). Hand-written data will not require amendment based on the re-assessment. In any instances where ratings are modified, a comment will be made in the cell in the spreadsheet or a log will be otherwise recorded to indicate that each change was agreed upon by the study personnel.

12.2.2 Performance

See Sections 9.4 and 9.5 for statistical methodology. A paired breath sample is defined as subject submitting a breath sample unassisted using the study device, waiting 3-5 minutes, and submitting a breath sample assisted by a health care professional (or test administrator) using the predicate device.

A final report will be created to capture the results and analyses of the findings.

12.3 REPORT

A final report will be issued upon completion of testing and will include the following:

- Report must include observations of task performance and occurrences of use errors, close calls, and use problems.
- Report must include feedback from interviews with test participants regarding device use, use errors and problems (as applicable).
- Report must include description and analysis of all use errors and difficulties that could cause harm, root causes of the problems, and implications for additional risk elimination or reduction.
- Report must include testing details such as description of products tested and identification numbers.
- Report must identify staff members who tested and evaluated/inspected samples. Test date(s) must be identified.
- Report must identify any deviation from the protocol, and any anomalies in sample testing. Justification and approval of deviation by Carrot Sense must be documented.
- Report must include test results section and must identify any changes to the testing samples.
- Report must reference completed data sheets. All data sheets will be signed and dated.
- Report must be signed by the primary investigator or study team designee. It must also be reviewed and approved by the study team.

12.4 DEVIATIONS FROM PROTOCOL

To be determined by the study team during usability study. Deviations will be assessed through a consensus review of the study team. All deviations will be identified, recorded and analyzed in the final report.

13.0 [redacted]

- [redacted]

14.0 RECORD RETENTION

Record keeping is performed in accordance with the SOP Control of Quality Records, SOP-1068.

15.0 LITERATURE REFERENCES

[redacted]

16.0 DOCUMENT REVISION HISTORY:

Rev. A	**Original Protocol (Combined Performance and Human Factors and Usability Study)**
Summary of Changes: [redacted]	
Rev. B	**Amendments March 2, 2017**
Summary of Changes: **Updated Figure 3, names of revised Attachments, content regarding how a smoker could get a green or orange level (deleted terms 'days' and 'hours') and dates on signatory page**	