STATISTICAL ANALYSIS PLAN

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A Proof-of-concept, Open-label, Feasibility Study to Evaluate Mobile Applications and Biosensing (mHealth) Devices to Monitor Physical Activity and Respiratory Function in Smokers with and without Respiratory Symptoms/COPD

Prepared by

Baurzhan Zhussupov, MS

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Principal investigator: Almaz Sharman, MD, PhD

Person conducting analysis: Baurzhan Zhussupov, MS

Tel. +7 777 482 21 71

Email: baurzhan.zhussupov@gmail.com

NCT: 04081961

Introduction

The current study is designed to investigate feasibility of using mHealth devices to improve the treatment, assessment, compliance, and outcomes in smokers with and without respiratory symptoms/COPD. The study aims to reveal and address the anticipated barriers to the acceptance and implementation of mHealth devices in this patient population and clinical setting. As is well documented, the more attention patients receive from medical personnel, the better their clinical outcomes. Here we are attempting to use device-driven monitoring applications, interactive reminders, and teaching modules to deliver a constant positive feedback loop to patients to improve their health decisions.

Study Objectives

To assess the feasibility and usefulness of mHealth devices in current smokers with and without respiratory symptoms/COPD.

To assess the utility (i.e., validity and reproducibility) of mHealth devices in detecting vitality parameters in current smokers with and without respiratory symptoms/COPD (e.g., heart rate; blood oxygenation; steps/motion; FEV_1, FVC, and their ratio).

Design

Overview

This is proof-of-concept, open-label, three-arm, observational, single-center study. Cohorts of twenty-seven participants each will be enrolled to use mHealth devices while undergoing the current standard of care based on smoking disease state or lack of disease state.

mHealth Devices Used in Arms 1–3:

- Arm 1: Nine “non-COPD”, otherwise healthy, smokers;
- Arm 2: Nine “grey zone” smokers (i.e., FEV_1/FVC ≥0.70 after bronchodilator treatment, CAT ≥10; 6MWT<450m);
- Arm 3: Nine smokers diagnosed with Stage 1 - 3 COPD.

Safety and tolerability will be evaluated through adverse events (AEs), lung function tests, vital signs, and supportive care medications.

This will be a 90-day study conducted in two stages

- Stage 1. Initial period of using the mHealth devices (Days 1–21).: To evaluate feasibility of the intervention the accuracy and precision of collecting vitality parameters (e.g., heart rate, blood oxygenation, steps/motion) on mHealth devices.

- Step 2 Main period of using the mHealth devices (Days 22–90): To evaluate the feasibility of utilizing mHealth devices in participants reminded daily versus not reminded to use them.

Sample size

The primary endpoints of the study are rates of recruitment rate, adherence and retention. In order to assess the feasibility of intervention, we plan to recruit 27 participants. We conservatively estimate that 30% of the people invited to participate will be recruited to the study with a 95% confidence interval within ± 9%. We also assume the dropout rate will be 15%. The accuracy of the estimated retention rate will be at least ± 13%. Further, we believe that 90% of participants will be adhere to use of mHealth devices. In this case, the accuracy of the estimate will be at least 11%. All calculations are based on two-way 95% confidence intervals.

Sampling method

This is a non-probability sample. We use various methods to recruit study participants including snowball sampling.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. 40–59 years of age.
2. Current smoker:
    - Asymptomatic current smokers: no symptoms or radiological findings (CAT, 6-minute walk test [6MWT]) and preserved pulmonary function based on spirometry (forced expired volume in 1 second/forced vital capacity [FEV_1/FVC] of at least 0.70 after bronchodilator and FVC is 80% or more of the expected value) and respiratory symptoms (COPD assessment test [CAT]<10); and functionally capable (6MWT≥450m);
    - "Grey zone" current smokers: initially preserved pulmonary function based on spirometry, but with clinical symptoms based on CAT (>10) and 6MWT (<450).
    - Current smokers with a confirmed diagnosis of COPD (GOLD stage I–III).
3. Able to use and willing to be trained to use mHealth devices.
4. Willing to provide written informed consent to participate in the study.

Exclusion Criteria

1. Smokers with COPD exacerbation (defined as a change in symptoms requiring increased doses of current medicines or the prescription of new medicines, e.g., corticosteroids or antibiotics) that has not resolved at least 28 days prior to screening. Smokers with COPD exacerbations occurring after screening but before the first study visit will also be excluded.

2. Smokers with pneumonia or other respiratory tract infections that have not resolved at least 14 days prior to screening. In addition, any participant that experiences pneumonia occurring after screening but before the first study visit will also be excluded.
3. Smokers with other active respiratory disorders: tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, bronchial asthma, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases.
4. Any co-morbid medical condition that in the opinion of the investigator would make participation in the study unsafe or unfeasible, including conditions that prohibit completion of exercise testing, such as orthopedic, neurological, cardiovascular, or other conditions that significantly impair normal biomechanical movement patterns and limit the ability to walk/cycle, as judged by the investigator.
5. Use of supplemental oxygen therapy.
6. Inability to abstain from smoking during the period in which the participant is admitted to the Kazakhstan Academy of Preventive Medicine (KAPM) COPD Center.
7. A history of allergy or hypersensitivity to metal, particularly stainless steel.
8. Any vital sign indicator, for example, hypertension or tachycardia at rest that, at the discretion of the investigator, would make participation in the study unsafe or unfeasible.
9. Women who test positive for pregnancy during screening, lactating women, or women planning on becoming pregnant during the study.
10. Participants using assistive devices like walking aids, as these are likely to interfere with physical activity.
11. Other patients who are considered ineligible for the study by the investigator.

Study measures

Primary Outcome Measure

Primary outcome measures are defined as rates of recruitment, retention, and adherence as well as safety of the intervention. Study participant-perceived acceptability is also included in the feasibility assessment.

Recruitment. Recruitment is defined as the number of potential participants screened for study eligibility versus the number of persons who enrolled in the study.

Retention. Retention is defined as the proportion of participants enrolled who completed the intervention and all study measures.

Protocol adherence. Adherence to the study protocol is determined as the proportion of participants enrolled from whom all mHealth parameters registered every day.

Statistical Methods

Graphical and/or statistical comparisons will be made between the mobile biosensing devices-derived data and the data derived from the clinical standards, and between the three different study groups.

The goal of statistical analysis is to determine accuracy and precision of mhealth biosensing devices in assessing such parameters as pulse oxymetry, heart rate, spirometric values where standard diagnostic procedures will be used as gold standards.

Descriptive statistics will be used to summarize required qualitative and quantitative study elements (e.g., proportion, mean, standard error, median and inter-quartile range, 95% confidence interval).

Exploratory graphical analysis will be done prior to numerical analysis. Histograms and two-dimensional scatterplots of raw data will provide information on the univariate and bivariate distributions of the variables, focusing on distribution of variables and relation between the variables (whether there is a linear or nonlinear relationship) and so on. Additionally, preliminary graphs will be used to screen raw data by highlighting obvious data errors.

Tabulations will be produced for appropriate disposition, demographics, baseline, safety, and clinical parameters.

Statistical comparisons will be made between the mobile biosensing devices-derived data and the data derived from the standard diagnostic equipment and methods:

- pulse oximetry
- heart rate
- breath rate
- number of steps
- FEV1
- FVC
- FEV1/FVC

Agreement analysis will be performed for both binary and quantitative measures. For binary variables, percent of agreement (overall, positive and negative agreement) as well as Kappa coefficient, p-value and 95% confidence interval will be calculated.

For two quantitative measures of a parameter, we will use the Bland-Altman method (Bland-Altman plot and limits of agreement). The Bland-Altman plot analysis will allow to evaluate a bias between the mean differences, and to estimate an agreement interval, within which 95% of the differences between two quantitative methods of measurement are included. We will define *a priori* the limits of maximum acceptable differences (limits of agreement expected) for each quantitative measurements (pulse oximetry, heart rate, breath rate, number of steps, FEV1, FVC). In addition, correlation analysis will be run: Pearson's coefficient and 95% confidence interval will be calculated.

The agreement analysis will be done for base-line, 7-day, 14-day, 21-day, 28-day, 56-day, and 90-day visits separately and for the data pooled from all measurements. A within-subject study design will be accounted to assess accuracy and precision for a single mobile device.

All statistical analysis will be done for all participants and by study group. Additionally, we will compare trends of binary and quantitative outcomes from three study groups wearing mobile devices.

Analyses will be performed using SPSS and R (version 3).