INVESTIGATOR INITIATED STUDIES
STUDY PROTOCOL

1. GENERAL INFORMATION

Date	**3 June 2019**
IIS Number	PMI.IIS.2016.1
NCT	04081961
Study Type	Open-label, Three-arm Study
Study title	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

Sponsor/Investigator details

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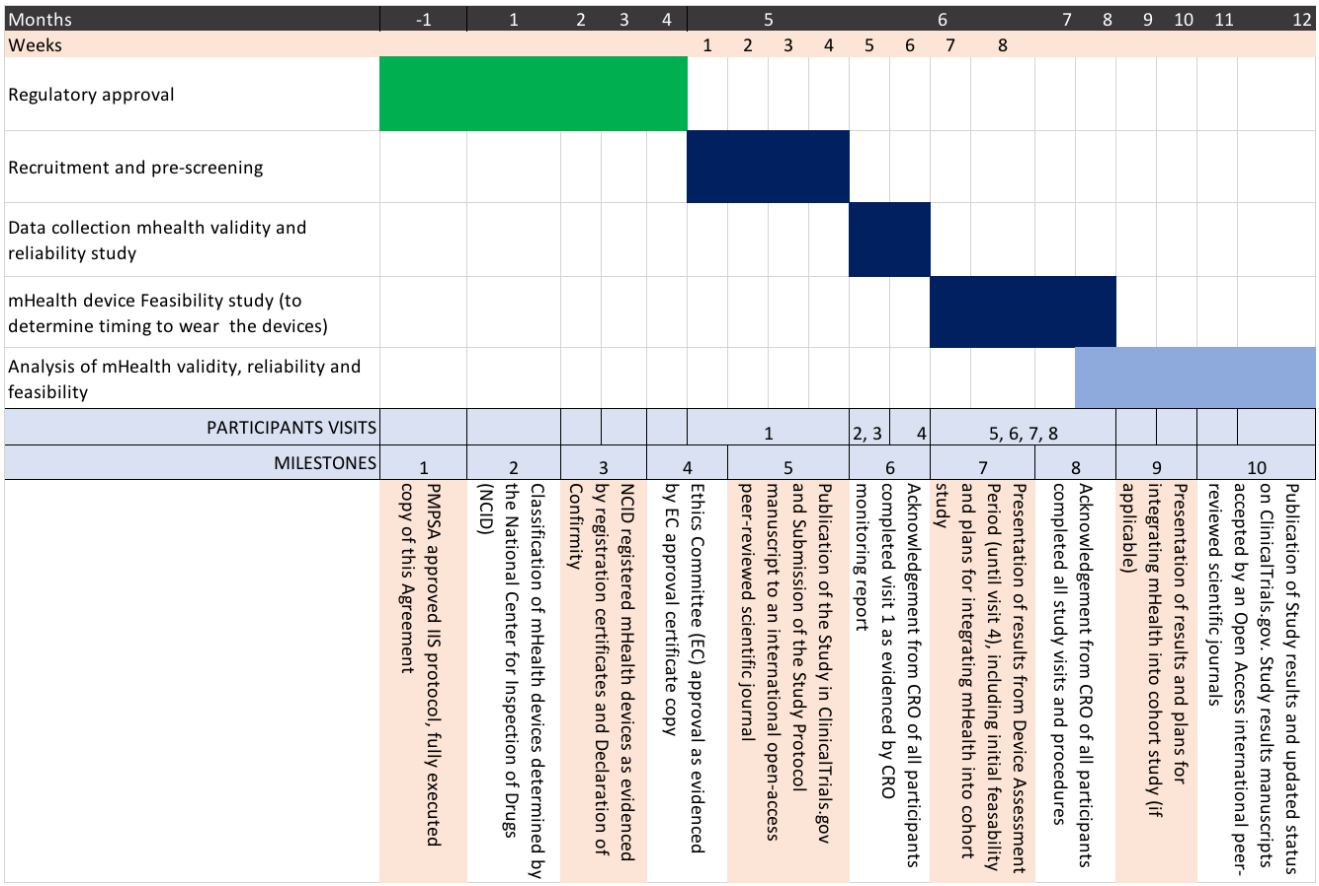
Project schedule/Gantt chart



Regulatory framework

The study will be conducted in accordance with the approved study protocol and standard operating procedures that meet the guidelines provided by the International Council for Harmonization E6 for Good Clinical Practice (GCP) in clinical studies (ICH, 2016).

The investigator will ensure that this study is conducted in accordance with the ethical principles founded in the most recent revision of the Declaration of Helsinki and in accordance with Order #142 of Kazakhstan's Ministry of Health, dated 2 April, 2018 **'On Approval of the Regulations for Conducting Biomedical Experiments, Preclinical (Non-Clinical) and Clinical Studies, As Well As the Requirements for Preclinical and Clinical Sites'.**

According to a letter from the National Center for investigation of pharmaceuticals, medical devices and medical equipment of the Ministry of Health No14-16-351/2955-03 dated 6 February 2019, the Center informs that "..observational studies in which medical interventions conducted within the framework a routine medical practice in accordance with approved protocols of diagnosis and treatment; in accordance with Regulations for conducting medical-biological experiments, pre-clinical (non-clinical) and clinical studies, and also requirements for pre-clinical and clinical facilities, approved by the Order of the Ministry of Health No 142 dated 2 April 2018

(hereinafter – order No 142), are considered to be non-interventional. Based on description that you presented in your letter No 1023-03 dated 15.01.2019, the study that you plan to conduct entitled "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" is non-interventional. Non-interventional studies are regulated by paragraph 8, chapter 3 of the Order No 142.

According to P2, item 14 pp6 of Regulations for classification of safety of medical devices and medical equipment approved by the Order No 764 of the Ministry of Health dated 24 November 2009, medical devices which are planned to be used in the abovementioned study – 1) Anamed OEM device for monitoring of physical activity and vital signs, and 2) Smart mobile spirometer AirNext are classified as Class 2a medical devices. Assessment of materials used in non-interventional studies that use class 2a medical devices is not necessary at the National Center for investigation of pharmaceuticals, medical devices and medical equipment of the Ministry of Health.

2. SCIENTIFIC INFORMATION

Executive Summary

Title of Study:

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.

Investigational mHealth Devices:

- Anamed OEM (Original Equipment Manufacturer) device - physical activity and vital signs monitoring;
- Air Next mobile spirometry device;

Investigational Software Applications:

mHealth software or websites:

- Symptomaster.com,
- Zdrav.kz, and
- Medintel.kz.

Study Objectives:

To examine the feasibility and acceptability of using mHealth devices in detecting vitality parameters in current smokers with and without respiratory symptoms/COPD (e.g., heart rate, blood oxygenation, steps/motion) for a future big-scale study.

To assess the utility (accuracy and precision) of using mHealth devices in detecting vitality parameters in current smokers with and without respiratory symptoms/COPD (e.g., heart rate, blood oxygenation, steps/motion)

Outcome measures:

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.

Study Design:

This is proof-of-concept, open-label, three-arm, observational, single-center study. Cohorts of nine participants each will be enrolled to use mHealth devices while undergoing the current standard of care based on their smoking disease states or lack of disease states.
Arm 1: Nine "non-COPD" healthy, smokers;
Arm 2: Nine "grey zone" smokers (i.e., $FEV_1/FVC \geq 0.70$ after bronchodilator, and CAT ≥10 and 6MWT<450m);
Arm 3: Nine smokers diagnosed with Stage I–III COPD.

Safety:
Safety and tolerability will be evaluated through adverse event (AE) assessment, lung function tests, vital signs, supportive care medications, and changes in laboratory parameters (chemistry and hematology).

Number of Planned Participants:

Twenty-seven smokers using mHealth devices.

Main Criteria for Inclusion:

Participants must meet all of the following criteria to be eligible to enroll in the study:
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.

Study Duration:

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.

Use of Investigational Devices:

Step 1 (Days 1–21): Participants will wear AnaMed OEM devices for 22+ hours per day, with a 2-hour break to charge the devices. They will also measure spirometric parameters using the Air Next spirometry device on Days 0, 7, and 14, and 21.

Step 2 (Days 22–90): Participants will wear AnaMed OEM devices 22+ hours per day, with a 2-hour break to charge the devices. They will also measure spirometric parameters using the Air Next spirometry device against standards on Days 28, 35, 56 and 90 of the study.

Access to device-derived data will occur via cloud to collect, store, and summarize data.
There will be a scalable infrastructure for integrating and processing sensor data, which involves the following:

- integration of data from the Garmin and AnaMed OEM device sensors;
- processing, storage, and auditing of data;
- dashboards for compliance and operational oversight;

Application Programming Interface (API) to transfer data to external analytics.

Statistical Methods:

<u>Sample Size:</u>

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.

Statistical Analysis Plan

Presented in details in relevant section

Study Context:

The proposed study is the first step in a series of studies aiming to investigate the utility (i.e., sensitivity, accuracy, and reproducibility) and feasibility/effectiveness of using mHealth devices in improving the treatment, assessment, compliance, and outcomes in smokers with and without respiratory symptoms/COPD.

The results from this proof-of-concept, open-label device feasibility study will be used to finalize the protocol for a randomized, open-label, placebo-controlled, single-center, two-arm, 12-month study designed to assess clinical feasibility of this intervention. The Study 2 will provide data on the clinical feasibility of using mHealth devices to monitor the health of current smokers with respiratory symptoms, including "grey zone" smokers and COPD stage I–III patients.

The long-term aim, after demonstrating proof-of-concept in this study, is to incorporate mHealth devices into an ongoing 5-year longitudinal cohort observational study in ~1,200 smokers to monitor selected vitality parameters and other co-morbidities.

Background & Rationale

Background

Chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in Kazakhstan, is an important global public health problem. COPD accounted for 3.2 million deaths worldwide in 2015 (GBD 2015 Risk Factors Collaborators, 2015) and is the fourth leading cause of death globally (Lozano et al., 2010). In Kazakhstan, 1.4 million people are believed to have COPD based on estimations from neighboring countries (Adeloye et al., 2015). COPD negatively affects the quality of life and is a major health care burden (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2017). COPD is the third leading cause of hospital readmission within 30 days (Shah et al., 2016).

COPD is a heterogeneous condition, with a variety of disease-related phenotypes (Friedlander et al., 2007; Silverman, 2007). The chronic airflow limitation that characterizes COPD is caused by obstructive bronchiolitis and parenchymal destruction (emphysema). Cigarette smoke is the most common risk factor for COPD. Although COPD is traditionally defined by airflow obstruction in a spirometry test, smoking-associated effects on the lungs related to COPD also include emphysema, gas trapping, and chronic bronchitis (National Center for Chronic Disease Prevention and Health Promotion, 2014). Systemic effects (e.g., on heart and muscles) and associated comorbidities (e.g., heart failure, metabolic disorders, sleep apnea syndrome, and depression) may complicate the course of disease posing challenges in the management of COPD (GOLD, 2017; Qaseem et al., 2011). Smokers with symptoms suggestive of COPD who do not qualify for diagnosis of COPD based on spirometry are referred to as "grey zone" COPD patients. They have preserved pulmonary function (forced expired volume in 1 second/forced vital capacity [FEV_1/FVC] of at least 0.70 after bronchodilator and FVC ≥80% of the expected value) and respiratory

symptoms (COPD assessment test [CAT] ≥10). Emphysema without airway obstruction is common in smokers (Woodruff et al., 2016; Regan et al., 2015).

Continuous monitoring is important for the management of COPD. Telemonitoring using mobile health (mHealth) devices has the potential to promote self-management, improve control, increase quality of life, and prevent hospital admissions (Stroetmann et al., 2015, Rubio et al., 2017; Liu et al., 2016; Himes and Weitzman, 2016; Ho et al., 2016). Technological advances in mHealth home telemonitoring (eHealth) programs and systems can affect patient care in COPD (Pedone et al., 2013; Hernandez et al., 2015; Blumenthal et al., 2014; Nowiński et al., 2015; Himes and Weitzman, 2016). mHealth devices are an emerging opportunity in clinical studies and their utility (i.e., sensitivity, accuracy, and reproducibility) has been assessed for telemonitoring in COPD (Pedone et al., 2013).

Telemonitoring is a promising alternative or adjunct to provision of traditional health care services in COPD (Nimmon et al., 2013). Although some studies have shown that telemonitoring may improve some clinical outcomes and reduce health care costs (Lundell et al., 2015, Cruz et al., 2014), the effects of telehealth interventions on emergency department attendance, hospital admissions, duration of admissions, health-related quality of life, costs, and mortality remain less certain (Nimmon et al., 2013; Pinnock et al., 2013; Bolton et al., 2011; Cartwright et al., 2013; Kenealy et al., 2015; Sanchez-Morillo et al., 2016).

In a recent study of telemedicine in the home setting using multiple activity sensor monitoring equipment in COPD patients, the augmentation of traditional telemedicine methods with motion sensing, spirometry, and symptom diaries appeared feasible (Tillis et al., 2017). In a literature review (141 randomized trials; n=37,695) of studies of eHealth practices such as telemetry, telephone calls, or home visits by nurse specialists, most studies were relatively short term (<6 months) and did not yield strong evidence for telemedicine in the management of chronic diseases (Wootton, 2012). However, the comparisons of outcomes in studies using telehealth applications are difficult due to advances in monitoring and communications technology and heterogeneity in the type of monitoring, disease entity and severity, and variations in the process of care brought about by the telemedicine intervention (Himes and Weitzman, 2016).

Implementing telemedicine and mHealth has allowed clinicians to intervene earlier and prevent complications but there remain the challenges of alarm frequency and response, which need to be implemented into the workflow (Mohktar et al., 2015). Data flow and workflow processes need to be designed with precision at the outset if telemedicine is to be applied in clinical practice.

Although peak flow monitoring has been used for the home detection of asthma exacerbations, and studies in the past have monitored vital signs and symptoms in patients with COPD (Antoniades et al., 2012), few studies have attempted to deploy spirometry in the home monitoring of COPD (Pradella et al., 2015). With technical advances, spirometry is increasingly being used to track the progress of COPD over time and to identify acute exacerbations (Ferguson et al., 2000; Lee et al., 2006; Schermer et al., 2003; Wilt et al., 2005; Chawla et al., 2014).

While the number of COPD mHealth devices is rapidly increasing, most have not been validated as clinically effective tools for the management of disease. In addition to empowering patients and facilitating disease self-management, the mHealth concept offers promise to aid COPD researchers in personalized treatments based on patient-specific profiles that integrate symptom occurrence and medication usage with environmental and genomic data. An integrated and targeted practice-managed approach that uses mHealth technologies in primary care settings will be most effective for the early identification, monitoring,

and management of chronic diseases, particularly COPD and cardio-metabolic syndrome (i.e., combined diabetes mellitus, systemic arterial hypertension, central obesity, and hyper-lipidemia).

Health information technologies are revolutionizing health care by assisting patients in self-monitoring and decision-making, driving a shift toward a care model increasingly centered on personal use of digital and web-based tools (Finkelstein et al., 2012; Mandl and Kohane, 2012; Eggleston and Weitzman, 2014; Sharman et al., 2017). Because there is a dearth of evidence that direct-to-consumer mHealth tools are effective or that they provide accurate disease recommendations, they are not yet widely used in clinical practice. Nonetheless, the preponderance of mHealth is gradually increasing in health care, industry, and as the subject of research (Vegesna et al., 2017).

Rationale

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.

Over the long-term, we hope to employ mHealth devices to monitor selected vitality parameters and other co-morbidities in a planned 5-year cohort observational study in ~1,200 smokers. Specifically, after we determine that AnaMed OEM device and Air Next mobile spirometer demonstrate accurate results and the most feasible way of wearing them, and depending on the outcome of the study, they will be introduced to record data from a randomized subsample of participants in an observational cohort study including smokers of combustible cigarettes and users of IQOS with heatsticks). Potentially, this methodology can be utilized to record FVC, FEV1 and their ratios as well as blood oxygenation, heart rate, respiratory rate and other important parameters from COPD patients. Should there be consistent differences between the results that come from mHealth devices vs standard diagnostic equipment, an adjustment coefficient can be applied to each measure.

The following items will be investigated in the current study to aid the identification of devices that are accurate, sensitive, and reproducible in their ability to collect and process information necessary to assist the treatment of smokers with or without respiratory symptoms/COPD:

- prevalence of technical data collection issues;
- similarity of device-collected data compared with those from established, clinically proven methods;
- ability to integrate and compare data across management platforms;
- operational ease of devices and their functions for patients and staff;
- convenience of patient and staff training programs or ongoing device support;
- device effectiveness in detecting compliance or ease of use in entering patient compliance;
- ability to monitor the patients at different times of the day and in different conditions (e.g., indoors vs. outdoors; at rest vs. during exercise);
- being suitable for both chronic monitoring and real-time “on demand” monitoring

Scientific hypothesis, objective(s) & intended methodologies

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).

Study Design and Study Plan

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.

Detailed study procedures can be found in Table 1.

Description of Study Days

Table 1. Schedule of Assessments and Study Activities

		Device Assessment Period			Clinical Feasibility Study Period			
	Screening	Baseline Visit	Interim Visit	Final Visit	Interim Visits			Final Visit
Visit	1	2	3	4	5	6	7	8
Days	1	7	14	21	28	35	56	90
Informed consent process	X							
Study eligibility and smoking status	X							
Review medical history (including physical examination and BMI measurement)	X	X	X	X	X	X	X	X
COPD assessment test	X							
Spirometry*	X	X	X	X	X	X	X	X
6-minute walk test	X	X	X	X	X	X	X	X

Provide the study requirements handout (explain study/visit requirements	X							
Dichotomous questionnaire for visit readiness	X							
Provide mHealth devices**	X							
Assessment of AnaMed OEM device+		Continuous monitoring						
Assessment of Air Next mobile spirometer against standard++		Continuous monitoring						

* Spirometry will be performed to diagnose and monitor COPD.

** Provision of AnaMed OEM device, Air Next mobile spirometer and instruction/review of how to use these tools (print and verbal instructions).

Morning video, text/voice reminders to wear AnaMed OEM device, perform spirometry using AirNext device.

Evening communication/feedback through video communication participants will share their experience and feedback on mHealth device usage. Feedback will be received by a clinical investigator..

[a] In each study group, there will be three participants who will be reminded every morning by text message or phone call and contacted every evening by phone or chat services (e.g., Skype, WhatsApp, Viber, SMS) to share their experiences and feedback on mHealth device usage; three participants who will receive morning reminders only, but no evening communication/feedback; and three participants will receive no morning reminders nor evening communication/feedback.

\+ Participants' peripheral capillary oxygen saturation (SpO2) will be measured at each Study Center visit using industry standard pulse oximetry devices.

++ Participants will host a mobile spirometer (Air Next) at home for once daily measurements. Measurements will be validated at Study Center visits using an industry standard device before and after the use of a bronchodilator.

Screening Period, Visit 1 (Days −10 to −1)

Procedures to be performed within 10 days prior to study start:

- informed consent process;
- study eligibility and smoking status;
- pregnancy test;
- recording of tobacco use history;
- review of medical history (including physical examination and BMI measurement);
- CAT;
- spirometry;
- 6-minute walk test;
- provision of the study requirements handout (explain study/visit requirements);
- provision of mHealth devices.

Device Assessment Period, Baseline, Visit 2 (Day 7)

Procedures to be performed on Day 7 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device. The latter will be worn by the participants while taking 6-minute-walk-test and measures on motion will be taken for the purpose of comparisons.
- Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Device Assessment Period, Interim Visit 3 (Day 14)
Procedures to be performed on Day 14 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.
- Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Device Assessment Period, Final Visit 4 (Day 21)
Procedures to be performed on Day 21 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.
- Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Observational Period with mHealth Device, Visit 5 (Day 28)

Procedures to be performed on Day 28 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Continued Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.

- Continued Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Observational Period with mHealth Device, Visit 6 (Day 35)

Procedures to be performed on Day 35 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Continued Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.
- Continued Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Observational Period with mHealth Device, Visit 7 (Day 56)

Procedures to be performed on Day 56 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Continued Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.
- Continued Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Observational Period with mHealth Device, Final Visit 8 (Day 90)

Procedures to be performed on Day 90 (Table 1):

- 6-minute walk test with heart and breathing rates before and after the test
- Continued Assessment of **AnaMed OEM device** SpO2 against standard pulse oximetry, heart rate and breath rate measurements.
- Comparison of **AnaMed OEM device** Step/Motion parameters with actual step counts and data from Garmin device.
- Continued Assessment of Air Next mobile spirometer against standard using BTL-08 SPIRO device for spirometry measurements.
- Administration of questionnaire of user experience.
- Administration of performance questionnaire on technical aspects.

Selection of Study Population

Inclusion Criteria

Participants will meet all of the following criteria to be eligible to enroll in the study:

- 40–59 years of age.
- Current smokers who are currently smoking conventional cigarettes with a minimum of 10 pack-year smoking history[1]:
    - *Asymptomatic current smokers*: no symptoms (CAT<10, 6MWT≥450m) and preserved pulmonary function based on spirometry (FEV_1/FVC of at least 0.70 after bronchodilation treatment and FVC ≥80% of the expected value) and respiratory symptoms (CAT ≥10); OR
    - *"Grey zone" current smokers*: initially preserved pulmonary function based on spirometry, but with clinical symptoms based on CAT (>10) and 6MWT (<450); OR
    - *Current smokers with a confirmed diagnosis of COPD* (GOLD stage I–III).
- Able to use and willing to be trained to use mHealth devices.
- Provide written informed consent to participate in the study.

Smokers will undergo the current standard of care based on their smoking disease states or lack of disease state.

Exclusion Criteria

Participants meeting any of the following exclusion criteria are not eligible to enroll in the study:

- 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.
- 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.
- 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.
- 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.
- Use of supplemental oxygen therapy.
- Inability to abstain from smoking during the period in which the participant is admitted to the Kazakhstan Academy of Preventive Medicine (KAPM) COPD Center.
- A history of allergy or hypersensitivity to metal, particularly stainless steel.
- 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.

- Women who test positive for pregnancy during screening, lactating women, or women planning on becoming pregnant during the study.
- Participants using assistive devices like walking aids, as these are likely to interfere with physical activity.
- Other patients who are considered ineligible for the study by the investigator.

Discontinuation Criteria

Early Discontinuation of the Study
The study may be discontinued at the sole discretion of KAPM, for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of participants.

Early Discontinuation of Individual Participants
Participants may be discontinued from study at the discretion of the investigator for any of the following reasons:

- unacceptable AE(s) or failure to tolerate wearing the device;
- participant decides to discontinue wearing device;
- any medically appropriate reason or significant protocol violation, in the opinion of the investigator.

Participants may decide to discontinue wearing device for any reason. The investigator must determine the primary reason for a participant ’s discontinuation of wearing device and record this information on the Case Report Form (CRF). Participants who are prematurely withdrawn from wearing device are not eligible to re-initiate wearing device on this protocol at a later date.

Study Procedures and Methods

Methodology
The mHealth devices will be compared for defined outcomes against industry standards. Additionally, a questionnaire will be administered to assess the participants’ perceptions of the mHealth technologies used.

Initial evaluations will include the assessment of biosensing devices based on selected vitality parameters, such as heart rate, blood oxygenation, steps/motion in healthy current smokers and current smokers diagnosed with COPD with and without respiratory obstruction. The main goal of the study is to assess the validity, reliability, and feasibility of the following mHealth devices:

- AnaMed OEM device - physical activity and vital signs monitoring device;

[1] Pack-years will be calculated by taking the average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked.

- Air Next mobile spirometry device; https://www.nuvoair.com/spirometry.html

Study Devices and Assessments

mHealth devices will be assessed for validity using the outcome measures and the established clinically proven methods outlined in Table 2

Table 2. Assessments of mHealth Devices Versus Standard of Care

Objectives	Technology Evaluated	Industry Standards	Outcome Measures/ Data Collection Instrument
Spirometry	Air Next mobile spirometer software-derived endpoints (FEV_1, FVC, PEF)	BTL-08 SPIRO before (without) and post-bronchodilator use	• FEV_1, FVC, PEF (Air Next) • FEV_1, FVC, PEF (BTL-08 SPIRO)
Physical activity/ Exercise capacity	AnaMed OEM device software-derived endpoints (step counts, distance)	6MWT	• Step counts (total number of steps taken during a 6MWT): software-derived from Garmin Vívofit 3 and AnaMed OEM device; manually counted • Distance walked (total meters achieved during a 6MWT): software-derived from Garmin Vívofit 3 and AnaMed OEM device; manually counted
Blood oxygenation saturation	AnaMed OEM device software-derived endpoint SpO2	Vive DMD 1003 pulse oxymeter	SpO2 (AnaMed OEM device; Vive DMD 1003 pulse-oximeter)
Heart rate	AnaMed OEM device software-derived endpoint heart rate	Manually counting heart rate during rest after and 6-minute-walk test	• Heart rate (AnaMed OEM device) • Heart rate (manually counted/determined during a period of rest and 6-minute-walk test) •
Skin temperature	AnaMed OEM device software-derived endpoint skin temperature	Measured temperature in armpit with a standard thermometer	• Skin temperature (AnaMed OEM device) • Temperature measured in armpit using a standard thermometer
User experience and			• Questionnaire (see • Table 3)

compliance			Wearing episodes as assessed by software-derived parameters
Prolonged data recording	Mobile biosensing device-derived endpoints over 2 weeks in ambulatory setting		• Distance (AnaMed OEM device): recorded 22+ hours per day • Energy expenditure (AnaMed OEM device): recorded 22+ hours per day • Heart rate, heart rate variability (AnaMed OEM device): recorded 22+ hours per day Spirometry (Air Next Mobile Spirometer): 1 measurement per day (evening)
Device performance			• Distance (AnaMed OEM device): recorded 22+ hours per day • Energy expenditure (AnaMed OEM device): recorded 22+ hours per day • Heart rate, heart rate variability (AnaMed OEM device): recorded 22+ hours per day • Spirometry (Air Next Mobile Spirometer): 1 measurement per day (evening)
Collection of AEs and SAEs			• From study start until end of follow-up period (Day 90)
			•

*The main potential technical issues that will be assessed include inaccurate readings/device malfunctions, inconsistent data transfer, inefficient battery usage, USB connections, step-dependent process, registration system difficulties, lack of streamlined support, cellular communication coverage, triggered false alerts to home health teams, and issues with availability of technical support.

Physical Examinations

Physical examinations will be conducted during each visit based on the Stanford Medicine 25 comprehensive clinical assessment to identify clinical signs of abnormalities. This will be in addition to standard anthropometric measurements and vital sign assessments.

Vital Signs

The following vital signs will be assessed during the participant's visits: pulse rate and blood oxygenation.

Pulmonary Function Test – Spirometry

The Air Next mobile spirometer will be used by patients to assess respiratory function. Patients will hold their hands on tubular grips or use wrist clamps. Subsequent respiratory efforts will allow the determination of inspiratory capacity and FEV_1.

Once the diagnosis of COPD has been established, GOLD nomenclature will be used to grade the severity according to the degree to which the measured FEV_1 is lower than the patient's predicted value (http://www.goldcopd.org):

- GOLD stage 1 (mild disease): FEV_1 ≥80% of the predicted value;
- GOLD stage 2 (moderate disease): FEV_1 ≥50% and <80% of the predicted value;
- GOLD stage 3 (severe disease): FEV_1 ≥30% and <50% of the predicted value;
- GOLD stage 4 (very severe disease): FEV_1 <30% of the predicted value.

At the KAPM COPD Center, standard spirometry data will be collected using the BTL-08 SPIRO (www.btlnet.com/products-spirometry-spirometry-btl-08-spiro-pro) spirometry system. Each spirometer used in this study will be tested and continuously standardized with a 3 L syringe. Each clinical coordinator will be certified after spirometry training and quality assessments will be performed throughout the study.

Participants will be categorized for analysis using the GOLD staging system according to their spirometry, which will be performed before and after two inhalations of salbutamol (0.1 µg per inhalation). Among the criteria needed to make a diagnosis of COPD are deficits in the rate at which one can forcefully exhale. Most experts consider a low ratio (<0.70) of the FEV_1 to the FVC after bronchodilator use to be a key diagnostic criterion.

Bronchodilator responsiveness will be considered positive if the participant has a ≥12% change in FEV_1 or FVC above pre-bronchodilator measurements.

6-Minute Walk Test

The 6MWT is a simple and effective test. A 100-ft hallway is needed and no exercise equipment or advanced training for technicians is required. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes.

COPD Assessment Test

The CAT is used as an add-on test with existing assessments in COPD (e.g., with FEV_1). It is a simple and reliable measure of health status in COPD. The CAT assists patients and their physicians in quantifying the impact of COPD on the patient's health. The CAT is a validated, short (8-item) questionnaire to be completed by patients..

User Experience Questionnaire

Participants will be administered a questionnaire to assess their mHealth device user experience. One questionnaire will be administered per each device. The questions will address comfort levels and ease of daily vital measurements. The results will be largely qualitative because of the small sample sizes but will help to reveal some early patterns for understanding patient attitudes toward these devices.

Interviews will be audio-recorded, fully transcribed, and analyzed thematically to explore the patient's experience of wearing the AnaMed OEM device device and using the Air Next mobile spirometer.

The interviews will be conducted by clinical investigators not involved with the quantitative monitoring or analysis to reduce the possibility of bias.

Participant Registrations and Training

The KAPM research team will register patients for each mHealth device. Installation and user guides for each technology will include labelled photographs and written instructions to be used by all teams and

patients during setup. All equipment will be tested before deployment. Training will be provided on setup and installation as well as individual checklists, decision trees, and troubleshooting information. The break for charging will be at a standard time (20:00) across arms. In addition to direct phone communication, Whastapp, SMS and other types of messaging systems will be used for sharing daily experiences each evening to assist with assessing the level of comfort and address issues with wearing AnaMed OEM device device and using AirNext mobile spirometer

Table 3 User mHealth Device Satisfaction Questionnaire

Question	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I feel comfortable using the equipment provided to complete my daily assessments.					
It was easy to learn how to use the equipment provided to complete my daily assessments.					
Overall, I am satisfied with how easy it is to complete my daily assessments.					
Instructions (such as online help, on-screen messages, and other documentation) provided with the equipment are clear.					
When problems arise, research and/or home health personnel are available to assist with troubleshooting, replacement of equipment.					
When problems arise that require the assistance of KAPM technical support, someone is available to assist and is helpful in troubleshooting equipment.					

DATA METHODS

Registration

The following items will be completed at registration:

- Study participants will register and identified as being part of the study based on their assigned code.
- After entering the activation code, wearable device study participants will complete the registration process and create a wearable account.
- Participants will sync their wearable devices (Garmin Vívofit 3 activity tracker and AnaMed OEM device multisensor) and Air Next mobile spirometry device by signing in to their account.
- Once registered, the wearable device account information will be authorized.
- Once associated, the system will inquire internal systems at regular intervals for newly synced data at the participant level. For example, for AnaMed OEM device device it will be important to determine the interval of data collection: every second, every 10 seconds, etc. Such parameter will be set at the time of device registration. The sampling rate will be documented during the data collection.

- Data will be stored in a local cloud system. The entire process of data ingestion and storage will be audited according to ALCOA standards (Food and Drug Administration, 2016).
- Whenever a participant syncs new activity data to their device cloud, those data will be ingested, processed, and archived and then aggregated and summarized in JSON data format by summarization services.

Data Collection

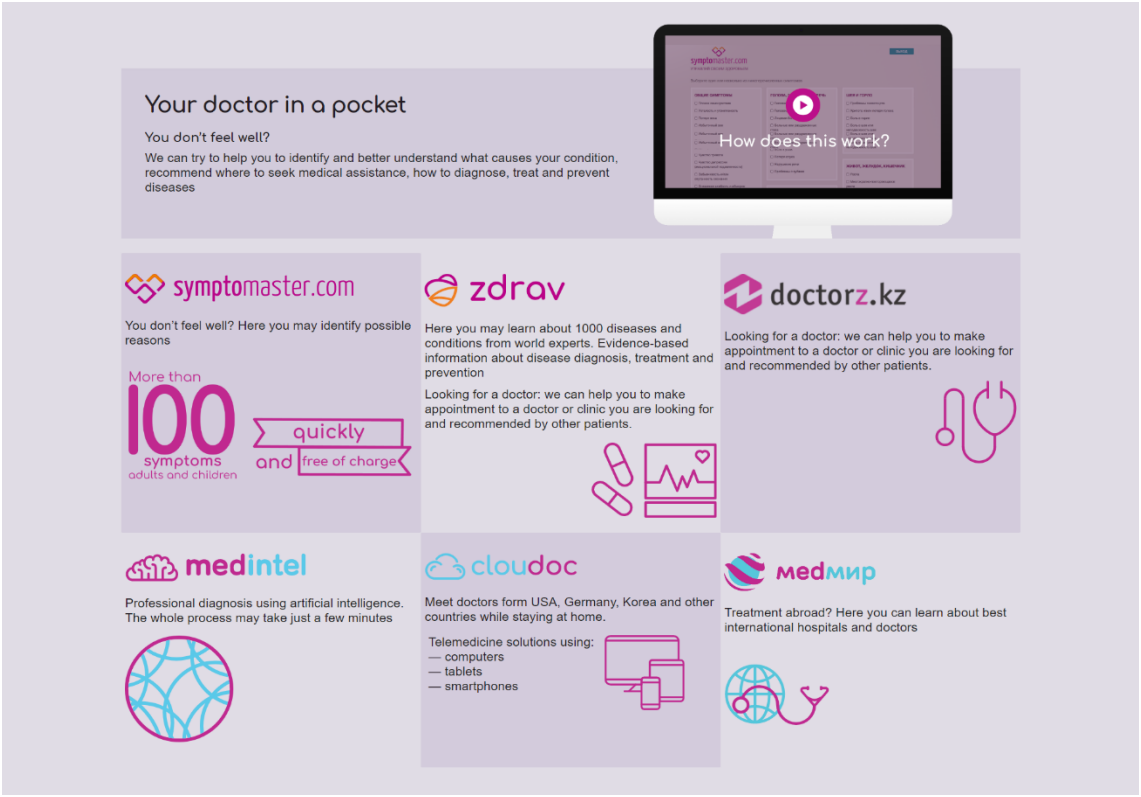
The data from the Garmin Vívofit 3 activity tracker, AnaMed OEM device multisensor and Air Next spirometer will be collected, stored, and summarized to allow for visualization dashboards to track participant compliance and extract sensor data when the study is complete. There will be a scalable infrastructure for integration and processing of sensor data that involves the following:

- integration of data from the Garmin, AnaMed OEM device, and Air Next spirometer sensors;
- processing, storage and auditing of data;
- dashboards for compliance and operational oversight;
- APIs to transfer data to external analytics.

Mobile Health Apps

Participants will be provided with a smartphone (iPhone) to perform and visualize measurements and to assess their health status using the symptomaster.com application and zdrav.kz database as tools to determine potential AEs. The participants are expected to keep smartphones, which will serve as compensation for participation in the study. The mHealth devices will be collected after the study completion. This will be reflected in the Informed Consent Form.

Figure 3. Interrelationship of our proprietary SmartHealth technologies in the early detection, diagnosis, and management of common diseases.



We developed an expert SmartHealth technology called symptomaster.com, which helps patients to establish the probable causes of the symptoms of diseases without assistance from a healthcare professional. Using a computer, a smartphone, or a tablet, a patient inputs his/her symptoms into the system when then produces the most likely preliminary diagnosis. After receiving the diagnosis, a patient can refer to zdrav.kz, an online library that contains information about 1000 most common diseases, and their causes, symptoms, and ways to prevent and treat them. Our technologies allow a patient to make an informed decision on whether they should seek immediate medical assistance by calling an ambulance or consult a doctor on their next routine visit (Sharman et al., 2017).

In partnership with developers from Poland and the United States we designed a new product called medintel.kz (known in Europe as dxmate.com), a technology that uses machine learning to diagnose diseases. The technology is publicly available to all medical professionals. It is designed in such a way so that the more information about symptoms and other manifestations of diseases and clinical conditions is entered into the system the more accurate are the algorithms that lead to more precise disease diagnosis (Sharman et al., 2017).

MedIntel.kz is updated in real time, and new information comes not only from scientific data but also from statistical information that doctors and clinics input into its machine learning algorithms. In the future, doctors can input genetic information from their patients and their relatives into the system to produce more accurate diagnoses and identify risk factors and conditions that predispose a patient to certain illnesses.

Symptomaster can be used to capture symptoms that may be related to AEs and severe AEs (SAEs). Further assessment can be done by a physician assistant during home visit or remotely by using MedIntel technology to make a decision about the need for a participant to visit KAPM's COPD Center for further assessment.

SAFETY ASSESSMENTS

The proposed study is an observational cohort study which uses study procedures with well-established risk profiles. According to classification based on risk determination (Institute of Translational Health Sciences, 2010), the study fits to the second category, for which independent study monitor is recommended. CRO (Synergy) will perform this function.

Safety Monitoring

The principal investigator (PI) will monitor the study, including review of study conduct, enrollment, and AEs with prompt reporting of AEs and other study-related information to the local and national ethics committees, sponsor, and other agencies as appropriate. Any deviations and changes in risks will be reported to the ethics committees, along with an annual status report. In addition, a detailed plan for oversight of the procedures by study staff will be provided.

Adverse Events

Adverse Event Report (AER) forms will be used to collect initial and follow-up information for non-serious and serious AEs, from Baseline through to Day 90. The following information will be collected for all AEs:

- date of onset;
- description of the AE;
- severity;
- relation to investigational devices;
- action taken with the study intervention;
- outcome;
- date of resolution.

If treatment is required for the AE, this will be recorded including the type of treatment, duration and any other relevant details. AE information will be captured on source documents and the investigator will sign off on each individual AE.

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized, or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered treatment-related (i.e., possibly related or related) will be followed until resolution or stabilization.

AE Severity

AE severity (intensity) will be classified as mild, moderate, or severe according to the following definitions:

- Mild: causing no limitation in normal activities.

- Moderate: causing some limitation in normal activities.
- Severe: causing significant limitation in or the inability to perform normal activities.

The PI will assess and assign the severity of all reported AE's.

Relationship
The PI is responsible for determining the relationship between an AE and the study products.

The relationship will be classified as one of the following:

- Probable: good reasons and sufficient documentation to assume a causal relationship.
- Possible: a causal relationship is conceivable and cannot be dismissed.
- Unlikely: the event is most likely related to an etiology other than the trial product.
- Definitely not related: the event is not related to the study product.

Expected AEs are those events which are reported to the study site by the sponsor or those that can be found in the peer-reviewed literature. By definition, unexpected AEs are those events which are not reported to the study site by the sponsor and not found in the literature, or are not consistent with the specificity or severity described by the sponsor or in the literature. An unanticipated problem is an unforeseen event that occurs during the course of a research trial that potentially increases the risk to participants or others; adversely affects the rights, safety, or welfare of participants; or affects the integrity of the study. All unanticipated problems involving risks to human subjects or others will be reported promptly to the ethics committees and sponsor (KAPM).

Serious Adverse Events
A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization (social admissions excluded), results in a persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is an important medical event.

Any SAE occurring in a participant after providing informed consent and until 30 days after completing the study will be recorded and reported.

All SAEs, whether related or unrelated to investigational devices, whether expected or unexpected, will be reported to the sponsor within 24 hours of site knowledge of the event.

All SAEs will also be reported to the ethics committees.

If an ongoing SAE changes in its intensity or relationship to study product or additional information becomes available, a follow-up SAE report will be sent to the sponsor and Ethics Committee.

It is KAPM's decision whether or not an SAE should be reported to Kazakhstan's health authorities.

ETHICAL CONSIDERATIONS

Ethical Conduct of the Study

The investigator will ensure that this study is conducted in accordance with the ethical principles founded in the most recent revision of the Declaration of Helsinki and in accordance with Order #142 of Kazakhstan's Ministry of Health, dated April 2, 2018.

The study will be conducted in accordance with the approved study protocol and standard operating procedures that meet the guidelines provided by the International Council for Harmonisation E6 for Good Clinical Practice (GCP) in clinical studies (ICH, 2016).

Participation Information and Consent

All participants in the proposed study shall be identified and contacted for informed consent pending approval of the National Ethics Committee of the Ministry of Health and a local ethics committee. The investigator will fully inform participants of all pertinent aspects of the trial, including the written information approved by the ethics committee.

Prior to the first study-specific procedure, the written ICF will be signed and personally dated by the participant and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form will be given to each participant and one copy will be retained in the investigator's study records.

Subject Confidentiality and Disclosure

Health records shall be handled according to Kazakhstan's Law on Protected Personal Information. All personal information will be removed, and demographic information will be anonymized, consistent with Kazakhstan legal requirements, GCP, and ethics committee policy.

Data on participants collected on CRFs during the trial will be documented in an anonymous fashion and the participant will only be identified by the participant number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the participant, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial participants. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a participant participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

Disclosure of Information

All information provided to the investigator, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

QUALITY CONTROL AND ASSURANCE

The sponsor (KAPM) will implement the quality assurance and quality control system in accordance with the standard operating procedures specified by the sponsor to ensure that the implementation of the study and the generation, recording, and reporting of data are in compliance with the following:

1) The clinical study protocol.
2) Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.
3) GCP ordinance.

In addition, the sponsor will perform quality control at each stage of data handling to ensure the reliability and proper processing of all study-related data. The methods for quality control will be prepared in advance in accordance with the standard operating procedure specified by the sponsor, and the implementation will be recorded.

The sponsor's responsible auditor will perform GCP auditing as part of quality assurance operations to determine whether the study is conducted in compliance with GCP, the clinical study protocol, and the written procedures independently and separately from the regular monitoring and study quality control operations.

Statistical Analysis Plan

For this proof-of-concept phase, access to device-derived data will be enabled via a cloud-to-cloud solution. 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.

The final statistical analysis plan will be written as a separate document and completed after finalizing the protocol before first subject in. 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).

Changes in the Planned Analysis

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

Data Management Plan

All study data will be stored at the IT Unit of the Academy of Preventive Medicine of Kazakhstan, Almaty, Kazakhstan. Verification of eligibility will be completed via a web questionnaire after participants sign the research consent form, and participants tracked for completion of all study data. If a participant is excluded or discontinues during or after the study procedures, the specific exclusion or discontinuation reason will be recorded in the database.

All electronic files will be encoded using 128-bit advanced encryption standard and password protected on a computer with both hardware and software firewalls. The locator form and any documents with identifying information will be kept in a separate folder and kept locked in filing cabinets.

Data analysis will be performed only in aggregate. All data will be used for research purposes only and no participant will be identified when the data are analyzed, presented, or published. No individually identifiable information will be published.

Publication & Presentation Strategy

The study targets clinicians, biomedical researchers, statisticians, health care policy makers, and interested public. Clinicians and biomedical researchers are considered to be professional users, data contributors, and key opinion leaders. Other professional users include statisticians and health care policy makers.

The use of the study results by the local and international scientific communities will depend on publications in peer-reviewed English and Russian language professional/academic society journals. The project is planned to result in numerous publications in peer-reviewed scientific journals as well as presentations at international conferences and symposiums. For now, we plan to publish paper(s) in international peer-reviewed journals presenting intermediate and final results of the proof-of-concept/Assessment study and the randomized control study.

The Academy of Preventive Medicine will confirm the values and outcomes of its programs through outcomes analysis and comprehensive reporting that will be meaningful and, most importantly, transparent.

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Appendices

ACADEMY OF PREVENTIVE MEDICINE OF KAZAKHSTAN

The Kazakhstan Academy of Preventive Medicine (KAPM) is nongovernmental organization founded in 1995 by a group of the nation's leading health care managers, business leaders, and physician-researchers (academypm.org). Based on its extensive track record of projects and experience in Kazakhstan and Central Asia region, the Academy can offer the best possible combination of technical expertise and local know-how. The Academy's main strengths and specific advantages in this context are as follows:

- Proven record of implementing international projects, and excellent knowledge of the national and international regulations and procedures.
- Extensive track record of implementing projects in the areas of clinical research, demographic and health surveys, medical technologies, health policy and health financing, policy formulation.
- In-house staff with expertise in clinical research, health surveys, biomedical statistics, computer engineering, health systems development and management, quality management and control.
- Strong linkages with the Ministry of Health and a range of hospitals and universities, research, and public health institutes in Kazakhstan and internationally.
- Access to highly experienced and qualified national, regional and international consultants with experience in and around the region of Central Asia and post-Soviet countries.
- In-depth and up-to-date knowledge of important health sector reform processes in the post-Soviet region gained through experience in long-term projects presented in numerous health policy white papers published on the academy's website academypm.org.

    National Public Health Services: http://www.academypm.org/language/ru/sluzhba-obshhestvennogo-zdorovya-respubliki-kazaxstan-the-white-paper/

    School Health: physical activity and healthy nutrition: http://www.academypm.org/language/ru/programma-zdorovya-shkolnikov-balaman-rukovodstva-po-ozdorovleniyu-shkolnikov-the-white-paper/

    Personalized and preventive medicine: regulation of biobanks and genetic research: http://www.academypm.org/language/ru/personalizirovannaya-i-preventivnaya-medicina-voprosy-regulirovaniya-biobankov-i-geneticheskix-issledovanij/

    Translational research: http://www.academypm.org/language/ru/perspektivy-translyacionnoj-mediciny-the-white-paper/

More details about the Academy of preventive Medicine is here: http://www.academypm.org/language/en/

CRO Responsibilities

TASK	SPONSOR (KAPM)	CRO
Model and review informed consent design	X	X
Informed consent local version final approval		X
Referral site selection		X
Develop patient questionnaire for referral site		X
Document review (protocol, CRF) and consultancy with KOL's (for complex documents)		X
Develop monitoring manual		X
STUDY START-UP ACTIVITIES		
CRA training		X
Kick-off meeting		X
Referral sites Identification and selection, list of site finalization		X
Collection, review and tracking of site regulatory documents		X
Prepare and collect the documents for submission to regulatory authority		X
ETHICS COMMITTEE / IRB & REGULATORY APPLICATIONS		
Preparation, submission of documents to the local ethics committee		X
Assist investigators in submitting the documents and obtaining approval from the local ethics committee		X
Start and end of study notification to regulatory agencies / ethics comittees		X
INVESTIGATOR MEETING		
Investigator meeting planning		X
Investigator meeting preparation, training investigators		X
SERVICES DURING CLINICAL STUDY CONDUCT		
PM work throughout the study (until first patient in)		X
PM work throughout the study (clinical study duration)		X
PM work throughout the study (LSO to End of CRO involvement)		X
Perform site initiation visits - LOCAL		X
Perform interim monitoring visits - REMOTE		X
Perform site closeout monitoring visits - LOCAL		X

TASK	SPONSOR (KAPM)	CRO
Maintain TMF IF throughout the study		X
Site management		X
SAFETY MONITORING		
Reporting SAEs to the local ethics committee, sponsor		X

The 6-Minute Walk Test

APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

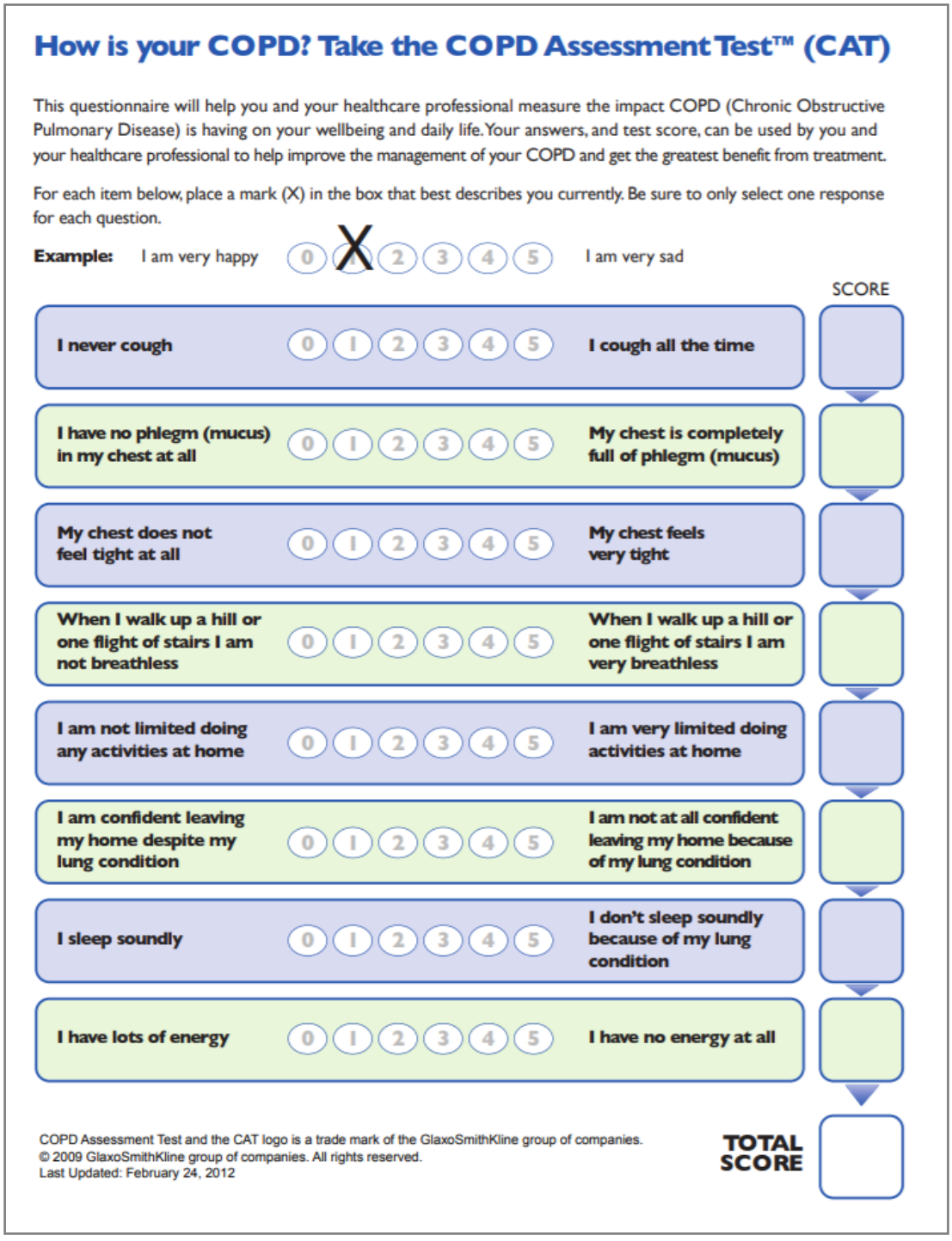
Predicted distance: _____ meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

Reference: ATS Statement: Guidelines for the Six-Minute Walk Test. Available at: https://www.thoracic.org/statements/resources/pfet/sixminute.pdf. Accessed on Dec 18, 2017.

The COPD Assessment Test (CAT)



How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 1 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

Last Updated: February 24, 2012

Table of CAT Scores: Impact and Clinical Implications

CAT score	Impact level	Broad clinical picture of the impact of COPD by CAT score	Possible management considerations
>30	Very high	The condition prevents the patient from doing what they want to do, and they never have any good days. If they can manage to take a bath or shower, it takes them a long time. They cannot go out of the house for shopping or recreation or do their housework. Often, they cannot go far from their bed or chair. They feel as if they have become an invalid.	Patient has significant room for improvement. In addition to the guidance for patients with low and medium impact CAT scores consider: • Referral to specialist care (if you are a primary care physician) Also consider: • Additional pharmacological treatments • Referral for pulmonary rehabilitation • Ensure best approaches to minimizing and managing exacerbations
>20	High	COPD prevents the patient from doing most things that they want to do. They are breathless walking around the home and when getting washed or dressed. They may be breathless when they talk. Their cough makes them tired and their chest symptoms disturb their sleep on most nights. They feel that exercise is not safe for them and everything they do seems too much effort. They are afraid and panic and do not feel in control of their chest problem.	
10-20	Medium	COPD is one of the most important problems that the patient has. They have a few good days a week, but cough up sputum on most days and have one or two exacerbations a year. They are breathless on most days and usually wake up with chest tightness or wheeze. They get breathless on bending over and can only walk up a flight of stairs slowly. They either do their housework slowly or have to stop for rests.	Patient has room for improvement – optimize management. In addition to the guidance provided for patients with low impact CAT scores consider: • Reviewing maintenance therapy – is it optimal? • Referral for pulmonary rehabilitation • Ensure best approaches to minimizing and managing exacerbations • Reviewing aggravating factors – is the patient still smoking?
<10	Low	Most days are good, but COPD causes a few problems and prevents the patient from doing one or two things that they would like to do. They usually cough several days a week and get breathless when playing sports and games and when carrying heavy loads. They have to slow down or stop when walking up hills or if they hurry when walking on level ground. They get exhausted easily.	• Smoking cessation • Annual influenza vaccination • Reduce exposure to exacerbation risk factors • Therapy as warranted by further clinical assessment
5		Upper limit of normal in healthy non-smokers	

Reference: Jones PW, Tabberer M, Chen W. Creating scenarios of the impact of COPD and their relationship to COPD assessment test (CATTM) scores. BMC Pulmonary Medicine 2011;11:42.