Use of ProAir Digihaler in COPD - Characterization of inhalation metrics from a cohort of patient at-risk for AECOPD in an outpatient setting

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Use of ProAir Digihaler in COPD - Characterization of inhalation metrics from a cohort of patient at-risk for AECOPD in an outpatient setting

Running Title: Digihaler in COPD

National Clinical Trial (NCT) Identified Number: N/A

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Funded by: Teva

Funding Agency Collaborators: Amanda Roe, Tanisha Hill

Version Number: v.1.2

21 March 2022

I confirm that I have read this protocol and understand it.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the terms and conditions of the contract. The Principal Investigators will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title	Use of ProAir Digihaler in COPD - Characterization of inhalation metrics from a cohort of patient at-risk for an acute exacerbation of COPD (AECOPD) in an outpatient setting
Study Description	The albuterol sulfate electronic multidose dry powder inhaler (Albuterol eMDPI) Digital System (DS) (ProAir® Digihaler®) is the first and only FDA approved inhaler rescue medication with a built-in sensor to detect and record inhaler use. The inhaler device measures peak inspiratory flow (PIF) and the app groups PIF into categories that can help to highlight potential patient inhaler technique errors. This study will deploy this product in COPD patients to establish foundational data on Digihaler metrics in a COPD population at greater risk for COPD exacerbations. Adult subjects with COPD recruited from two sites (UNC and Wake Forest) will participate in a longitudinal study to collect data regarding the normal variation in Digihaler metrics (PIF, inhalation volume, # inhalations), a daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale as well as responses to a Digihaler metric algorithm-triggered digital automated questionnaire (DAQ) in a stable COPD population with history of an AECOPD, to assess correlations of Digihaler metrics to daily self-assessment and DAQ responses, correlations of self-reported to actual short acting beta agonist (SABA) use and symptoms, and the changes in inhaler paramenters and SABA use around incidental AECOPD.
Objectives	**Primary Objective**. • To determine the variation in ProAir Digihaler metrics (PIF, inhalation volume, number of inhalation events) amongst COPD patients in the ambulatory setting.

Secondary Objectives.

- To determine the correlation of self-reported SABA use with actual SABA use collected by the ProAir Digihaler.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with monthly CAT score domains.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with the daily daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale.

Exploratory Objectives.

- To determine the change in inhaler metrics in patients experiencing an AECOPD during study period.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with the Digihaler metric algorithm-triggered DAQ.
- To describe COPD-related health-care resource utilization (HRU):
    - Number of COPD exacerbations-associated hospitalizations
        - Proportion of patients with 30-day COPD-related hospital re-admission
    - Number of COPD exacerbations-associated emergency room visits
        - Proportion of patients with 30-day COPD-related emergency room re-admission
    - SABA utilization
- To describe patient treatment/device satisfaction/ease of use.
- To describe patient APP satisfaction/ease of use.

Study Design

Multicenter 3-month observational study

Outcome Measures

Primary Outcome Measure:

1. Variability in Peak Inspiratory Flow (PIF) Measured via Digihaler Device (Time Frame: Three months)
    a. PIF is the maximal flow occurring during an inhalation effort, expressed in Liters/minute. Mean, standard deviation and coefficient of variation (calculated by dividing standard deviation of PIF by the mean of the PIF) of daily PIF measurement collected over three months will be calculated. PIF will be measured using the Digihaler device.

Secondary Outcome Measures:

1. Correlation of Self-Reported Inhaler Use with Actual Inhaler Use (Time Frame: 3 months)
    a. Correlation between self-reported inhaler use and actual inhaler use over three months will be calculated with Spearman rank-order correlation coefficient. Self-reported inhaler use will be determined with an investigator-

developed single question categorizing average use over the last four weeks with five groups (not at all, once a week or less, two or three times a week, one or two times a day, three or more times a day). Actual inhaler use will be directly measured via Digihaler device and categorized into one of the five groups described above.

2. Variability in Inhalation Volume Measured via Digihaler (Time Frame: Three months)
    a. Inhalation volume is the volume of air inspired during an inhalation effort, expressed in Liters. The mean, standard deviation and coefficient of variation (calculated by dividing standard deviation of inhalation volume by the mean of the inhalation volume) of daily inhalation volume measurements collected daily over three months will be calculated. Inhalation volume will be measured using the Digihaler device.

Analysis Strategy

The primary analysis will be descriptive, with analytical plans as defined above for each primary and secondary outcome.

Additional exploratory analysis will include linear regression (continuous) or negative binomial regression (count) of the clinical and demographic factors associated with inhaler from primary and secondary outcomes; descriptive statistics (mean, median, variance estimate and 95% confidence intervals) of number of inhalation events, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with CAT score, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with responses to metric algorithm-triggered DAQ; change in inhaler metrics (during the 7 days after and/or leading into hospitalized AECOPD or home treatment of a moderate AECOPD defined by a prescription for steroids and/or antibiotics); descriptive statistics (proportion, 95% CI) of COPD-associated hospitalizations and emergency room visits as well as SABA utilization; and patient satisfaction will be assessed with a post-study survey.

Target Population

Inclusion Criteria:

- Age >40 years old
- History of cigarette smoking >=10 pack-years
- Established COPD defined as physician diagnosis along with spirometry confirmation (post-BD FEV1/FVC<0.70) within the last two years and an FEV1 ≤80% predicted
- Regular albuterol use (defined as at least one puff weekly for each of the last four weeks)
- Currently non-hospitalized

- Medical records confirmed history of two moderate AECOPD (defined as use of antibiotic or steroids to treat clinical event consistent with AECOPD) or one severe AECOPD (defined as ED/hospital visit) in prior 12 months
- Access to smartphone, tablet or computer and internet
- Willingness to switch current rescue inhaler/device to ProAir Digihaler

Exclusion Criteria:

- Allergy or inability/contraindication to use Albuterol Sulfate
- Any condition that, in the opinion of the site investigator, would compromise the subject's ability to participate in the study

Study Cohort

Patients (n=60) with documented COPD and a history of two moderate or one severe AECOPD in prior 12 months.

Phase

This is an early-stage preparatory study that paves the way for this line of research moving forward into multicenter clinical trials.

Research Sites

This study will enroll patients who are currently followed at The University of North Carolina at Chapel Hill (N=30) or Wake Forest University in Winston-Salem, NC (N=30). Participants will be recruited from existing clinical pools at both sites including COPD registries, virtual and in-person outpatient clinics (routine or post-hospital discharge).

Description of Study Intervention:

In light of the COVID pandemic, this study is designed to be conducted entirely virtually to minimize any potential interruptions related to COVID. After identification and consenting, participants will be mailed the ProAir Digihaler (provided by Teva). The study coordinator will contact the participant to ensure set-up and correct usage. Participants will be asked to use the ProAir Digihaler as their primary mode of SABA therapy as they would in usual treatment and indicated in the product package insert and Instructions for Use. They will be provided a COPD Action Plan to ensure they have appropriate instructions to handle a possible AECOPD. They will answer a daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale on the DAQ App, as well as Digihaler metric algorithm-triggered DAQ on the DAQ app. The DAQ will collect yes/no responses to questions focused on change in respiratory symptoms, sleep disturbances, daily activity limitation, and anxiousness.. The participants will be contacted once per month to collect CAT score and self-reported average albuterol use over the preceding month. They will also be asked about any AECOPD events requiring treatment with antibiotics and/or steroids or hospitalization in the prior month. Participants will be enrolled for three months duration. All individuals will be provided three inhalers at enrollment. In the event their ProAir Digihaler does not last three months, they will be prescribed another ProAir Digihaler (provided by Teva).

Study Duration:

This study is intended to last 18 months.

Participant Duration:

There will be no in-person visits. Participants will undergo a virtual screening/enrollment visit, followed by an initial check-in call to ensure device set up within one week of receipt. They will then receive three monthly calls during study. In the event the participant has an AECOPD

within two weeks of end of study, they will be followed for 14 days after AECOPD resolution. Total participant duration is three months (+21 days to account for 14 days in event of AECOPD and seven day window at end of study).

1.2 SCHEMA

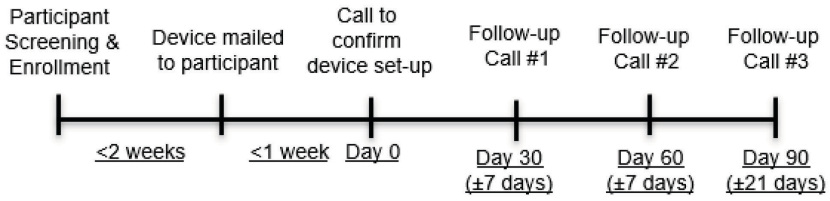

Figure 1.2.1: Timeline of planned study events.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening & Enrollment Virtual Visit	Confirmatory Phone Call	Phone visit #1	Phone visit #2	Phone visit #3
Time Window (days)	-21	0	30±7	60±7	90±21
Informed consent	X				
Demographics	X				
Medical history	X				
Confirmation of Device Set-Up		X			
COPD Assessment Test	X		X	X	X
COPD Exacerbation History	X		X	X	X
Inhaler Use and Compliance	X		X	X	X
Adverse Event Assessment		X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

The ProAir Digihaler is the first and only digital inhaler with a built-in sensor to detect inhaler use, measure inspiratory flow, and capture potential technique errors. This device has been studied in asthma, but little information is available regarding the measurement characteristics in COPD patients. This device has the potential to help assess SABA use as a marker of COPD control and identify inspiratory flow metrics representing the onset of an AECOPD. In order to inform these purposes, it is necessary to first characterize the normal variation in Digihaler metrics (PIF, inhalation volume, # inhalations) in a stable COPD population with history of AECOPD as well as assess the changes around incidental AECOPD and

correlations of self-reported with actual SABA use and COPD patient reported outcomes. The accompanying app also permits collection of a daily self-assessment asking “How are you feeling?” with responses provided on a Leikert scale and responses to a Digihaler metric algorithm-triggered DAQ on the DAQapp. The DAQ will collect yes/no responses to questions focused on change in respiratory symptoms, sleep disturbances, daily activity limitation, and anxiousness.. Collecting these foundational data are the specific objectives of this proposal.

2.2 BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the United States. It is characterized by fluctuating respiratory symptoms punctuated by transient acute worsening termed acute exacerbations of COPD (AECOPD). The optimal management COPD requires accurate assessment of respiratory symptom burden, prevention, timely identification and early intervention on AECOPD (www.GOLD.org). A key component of symptom management is the use of inhaled short-acting beta-agonists (SABA). Per treatment strategies, all individuals with spirometry-confirmed COPD (regardless of severity) should be prescribed SABA therapy. Accurate assessment of SABA use is essential in COPD, as it not only informs overall symptom control but also may also herald onset of an AECOPD event. Unfortunately, several studies have demonstrated that physicians are ineffective at accurately assessing SABA usage as a marker of disease control, as patients often misreport their actual use. Moreover, there are no technologies that could serve to automatically alert a patient or provider about abrupt increases in SABA use or decreases in inspiratory flow rate, which may both identify an impending AECOPD. Closing these assessment gaps through real-time electronic capture of SABA use has the potential to improve the assessment and care of COPD patients in the chronic setting and during acute decompensation.

There are several factors that can impact successful SABA administration. These include inhalation technique, duration, and inspiratory effort. Dry-powder inhalers (DPIs) are breath-actuated and tend to be easier for patients to use than metered dose inhaler or soft mist inhalers. However, there is emerging evidence that delivery from DPI may be suboptimal in some patients and settings. It has recently been shown that COPD patients can exhibit suboptimal peak inspiratory flow (PIF) in the stable outpatient setting (Ghosh, Sulaiman) and during hospital exacerbations (Loh, Sharma). Although published evidence regarding suboptimal delivery from DPIs in the COPD population is emerging, substantial knowledge gaps exist including the day to day variation in PIF in ambulatory COPD patients when clinically stable and during periods leading up to and recovery from AECOPD.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study is considered low risk as all participants enrolled will already by using albuterol in their clinical care. Potential risks include albuterol side effects or loss of confidentiality.

Inhaled albuterol is the most commonly used rescue medication used in the COPD population as part of their normal clinical care. Standard doses of inhaled albuterol can cause transient cough, mild tachycardia, and tremors.

There is a chance of emotional distress if data from questionnaires or other home testing domains are not kept private. Safeguards are taken to ensure that subjects' confidentiality is maintained. General study measures include: 1) unique study numbers on documents containing de-identified data; 2) maintaining identifiers on linking file in a locked drawer in a private office; and 3)restricting access to files and

password protected databases to essential study personnel. All data are reported without personal identifiers. The study investigators, who will have access to the medical chart and personal data for study participants, have already received training and certification according to the institutions obligations under the Health Insurance Portability and Accountability Act (HIPAA). We will use unique study numbers. The linking form will be the only form linking study ID to personal data. This will be maintained in a locked drawer in a private office. We will maintain all other data linked to study ID on REDCap. All study related forms (regardless of identified or de-identified) will be placed in locked files and kept in a separate office from the linking file. Electronic data will be retained on a secure network via REDCap or password protected files.

The DAQApp provides patients with a Privacy Notice within the App explaining Teva's policies and practices for handling information and the choices that patients can make about the how their information is collected and used. Information that is collected and its use is described in detail in the Privacy Notice. Patients must accept the privacy notice within the App and provide in-App consent to store their information in a cloud prior to using the App functionality. Information stored may include inhalation events, inhalation metrics as well as DAQ App diagnostic data. Patients must also provide a separate consent to share their information with a specific healthcare provider or research study site by signing up to a restricted access “Healthcare Program” within the DAQ App. A healthcare provider or research study personnel can view the information via a web-based application, the Digihaler® Dashboard.

Teva has enacted commercially reasonable physical, technical, and administrative safeguards to secure information that is collected and stored on the Teva Digital System, which includes the App, the dashboard and the cloud. To prevent unauthorized access to their personal information, the App or any portion thereof, to maintain information accuracy, and to ensure the correct use of information, patients are strongly encouraged to password protect their device and refrain from providing any third party with unsupervised access to their device.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known individual benefits that are expected as a result of this trial. Rather, we expect that the benefit will be to society as a whole if this study helps to advance the understanding of the ProAir Digihaler in the COPD population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Before participating in the study, subjects will be asked about history of intolerance to albuterol. The study team will also confirm that the participant is using albuterol on a regular basis (defined as at least one puff weekly for each of the last four weeks). If the safety of albuterol use cannot be assured, the subject will be excluded from the study.

3 OBJECTIVES

Primary Objective:

- To determine the variation in ProAir Digihaler metrics (PIF, inhalation volume, number of inhalation events) amongst COPD patients in the ambulatory setting.

Secondary Objectives.

- To determine the correlation of self-reported SABA use with actual SABA use collected by the ProAir Digihaler.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with monthly CAT score domains.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with the daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale.

Exploratory Objectives.

- To determine the change in inhaler metrics in patients experiencing an AECOPD during study period.
- To determine the correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with the Digihaler metric algorithm-triggered DAQ.
- To describe COPD-related health-care resource utilization (HRU):
    - Number of COPD exacerbations-associated hospitalizations
        - Proportion of patients with 30-day COPD-related hospital re-admission
    - Number of COPD exacerbations-associated emergency room visits
        - Proportion of patients with 30-day COPD-related emergency room re-admission
    - SABA utilization
- To describe patient treatment/device satisfaction/ease of use.
- To describe patient APP satisfaction/ease of use.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multisite, observational, 3-month pilot study of ProAir Digihaler use in 60 COPD patients at-risk for AECOPD. Participants will be recruited from two sites (Wake Forest University, N=30; University of North Carolina at Chapel Hill, N=30). All participants will have spirometry-confirmed COPD with an increased AECOPD risk (defined as two moderate or one severe AECOPD in the last 12 months).

Participants will be recruited from existing clinical pools at both sites including COPD registries, virtual and in-person outpatient clinics (routine or post-hospital discharge). Although this study will not be powered to make meaningful assessments of inhaler metric changes at the time of an AECOPD, we are permitting patients recently discharged for an AECOPD event to be enrolled, which will permit assessment of changes during the recovery phase as well as enrich for individuals more likely to have an AECOPD event during study.

In light of the COVID pandemic, this study is designed to be conducted entirely virtually to minimize any potential interruptions related to COVID. Both UNC and Wake Forest have experience conducting virtual studies with local IRB approval. Potentially eligible patients will be identified and screened for possible inclusion through existing registry review, virtual clinic visits or in-person visits.

Potentially eligible participants will be contacted, with the permission of their care providers, by study investigators or research coordinators and assessed for interest. Based on local IRB approval, they will either be mailed an informed consent (ICF) for phone review with the research coordinator or will complete verbal consent over the phone. After consenting, participants will be mailed the ProAir Digihaler (provided by Teva) The study coordinator will contact the participant to ensure set-up and correct usage.

Participants will then be asked to use the ProAir Digihaler as their primary mode of SABA therapy as they would in usual treatment and indicated in the product package insert and Instructions for Use. They will be provided a COPD Action Plan to ensure they have appropriate instructions to handle a possible AECOPD. They will answer a daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale on the DAQ App, as well as Digihaler metric algorithm-triggered DAQ on the DAQ app.

The participants will be contacted once per month to collect CAT score and self-reported average albuterol use over the preceding month. They will also be asked about any AECOPD events requiring treatment with antibiotics or steroids in the prior month. If there is evidence during the calls of clinical deterioration by self report or an abrupt increase in CAT by > 4 units patients will be advised to contact their primary care or COPD provider.

Participants will be enrolled for three months duration. In the event the participant has an AECOPD within two weeks of end of study, they will be followed for 14 days after AECOPD resolution. Total participant duration is three months (+21 days to account for 14 days in event of AECOPD and seven day window at end of study). In the event their ProAir Digihaler does not last three months, they will be prescribed another device (provided by Teva). Hospital admission during the course of the study will not prohibit continued participation.

4.2 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last phone visit shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Age >40 years old
- History of cigarette smoking >=10 pack-years
- Established COPD defined as physician diagnosis along with spirometry confirmation (post-BD FEV1/FVC<0.70) within the last two years and an FEV1 ≤80% predicted
- Regular albuterol use (defined as at least one puff weekly for each of the last four weeks)
- Currently non-hospitalized
- Medical records confirmed history of two moderate AECOPD (defined as use of antibiotic or steroids to treat clinical event consistent with AECOPD) or one severe AECOPD (defined as ED/hospital visit) in prior 12 months
- Access to smartphone, tablet or computer and internet
- Willingness to switch current rescue inhaler/device to ProAir Digihaler

5.2 EXCLUSION CRITERIA

Subjects presenting with any of the following will not be included in the trial:

- Allergy or inability/contraindication to use Albuterol Sulfate
- Any condition that, in the opinion of the site investigator, would compromise the subject's ability to participate in the study

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

The target number of study participants is 60 adult subjects (N=30 at each site). We expect that all, or nearly all, subjects will be recruited within 12 months. Subjects participating in other observational studies will not be excluded from participation, as long as they meet all other inclusion criteria, but interventional pulmonary drug studies will not be concurrently allowed. Participants will be recruited from existing clinical pools at both sites including COPD registries, virtual and in-person outpatient clinics (routine or post-hospital discharge). Although this study will not be powered to make meaningful assessments of inhaler metric changes at the time of an AECOPD, the purposeful enrollment of patients recently discharged for an AECOPD event will permit assessment of changes during the recovery phase as well as enrich for individuals more likely to have an AECOPD event during study. Given the purposeful design of the study through an all virtual process, we do not anticipate impediments to recruitment in light of the dynamic COVID pandemic.

As this is a study of short duration that incorporates a medication already part of a patient's routine care, we anticipate that there will not be significant issues with retention. Monthly phone calls will occur to record interval medical history. Such contacts also reinforce study participation and retention. Additionally, the provision of the inhaled medication by the study sponsor will further facilitate participant retention during the study. The use of a completion fee (described below) further facilitates study retention.

Subjects will be reimbursed $50 for completion of each of the three calls, along with a $50 completion fee (Totaling $200) as a means of compensating patients for their time on calls and completing study questionnaires. As this is an all virtual study, there will not be any reimbursements for travel.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Participants will be recruited from two sites (Wake Forest University, N=30; University of North Carolina at Chapel Hill, N=30). Participants will be recruited from existing clinical pools at both sites including COPD registries, virtual and in-person outpatient clinics (routine or post-hospital discharge).

In light of the COVID pandemic, this study is designed to be conducted entirely virtually to minimize any potential interruptions related to COVID. Both UNC and Wake Forest have experience conducting virtual studies with local IRB approval. Potentially eligible patients will be identified and screened for possible inclusion through existing registry review, virtual clinic visits or in-person visits.

Potentially eligible participants will be contacted, with the permission of their care providers, by study investigators or research coordinators and assessed for interest. Based on local IRB approval, they will either be mailed an informed consent (ICF) for phone review with the research coordinator or will complete verbal consent over the phone. After consenting, participants will be mailed the ProAir Digihaler (provided by Teva) The study coordinator will contact the participant to ensure set-up and correct usage. Patients will participate in a monthly call to capture CAT score, albuterol use recall and AECOPD events during study period.

Participants will then be asked to use the ProAir Digihaler as their primary mode of SABA therapy as they would in usual treatment and indicated in the product package insert and Instructions for Use. They will answer a daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale on the DAQ App, as well as Digihaler metric algorithm-triggered DAQ on the DAQ app. The DAQ will collect yes/no responses to questions focused on change in respiratory symptoms, sleep disturbances, daily activity limitation, recent AECOPD diagnosis and treatment, and anxiousness, as well as the Leikert "How are you feeling?" scale. The DAQ questionnaire will be triggered in the app based on an algorithm incorporating data from the digihaler metrics. The DAQ will be only deployed when indicated by the algorithm or on an ad-hoc basis by the patient (but not necessarily daily). They will be provided a COPD Action Plan to ensure they have appropriate instructions to handle a possible AECOPD.

The participants will be contacted once per month to collect CAT score and self-reported average albuterol use over the preceding month. They will also be asked about any AECOPD events requiring treatment with antibiotics or steroids in the prior month.

Specific Data Collection Includes:

Clinical Data: Enrollment characteristics including age, race, sex, smoking history, prior spirometric data (FEV1, FEV1% predicted, FVC, FVC % predicted, FEV1/FVC), exacerbation history, enrollment inhaler regimen, self-reported frequency of albuterol use, baseline CAT score

Data Collection Tools: Enrollment questionnaire, CAT questionnaire, monthly AECOPD and self-reported albuterol use questionnaire, and Digihaler device. The Digihaler uses integrated sensors to capture inhalation data and stores it onto an e-module inside the device. When within range, the e-module transfers the stored data using Bluetooth technology to a paired app on the users' phone. The app can display the data in various reports as well as export the reports in the form of pdfs which can be emailed. The app also shares the data to a server via a wifi connection which enables real-time data sharing to a provider facing dashboard. The data the provider sees is the same as what patients see and also have the ability to be exported into a .csv file for further analysis. For additional data points, beyond what the patient and provider currently see, our team has the ability to export more information in the form of data extracts from the back end cloud server. This can be setup to send at a predetermined interval for further analysis.

Patient Reported Outcomes (PROs): CAT questionnaire, self-reported monthly average albuterol use during study, daily self-assessment asking "How are you feeling?" with responses provided on a Leikert scale on the DAQ app, and Digihaler metric algorithm-triggered symptom questions using the DAQ app.

6.1.2 DOSING AND ADMINISTRATION

ProAir Respiclick will be dosed and administered in accordance with the package insert (*https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205636s000lbl.pdf*). Specifically, albuterol sulfate 117 mcg will be administered 2 inhalations repeated every 4 to 6 hours as needed.

6.2 STUDY INTERVENTION COMPLIANCE

Compliance with study interventions will be ensured by the study team during monthly.

6.3 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. There will be no disallowed medications in this study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Vital signs, if available
- Related medical records, if available

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded in the study file. Subjects who sign the informed consent form but who do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the initial study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will also be replaced, to ensure 60 complete adult data sets.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she is not able to be contacted on phone visit and no-longer is transmitting data via the DAQ app.

The following actions must be taken if a participant cannot be contacted:

- The site will attempt to contact the participant and reschedule the missed phone contact within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

No study results will be specifically distributed to the study subject.

8.1 OUTCOME ASSESSMENTS

- Digihaler PIF: mean, median, standard deviation
- Digihaler Inspiratory volume: mean, median, standard deviation
- Digihaler Inhaler usage: count
- Self-reported inhaler usage: Average use over the preceding month
- COPD Assessment Test (CAT) questionnaire: Collected monthly
- Self-report of COPD exacerbation events on study
- Responses to daily self-assessment asking "How are you feeling?" on Leikert scale (mean, median, standard deviation, variability)
- Responses to DAQ on the DAQ app (cumulative score and individual domains mean, median, and standard deviation; variability of the responses and adherence to daily reporting)

8.2 SAFETY AND OTHER ASSESSMENTS

Before participating in the study, subjects will be asked about history of intolerance to albuterol. The study team will also confirm that the participant is using albuterol on a regular basis (defined as at least one puff weekly for each of the last four weeks). If the safety of albuterol use cannot be assured, the subject will be excluded from the study. If any AE's or SAE's are detected, they will be followed by the investigator until symptoms have resolved.

8.3 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE DEVICE EFFECTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE) AND ADVERSE DEVICE EFFECTS (ADE)

An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Preexisting condition (i.e., a disorder present before the adverse event reporting period started) should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. This is particularly relevant for subjects with COPD who may have substantial symptoms at baseline.

An adverse device effect is an adverse event related to the use of an investigational medical device or combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Generally, adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Because of the nature of the disease population being studied, and the fact that part of the study includes evaluating subjects experiencing a COPD exacerbation with may require hospitalization, hospitalization will NOT obligatorily be considered an SAE for this study. Hospitalization will be reported as an SAE if, in the discretion of the investigator, it is temporally related to albuterol use.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a Serious Adverse Event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pretreatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Preplanned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) and Adverse Device Effects (ADEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality for adverse events will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other

concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician. As noted in 8.3.2, because of the nature of the disease population being studied, and the fact that that part of the study includes studying subjects experiencing a COPD exacerbation which may require hospitalization, hospitalization will NOT obligatorily be considered an SAE for this study. Hospitalization will be reported as an SAE if, in the discretion of the investigator, it is temporally related to albuterol use.

8.3.3.3 EXPECTEDNESS

The principal investigator or co-investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All ADEs, SAEs, and AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 24 hours after the last day of study participation. Events will be followed for outcome information until resolution or stabilization. Given the duration of the study, these events will be collected during the monthly phone calls by the study coordinator, unless the information is voluntarily provided by the subject in between study visits or phone calls.

8.3.5 ADVERSE EVENT REPORTING

In keeping with good clinical practice or good pharmacovigilance practice, and 21 C.F.R. Part 314 as the case may be, the external investigator will be required to report and notify the Teva Pharmaceuticals (Teva) of all situations mentioned below, within twenty-four (24) hours from receiving information of the situation. The event will be reported to Teva by submitting the collected information to the Teva Local Safety Officer. The event will also be reported to the FDA, Institutional Review Boards (IRBs), and any other collaborators/investigators according to national, and local safety reporting requirements.

(a) All related Serious Adverse Events

(b) All Serious Adverse Device Effects

(c) Any exposure of a pregnant study participant to the study drug within thirty (30) days of exposure

(d) Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the study

Each adverse event is to be classified by the investigator as serious or non-serious. This classification determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting will follow FDA and IRB regulations. If an adverse event is both serious and unexpected, reporting will follow IRB reporting regulations as appropriate. SAEs are reportable from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the trial (i.e., prior to undergoing any trial-related procedure through and including 24 hours after the final call). Any serious adverse event occurring at any other time during the study must be promptly reported if a causal relationship to study drug is suspected.

If a serious adverse event occurs, the Institutional IRB will be notified within five business days of awareness of the event by the investigator. The study coordinator may initiate the IRB notification, but it must be filed by the study investigator or co-investigators. If the serious adverse event is fatal or life threatening, notification to the Institutional IRB must be made within 24 hours, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

The MedWatch 3500A form should be utilized to report serious adverse events to the FDA.

All adverse events (serious and non-serious) will be reported on the adverse event page(s) of the CRF. Adverse events should be reported using concise medical terminology on the CRFs. Non-serious AE's will be reported annually to the IRB as appropriate.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.7 ADVERSE EVENTS OF SPECIAL INTEREST

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 HYPOTHESIS

We hypothesize that inhaler metrics (PIF, inhalation volume, rescue inhaler use) will vary among COPD populations. We also hypothesize that increased albuterol use will positively correlate with worse daily Leikert scores, declining PIF, lower inhalation volume and higher CAT scores. We hypothesize that self-reported albuterol use will be lower than actual albuterol use captured by the DAQ app. We hypothesize that increased albuterol use will positively correlate with more symptomatic DAQ responses. The proposed study is designed to yield an initial exploration of the metrics captures by the Digihaler in a COPD population.

9.2 SAMPLE SIZE RATIONALE

The primary considerations in choosing the proposed target sample size were patient availability, fiscal costs, time required to complete the study, the proportion of subjects expected to complete the protocol, and conjectures about the precision of the estimators of interest. As such, this pilot study does not have pre-specified power calculations. Although this study will not be powered to make meaningful assessments of inhaler metric changes at the time of an AECOPD, we are permitting patients recently discharged for an AECOPD event to be enrolled, which will permit assessment of changes during the recovery phase as well as enrich for individuals more likely to have an AECOPD event during study.

9.3 MISSING DATA

The primary analyses will be “per protocol” analyses. Adult subjects must complete baseline and one month phone visit at minimum to be included in analysis. Subjects who complete these required visits will be included for analysis, and subjects who do not complete required visits will be excluded from the statistical analyses. Safety analyses will be included for all subjects. Reasons for drop-out and missing data values will be documented in the database. The occurrences of drop-out and missing data will be examined to investigate potential induction of selection biases. Missing data (i.e., occurring during hospitalization) will be assumed to be missing not at random. These missing data will not be imputed.

9.4 STATISTICAL ANALYSES

Below are the pre-specific outcome measures:

Primary Outcome Measure:

1. Variability in Peak Inspiratory Flow (PIF) Measured via Digihaler Device (Time Frame: Three months)
    b. PIF is the maximal flow occurring during an inhalation effort, expressed in Liters/minute. Mean, standard deviation and coefficient of variation (calculated by dividing standard deviation of PIF by the mean of the PIF) of daily PIF measurement collected over three months will be calculated. PIF will be measured using the Digihaler device.

Secondary Outcome Measures:

1. Correlation of Self-Reported Inhaler Use with Actual Inhaler Use (Time Frame: 3 months)

   a. Correlation between self-reported inhaler use and actual inhaler use over three months will be calculated with Spearman rank-order correlation coefficient. Self-reported inhaler use will be determined with an investigator-developed single question categorizing average use over the last four weeks with five groups (not at all, once a week or less, two or three times a week, one or two times a day, three or more times a day). Actual inhaler use will be directly measured via Digihaler device and categorized into one of the five groups described above.
2. Variability in Inhalation Volume Measured via Digihaler (Time Frame: Three months)
   a. Inhalation volume is the volume of air inspired during an inhalation effort, expressed in Liters. The mean, standard deviation and coefficient of variation (calculated by dividing standard deviation of inhalation volume by the mean of the inhalation volume) of daily inhalation volume measurements collected daily over three months will be calculated. Inhalation volume will be measured using the Digihaler device.

The primary analysis will be descriptive, with analytical plans as defined above for each primary and secondary outcome.

The primary analysis will be descriptive, with analytical plans as defined above for each primary and secondary outcome.

Additional exploratory analysis will include linear regression (continuous) or negative binomial regression (count) of the clinical and demographic factors associated with inhaler from primary and secondary outcomes; descriptive statistics (mean, median, variance estimate and 95% confidence intervals) of number of inhalation events, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with CAT score, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with daily self-assessment asking “How are you feeling?” with responses provided on a Leikert scale, correlation of inhaler metrics (PIF, inhalation volume, number of inhalation events) with responses to metric algorithm-triggered DAQ; change in inhaler metrics (during the 7 days after and/or leading into hospitalized AECOPD or home treatment of a moderate AECOPD defined by a prescription for steroids and/or antibiotics); descriptive statistics (proportion, 95% CI) of COPD-associated hospitalizations and emergency room visits as well as SABA utilization; and patient satisfaction will be assessed with a post-study survey. The Leikert scale will be modeled using an ordinal scale with lower number signifying worse daily overall feeling. The DAQ will be comprised of yes/no responses to a set of questions (categorized as No=0; Yes=1) with higher score calculated in the analysis indicating worse symptoms. In exploratory analyses, individual DAQ domains and cumulative score will be evaluated as outcomes. Because the DAQ also includes the Leikert scale, on days where both the DAQ Leikert and daily Leikert are completed, the DAQ Leikert will be used for analysis.

9.4.1 SAFETY ANALYSES

As there is a small number of subjects in this study, we anticipate simple categorization of reported AEs.

9.4.2 PLANNED INTERIM ANALYSES

No interim analyses will be performed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms (ICF) describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. An informed consent checklist is an SOP for our research group, and SOPs are followed by all study personnel engaged in the study.

The following consent materials are will be prepared for the IRB submission with this protocol: adult participant consent form and HIPAA authorization.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Given the current COVID landscape, we are requesting permission for a waiver of signatures of ICF and HIPAA by obtaining and documenting verbal consent. Once a participant has been identified, they will be contacted via phone and screened using the phone screener embedded in the verbal consent form. If they express interest in the study, we will then proceed with obtaining verbal consent using the verbal consent attached to this document. The entire ICF will be read to the participant, and after completion, asking them to briefly describe the study (to assess comprehension). They will then be provided the chance to ask any questions. If they are agreeable to study, we will then document this in their record. We will follow a similar plan for the HIPAA form (reading the entire HIPAA to the participant verbatim and asking at the end if they agree and then, marking this in their chart). Recruitment conversations will occur in a private office with a trained study team member. We will include a copy of the consent form and HIPAA authorization with the study material mailing.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants (if active on the study), investigator, funding agency and regulatory authorities. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary outcome variable has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB or investigators.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The representatives of the Institutional Review Board (IRB) or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Marsico Clinical Research Center (UNC) and Wake Forest Pulmonary Division (Wake Forest). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number; linkage files will be secured and password protected. At the end of the study, all study databases will be de-identified and may be archived at an off-site facility.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator (UNC)	**Principal Investigator (Wake Forest)**
M. Bradley Drummond, MD	*Jill Ohar, MD*
The University of North Carolina at Chapel Hill	Wake Forest Baptist Medical Center
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Team Roles:
Brad Drummond, MD, MHS – co-investigator (UNC)
Jill Ohar, MD – co-investigator (WF)
Caleb Hemphill and Annette Babu – study RC (UNC)
Sharon Cornelison – study RC (WF)
Marc Tian, PhD – study biostatistician

10.1.6 SAFETY OVERSIGHT

As this study is deemed low risk, using technology frequently prescribed for use by COPD patients at home, oversight for this feasibility study will be conducted by the PIs (Dr. Drummond and Ohar). The PIs will monitor data to ensure the safety of participants.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Given the pilot nature of the study, the study team will be responsible for regular on-site monitoring with 100% data verification. This will primarily be conducted by the study research coordinators.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated.

Following written Standard Operating Procedures (SOPs), the team will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both. A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of UNC or Wake Forest and should not be made available in any form to third parties, except for authorized representatives of the University or appropriate regulatory authorities. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be reviewed by the investigator or by an authorized staff member. Signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a secure database that is password protected with limited access. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

As required by law and to enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (i.e., sufficient information to link records to identity), all original signed informed consent forms, and copies of all CRFs, other source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to International Conference on Harmonization (ICH), or federal and local regulations, whichever is longer.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and if resulting in an AE, follow the protocols for reporting detailed in that section. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the publication and data sharing policies outlined in the clinical trials agreement.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Institutional IRBs have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
CAT	COPD Assessment Test
CI	Confidence interval
CFR	Code of federal regulation
CRF	Case report form
COPD	Chronic obstructive pulmonary disease
DAQ	Digital automated questionnaire
DPI	Dry powder inhaler
ED	Emergency department
HIPAA	Health Insurance Portability and Accountability Act
HRU	Health-care resource utilization
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICF	Informed consent form
IRB	Institutional review board
PIF	Peak inspiratory flow
SABA	Short acting beta-agonist
UNC	University of North Carolina
WF	Wake Forest

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	01Dec2021	Administrative staffing updates	To update personnel on study
1.2	21Mar2022	Remove exclusion criteria “Frequent use of nebulizer (i.e. >1 time per day)”	Concominant use of nebulizers frequent in this population limiting recruitment and impacting generalizability

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