TITLE: Differentiating the Effects of Long-acting Bronchodilators Administered by Nebulizer versus Dry Powder Inhaler in Symptomatic Patients with Chronic Obstructive Pulmonary Disease

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1. Background

COPD and inhaled treatment

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the U.S., affecting over 15 million Americans[1] and over 300 million individuals worldwide.[2] Patients with COPD rely heavily on inhaled bronchodilators and corticosteroids (ICS) to control symptoms, maximize quality of life, and avoid exacerbations and costly hospitalizations. These drugs are typically delivered by inhalers, either pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), or soft mist inhalers (SMIs), or by nebulizers. Each aerosol delivery device has advantages and disadvantages related to portability, ease and speed of use, and cost.[3, 4] The relative convenience of inhalers has led to their widespread acceptance by physicians as the primary mode of inhalation delivery for maintenance therapy in ambulatory settings,[5] whereas nebulizers are mainly prescribed for rescue treatment with short-acting bronchodilators for relief of acute dyspnea. However, a large majority, up to 94%, of patients with COPD do not receive optimal relief from disabling symptoms because they do not use their inhalers appropriately (**Table 1**).[6] Hence, it has been hypothesized that the widespread preferential use of inhalers over nebulizers may account for substantial excess morbidity and healthcare costs related to COPD.[7]

Choice of Inhalation Device

Besides the choice of inhaled drugs, key aspects influencing effectiveness of treatment are the choice of the most appropriate aerosol delivery device, proper education, device training, and adherence.[5] For patients with COPD, the lack of a large clinical trial of inhalers vs. nebulizers using comparable, newly available long-acting drugs in both devices, especially studies that account for aerosol delivery device training and patient-reported outcomes, has been described as a notable gap in the current literature by leading experts in the field.[8] In this proposal, we will address this gap by comparing measures of lung function and patient-reported outcomes using therapy with long-acting bronchodilators (umeclidinium and vilanterol) administered by DPI and long-acting bronchodilators of similar pharmacological classes (revefenacin and formoterol) administered by jet nebulizer in a prospective, randomized, parallel group, double dummy, phase four, 12-week clinical trial.

Table 1: Frequency of Correct, Acceptable, and Poor Inhalation Techniques and Changes Over Time

Time Period	Device	Correct, %	Acceptable, %	Poor, %
1975-1995	All	33	35	32
1996-2014	All	31	44	31
1975-2014	All	31	41	31
1975-2014	MDI	--	37	38
1975-2014	DPI	--	44	23

Sanchis J, et al. *Chest*. 2016;150(2):394-406

Lung function: Inhalers vs. Nebulizers

The comparative effectiveness and outcomes of nebulized versus inhaler-based therapy for COPD maintenance remains unclear.[9] In 2005, Dolovich and colleagues published a systematic review of device selection and outcomes of aerosol therapy,[10] which included only two studies that compared the effectiveness of inhalers versus nebulizers in patients with stable COPD. A randomized crossover trial by Balzano and coworkers[11] found a 19% greater change in FEV_1 after treatment with a multidrug combination via nebulizers compared with inhalers among 20 patients (12 with COPD and 8 with asthma), a result that was not statistically significant. Another randomized crossover trial by Hansen and colleagues[12] found no appreciable or statistically significant difference in lung function between terbutaline delivered by a DPI and nebulizer in 22 patients with severe COPD. These studies examined short-term effects of short-acting drugs over short study periods, with small sample sizes; in other words, the two studies are methodologically very weak. Nonetheless, the review by Dolovich and colleagues has been often cited as evidence for the equivalent

treatment effectiveness of inhalers and nebulizers in patients receiving long-term therapy for COPD. A few additional trials were weak in similar ways, and some even compared different drugs in the two devices.(7) These limitations may explain the conflicting results of those studies, which alternatively showed nebulizer-inhaler equivalence, nebulizer superiority, or nebulizer inferiority. Participants in those clinical trials also tended to receive atypical training to use their prescribed inhalers until they were able to show proficiency, in contrast with "real life" situations where most patients with COPD do not use inhalers appropriately, due to inadequate training or physical/cognitive limitations.[6] Moreover, those studies tended to focus on objective measures of FEV_1, which does not correlate well with patient-reported dyspnea symptoms or quality of life measures.[13]

Adherence and Training

Poor adherence to inhalation therapy further compounds the problem of "inhaler misuse"[6] and frequent monitoring is essential for patients with COPD to achieve maximal benefits from their treatment. Among the available aerosol generating devices, it is easier to train patients to use nebulizers because minimal coordination and effort is needed for proper use. Because drug aerosol is delivered over several breaths, compared to one or two breaths with inhalers, nebulizers are more forgiving to poor inhalation technique than inhalers. Regarding training, there is evidence that even extensive training may not largely mitigate patients' misuse of inhalers because of physical/cognitive limitations in patients with COPD. For example, in the survey conducted by Hanania and colleagues,[14] 79% of patients with COPD reported at least one physical or cognitive impairment that could limit their ability to correctly manipulate an inhaler device, including arthritis, poor eyesight, poor hearing, memory problems, tremor, difficulty with fine motor activities, depression, or anxiety, and more than half of the respondents had multiple limitations. In a previous publication,[15] the PI and several expert colleagues from North America identified key clinical situations where nebulizers are preferred over inhalers for maintenance therapy in patients with COPD (**Table 2**).

Table 2. Clinical Scenarios Where Maintenance Nebulizer Therapy is Preferred in Patients with COPD*
1. Cognitive impairment that precludes effective handheld inhaler use
2. Impaired manual dexterity
3. Severe pain or muscle weakness due to neuromuscular disease
4. Inability to use pMDIs or DPIs in an optimal manner despite adequate instruction and training, such as patients who are generally debilitated after hospitalization or by chronic illness and are unable to coordinate their breathing with a pMDI or they cannot generate adequate inspiratory flow for effective aerosol delivery from a DPI
5. Inadequate symptom relief with appropriate use of pMDIs/DPIs
6. Non-compliance with the use of pMDIs and DPIs or preference for use of nebulizers
7. Need for higher bronchodilator or corticosteroid doses to optimally control disease
8. Inability to afford therapy with pMDIs or DPIs.
*Modified from Dhand et al, COPD 2012;9:58-72.

Patient-reported outcomes: Inhalers vs. nebulizers

There is additional evidence to suggest that use of nebulizers may improve symptoms in patients with COPD more than use of inhalers, even without producing significant differences in tests of lung function **(Table 3**). For example, nebulizers were shown to provide more patient-reported symptom relief than pMDIs.[16] Likewise, data from 2,164 clinically stable COPD patients in the ECLIPSE Cohort[17] found that forced expiratory volume (FEV_1) was an unreliable marker of the severity of breathlessness, exercise limitation and health status impairment. Patients preferred nebulizers over inhalers for long-term therapy.[18, 19] It has been suggested that hospitalizations can be reduced[20] and quality of life improved[21] with nebulized therapy. A survey of patients with COPD showed that nebulized treatment helped them feel comfortable and more in charge of their own symptom control.[22] In another random survey of 400 patients and 400 caregivers, participants showed preference for nebulized therapy (~80%) and patients believed that their overall quality of life had improved since beginning nebulized treatments.[23] Two web-based surveys, one in patients with COPD and another in

U.S. pulmonologists reported responses that were favorable for use of nebulizers.[24, 25]The majority of patients (54%) who had used nebulizers preferred them to other inhalation devices.[25]

Table 3. Limited evidence supporting better symptom control with nebulizers vs. inhalers

Author, year	Study type	Sample size	Study Findings
O'Driscoll, 1992[19]	Clinical trial of usual inhaler treatment followed by nebulizer treatment	34 with COPD	About half of patients who remain breathless despite receiving bronchodilators delivered by pMDIs or DPIs derived additional benefits from home nebulizer use; the majority of patients with COPD in this study chose to remain on nebulizers for long term therapy
Corden, 1997[21]	Nebulizer therapy compliance vs. self-reported quality of life and St. George's Respiratory Questionnaire	82 with COPD	Compliance with nebulized therapy positively associated with quality of life scores
Godden, 1998[20]	In-home questionnaires and hospital records were reviewed	208 with COPD	Hospitalizations can be reduced when patients are given nebulizers
Barta, 2002[22]	Patient survey (via postal questionnaire)	82 with COPD	Nebulized treatment at home helped patients feel comfortable and more in charge of their own symptom control; compliance was generally excellent
Tashkin, 2007[16]	A 12-week randomized clinical trial of patients comparing inhalers, nebulizers, and concomitant therapy	126 with COPD	Nebulizers showed better patient-reported outcomes including questionnaire symptoms and quality of life; peak flow and FEV_1 showed no significant differences; concomitant therapy was better than either alone
de Monte, 2007[18]	Postal survey regarding use of nebulized therapy	3,674 physicians in France	"Patient request" was a significant reason for prescribing nebulized therapy; however, no question pertained specifically to hand-held inhalers
Agusti, 2010[17]	Prospective cohort study (ECLIPSE)	2,164 with stable COPD	Severity of airflow limitation was poorly related to the degree of breathlessness, health status, exercise capacity and number of exacerbations
Sharafkhaneh, 2013[23]	Telephone survey of randomly selected patients and caregivers	400 patients with COPD and 400 caregivers	Most patients and caregivers (~80%) preferred therapy with nebulizer vs. inhalers for controlling symptoms and improving quality of life
Dhand, 2018[25]	Online survey using the Harris Poll Online panel	254 patients with COPD	54% of patients with COPD preferred nebulizers to other inhalation devices

Likewise, the majority of pulmonologists (70%) believed that nebulizers were more effective than DPIs or pMDIs and 56% were of the opinion that nebulizers were essential for some patients.[24] Thus, in contrast with earlier small, short-term trials of device choice and lung function, patient-centered research tends to show better symptom relief with use of nebulized therapy.

Long-acting bronchodilators

Long-acting bronchodilators, LABAs and LAMAs, are currently the preferred agents for use in the management of stable COPD and have several advantages over shorter-acting drugs.[5, 8] Until recently, there were no FDA approved LAMAs for nebulizer delivery. Recently, 2 LAMAs (glycopyrrolate (Lonhala Magnair™, Sunovion) and Revefenacin (Yupelri™; Mylan/Theravance) were approved for maintenance therapy with nebulizers in COPD. Because glycopyrrolate is administered by a dedicated, specialized vibrating mesh nebulizer, its use would require the use of a separate nebulizer for delivery of formoterol, which would not be convenient for patients. Revefenacin is a once-daily, bronchodilator administered by jet nebulizer which is well tolerated, with minimal reports of systemic anti-cholinergic effects. It has been shown to be an effective bronchodilator in patients with severe COPD. Thus, a combination of nebulized revefenacin with formoterol administered by jet nebulizer provides a LAMA/LABA combination that are available as solutions for nebulization and have similar pharmacological classes as medications delivered by inhalers. In long-term studies, both revenfenacin and formoterol have been shown to be safe and effective in patients with COPD.[26, 27] In combination, nebulized formoterol and revefenacin improved lung function to a similar extent compared to sequential administration of the two drugs.[28]

In patients with stable COPD, the combination of beta agonists with anticholinergics produces additive bronchodilation with a good safety profile.[29] In such patients, long-acting bronchodilators, both anticholinergics and beta-2-adrenergic agonists provide larger reductions in hyperinflation compared to short-acting bronchodilators.[30] However, the differential effects of long-acting bronchodilators administered by nebulizers versus DPIs on hyperinflation have not been determined in patients with COPD.

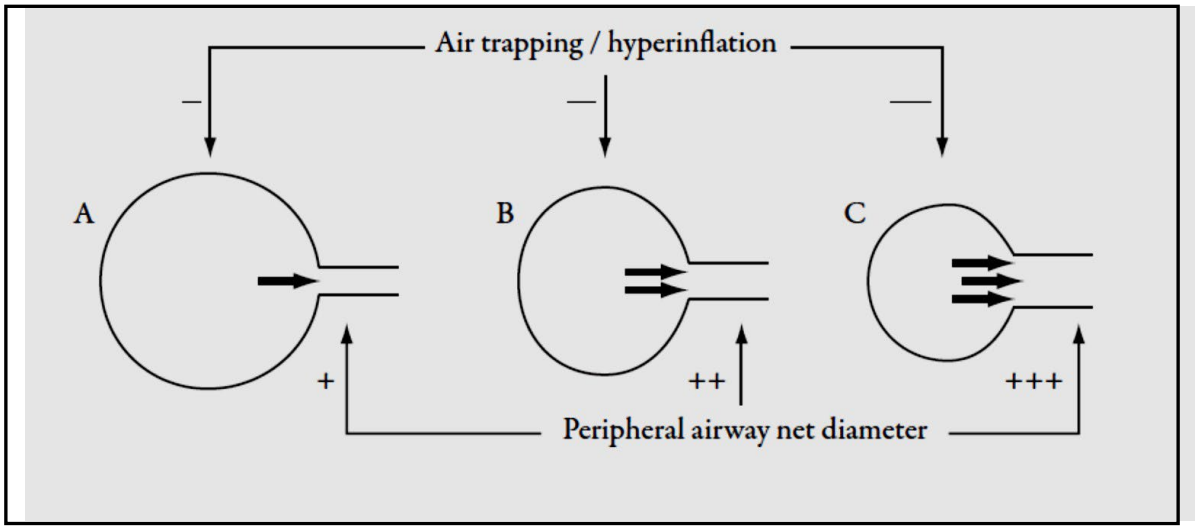

Figure 1: Effects of bronchodilation on air trapping/hyperinflation. Nebulizers produce fine particle aerosols which may deliver bronchodilators to more peripheral airways than dry powder inhalers and offer greater relief from air trapping/hyperinflation (as in panel C). This differential effect could explain greater relief of symptoms with long-acting bronchodilators administered by nebulizers than dry powder inhalers. **(**Reproduced from Beeh KM, Beier J. *Adv Ther* 2010;27:150-59**)**

Lung hyperinflation

In a significant proportion of people with COPD, reduced lung elastic recoil (due to emphysema) combined with expiratory flow limitation (due to luminal narrowing of peripheral airways) leads to lung hyperinflation during the course of the disease.[31] Increased frequency of breathing (tachypnea), increased respiratory neural drive, and fear or anxiety are also major contributors to development of dynamic hyperinflation. The consequences of lung hyperinflation include increased elastic load, increased inspiratory threshold load, decreased inspiratory muscles pressure generating capacity, impaired gas exchange, impaired cardiopulmonary interaction, mechanical volume restriction, increased functional residual capacity (FRC) and reduced inspiratory capacity (IC).[31] These pathophysiologic features contribute significantly to the development of dyspnea, exercise intolerance, skeletal muscle limitations, reduced physical activity levels, various morbidities, and mortality associated with COPD. [31, 32]

The major goal of treatment in patients with severe COPD is lung deflation by intensive bronchodilator therapy that reduces airway resistance, accelerates time constants for lung emptying, restores neuromechanical coupling and relieves dyspnea. In subjects with COPD, bronchodilators of all classes consistently reduce lung hyperinflation and pulmonary gas trapping, resulting in increases in inspiratory capacity (IC) and vital capacity (VC).[33, 34] Both β2-agonists and anti-muscarinic bronchodilators increase IC by ~10-15% in people with COPD,[34, 35] with the largest increase in IC observed in those people with the greatest lung hyperinflation at baseline.[36] This clinical trial seeks to determine if use of long-acting bronchodilators

given by nebulizer reduce hyperinflation to a greater extent than long-acting bronchodilators of similar classes administered by DPI.

Biological mechanisms

The biological mechanisms that might underlie the differences in response between nebulizers and inhalers are unknown, but it is possible that with several slow inhalations over time, aerosolized medications delivered by nebulizer have more peripheral versus central deposition compared with inhalers.[37-39] Conceivably, the longer duration of inhaling bronchodilators by nebulization leads to more effective reduction in resting and dynamic lung hyperinflation (**Figure 1**), with consequent improvements in exercise tolerance and perceived breathlessness during exertion, even if nebulizers and inhalers still produce similar effects on FEV_1.[40] In any case, as detailed above, patients appear to sense a difference in response to medication delivered by nebulizer compared with inhalers, in that they perceive an improvement in their breathlessness. Hence, studies that compare inhaler devices and only consider objective measures of lung function, such as FEV_1, may not adequately capture meaningful differences in patients' subjective disease and treatment experiences, leading to a considerable knowledge *gap* when choosing the appropriate inhalation device for each patient. For this reason, it is important to consider the patient's perspective(s) in how they perceive relief of dyspnea with various inhalation delivery devices

2. Specific Aims and Hypotheses

In this study, we will compare the effectiveness of inhaled bronchodilators delivered via nebulizers vs. DPIs in symptomatic participants with COPD who have airflow obstruction ($FEV_1/FVC \leq 70\%$) and show significant air trapping ($RV \geq 120\%$ of predicted).

Underlying hypothesis

In patients with symptomatic COPD, therapy with a LAMA/LABA combination administered by nebulizer will improve hyperinflation (increase in inspiratory capacity and reduction in residual volume) and reduce symptoms related to COPD to a greater extent than LAMA/LABA therapy given by a DPI.

Specific Aim 1: Compare the values of IC and RV in patients receiving LAMA/LABA by DPI with those receiving LAMA/LABA by nebulizer

Specific Aim 2: Compare patient reported outcomes (COPD Assessment Test (CAT score), Baseline/Transition Dyspnea Index (BDI/TDI) and the ST. George Respiratory Questionnaire (SGRQ) in symptomatic patients with COPD receiving LAMA/LABA by DPI with those receiving LAMA/LABA by nebulizer.

3. Significance

If our central hypothesis that nebulizers are more effective than inhalers in reducing patients' symptoms and improving their quality of life is shown to be correct, then there exists a tremendous potential to improve the lives of many millions of patients with COPD. Whether the choice of the inhalation device (nebulizer vs inhaler) influences hyperinflation, symptoms, health-related quality of life (QOL), or other clinical outcomes will be of enormous clinical and economic significance. This hypothesis has yet to be adequately tested given the lack of large-scale, long-term prospective data addressing inhaler device selection and technique, as well as therapy adherence, as a means to improve dyspnea symptom control and QOL in patients with COPD using newly-available long-acting drugs by nebulizers.[8, 14] A rigorous test of this hypothesis, whether supported or refuted, will lead to better understanding of the roles of device selection, training, and adherence in COPD maintenance from the patient perspective, information currently deemed to be necessary but lacking.[8, 9]

In their statement of vital research questions in COPD, the American Thoracic Society / European Respiratory Society noted the importance of addressing the comparative efficacy and outcomes of nebulized versus handheld long-acting bronchodilator therapy for COPD maintenance.[9]

The present study seeks to address this important gap in knowledge. We anticipate that our results will be of immense interest not only to patients and their caregivers, but also to their physicians, and many other stakeholders including the national American Thoracic Society (ATS), American College of Chest Physicians (ACCP), American Association for Respiratory Care (AARC) and the International (European Respiratory Society (ERS), Global Initiative for Chronic Obstructive Lung Disease (GOLD), International Society for Aerosols in Medicine (ISAM) specialist organizations. The outcome of this project will also be actively supported by many national patient advocacy groups, such as the American Lung Association (ALA), COPD Foundation and US COPD Coalition.

4. Outcomes

The primary outcome measures

- Difference between the values of area under the response curve for inspiratory capacity (IC) from baseline through six hours (AUC $IC_{0\text{-}6h}$) after inhalation of LAMA/LABA combination with a nebulizer versus a DPI OR
- Proportion of participants achieving improvement of >2 points in their CAT score compared to baseline OR
- Proportion of participants achieving reduction of 4 points in SGRQ score compared to baseline

Secondary outcomes

Secondary outcomes that will be analyzed include comparing the following parameters after inhalation of LAMA/LABA combination with a nebulizer versus a DPI:

- Percentage change in RV from baseline after inhalation of LAMA/LABA combination
- Percentage change in TLC from baseline after inhalation of LAMA/LABA combination
- Percentage change in airway resistance (Raw) from baseline after inhalation of LAMA/LABA combination
- Maximum % change in inspiratory capacity between 0 and 6 hours after LAMA/LABA combination
- Maximum % change in RV between 0 and 6 hours after LAMA/LABA combination
- Maximum % change in airway resistance between 0 and 6 hours after LAMA/LABA
- Correlation of peak inspiratory flow rate with peak IC change from baseline
- Comparison of CAT scores in patients receiving medications with DPI vs nebulizer
- Comparison of SGRQ scores in patients receiving medications with DPI vs nebulizer
- Change in TDI in patients receiving medications with DPI vs nebulizer
- Change in CAT scores in patients receiving medications with DPI vs nebulizer
- Change in SGRQ scores in patients receiving medications with DPI vs nebulizer
- Correlation of CAT with LF and LH change (inspiratory capacity and residual volume change) with patient-reported outcomes.
- Correlation of LH with patient-reported outcomes
- For select variables, we will compare VISIT 1 with VISIT 2 to identify variation

5. Study Design

A prospective, randomized, parallel group, double dummy, phase four, 13-week clinical trial with 1:1 allocation comparing long-acting anti-muscarinic agent (LAMA; Umeclidinium 62.5 *μg* once daily) and long-acting beta-agonist (LABA; Vilanterol 25 *μg* once daily) delivered by DPI (Group A), vs a nebulized LAMA/LABA combination (revefenacin 175 *μg* once daily and formoterol 20 *μg* twice daily) (Group B) among symptomatic subjects with stable COPD.

6. Study Population

Seventy-two symptomatic patients (36 in each group) with a primary diagnosis of COPD will be enrolled if they meet all inclusion and exclusion criteria.

7. Selection of Study Participants

Patients will primarily be recruited from the UTMC Pulmonary Function Testing Lab and the Internal Medicine resident clinic. GSM faculty, staff, UPCC clinicians, and respiratory testing staff will help identify and refer potential patients.

The nature and purpose of the study will be explained to patients who meet inclusion and exclusion criteria by one of the study team members. The patient will be given a copy of the informed consent to review. The investigator or study coordinator will answer any questions the patient may have prior to their signing the consent. The signed informed consent will be kept in the patient's research chart and a copy will be given to the patient. No study related interventions will be performed until the patient signs the informed consent.

8. Inclusion/Exclusion Criteria

Inclusion criteria

1. Age $\geq$ 40 years
2. Either sex
3. Current smoker or past cigarette smoking history of $\geq$ 10 pack-years
4. Symptoms of COPD (cough, sputum production, shortness of breath)
5. Modified Medical Research Council Dyspnea Scale (mMRC) score ≥2 or CAT score ≥10 at Screening/Run-in visit
6. A PIFR > 30 at screening
7. FEV_1/FVC ratio $\leq$ 70% (within the past 12 months)
8. Residual volume (RV) ≥ 120% predicted (within the past 12 months)

Exclusion criteria

Subjects with any of the following conditions will be excluded:

1. Diagnosis of asthma (Verification via medical record and/or patient report)
2. Previously diagnosed atrial fibrillation with rapid ventricular response (heart rate > 110 bpm) or ventricular arrhythmia (ventricular tachycardia) (Verification via medical record and/or patient report)
3. Acute myocardial infarction within 12 weeks of patient study registration (Verification via medical record and/or patient report)
4. Acute exacerbation of congestive heart failure (Verification via medical record and/or patient report)
5. Acute exacerbation of COPD within 8 weeks (Verification via medical record and/or patient report)
6. Recent (within 8 weeks) h/o eye surgery (Verification via medical record and/or patient report)
7. Uncontrolled glaucoma (Verification via medical record and/or patient report)

8. Known diagnosis of liver cirrhosis (Verification via medical record and/or patient report)
9. Known diagnosis of chronic renal insufficiency (defined as a previous serum creatinine > 2.5 mg/dL - Verification via medical record and/or patient report)
10. Intolerance to any of the study drugs
11. Patients receiving long-term azithromycin
12. Planned surgery requiring hospital admission within 3 months
13. Currently enrolled in a pulmonary rehabilitation program
14. Inability to give informed consent
15. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm, or subdermal implants)
16. Inability to understand instructions or comply with the study protocol
17. Participation in another investigational drug clinical trial within 30 days of patient study registration

Medical history can be confirmed by medical records and/or verbal confirmation from patients. However, Inclusion criteria 6 & 7 must be verified by a previous PFT report dated within 6 months of screening.

9. Study Duration:

The anticipated length of this study is 18 months (**Figure 3**). Months 1 and 2 are for startup, including regulatory compliance. We anticipate patient enrollment to take 13 months (i.e., enrollment of 1-2 patients/week on average). The final two months are for data analysis and manuscript writing.

10. Study Environment and Facilities:

The study has clinic and office space, data storage and computer facilities, and access to the equipment necessary for completing study procedures, including spirometry, body plethysmography, **Figure 2**., and In Check Dial for measuring PIFR. The PFT lab has approximately 1200 square feet of dedicated space, seven respiratory therapists available for study procedures, and the equipment shown below to perform the required plethysmography testing. Patients will be scheduled for required testing in the PFT lab as needed, and the PFT Lab will be reimbursed for services.

Figure 2: **Vyntus™ BODY Plethysmograph**

11. Summary of Study Visits and Timeline

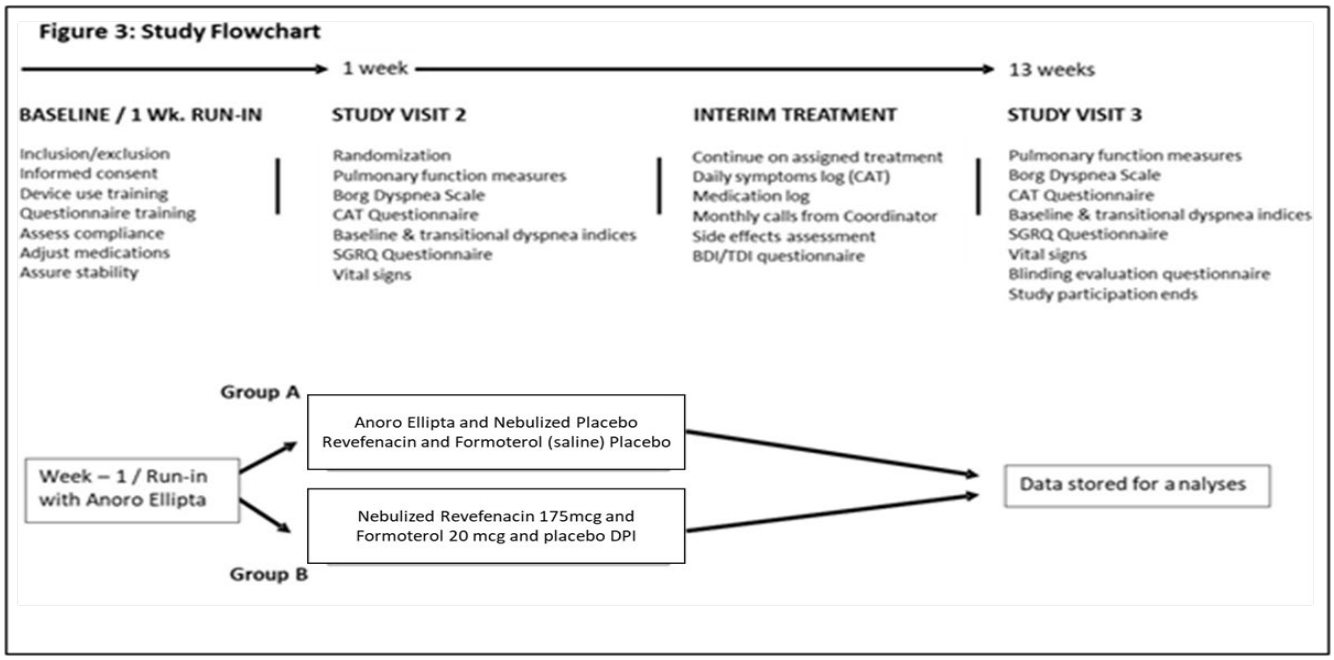

Table 4: Procedure Schematic:

	Screening/ Run-in	Baseline/Day 1	Week 4 Phone Call	Week 8 Phone Call	12 Week / Final Visit
Informed Consent	x				
Past Medical History	x	x	x	x	x
Review Medications	x	x	x	x	x
Demographics	x				
Smoking history Review *(≥ to 10 pack years at screening)*	x				
Vital Signs *(HR, RR, Temp, BP, and SpO2)* **Vital signs will be recorded at 1, 2, 4, and 6 hours post dosing prior to performing PFTs*	x	x*			x*
Review Previous PFT for Inclusion (test must be performed within 6 months of screening) • *FEV1/FVC ratio ≤ 70%* • *Residual volume (RV) ≥ 120% predicted*	x				
Physical Exam	x	x			x
Adverse Event Review		x	x	x	x
Confirmation of Inclusion/Exclusion Review	x	x			
MRC Questionnaire *(≥ 2 at screening)*	x				
CAT Score Questionnaire *(≥ 10 at screening)* *(Completed **daily** at home after randomization)*	x	x	x	x	x
SGRQ Questionnaire		x			x
BDI Questionnaire	x				
TDI Questionnaire			x	x	x
Pulmonary Function testing *(Pre-dose and 1, 2, 4, and 6 hours post dose plethysmography)*		x			x
Subject Diary Training and Dispensing	x	x			
Subject Diary Review and Reconciliation		x	x (verbal review with pt)	x (verbal review with pt)	x
Run-in Drug Dispensing & Training	X				
Randomization		X			
Study Drug Dispensing		X			
Study Drug use Training		x			
Study Drug Reconciliation		X			X

Screening Visit/Run-in period

On the day of screening, patients will have assessments including:

- If eligible and willing to participate, patients will sign an informed consent
- Medical history and concurrent medication review
- Determination of eligibility
- Patients will be trained on use of DPI with a placebo inhaler (Ellipta, GSK) and the nebulizer using nebulized saline. The techniques of nebulizer cleaning and disinfection will be demonstrated.
- Vital signs (heart rate, respiratory rate, temperature, blood pressure and SpO2) and physical examination will be recorded by the study coordinator.
- Patients will be trained on various questionnaires (CAT, BDI/TDI, SGRQ) by the study coordinator.
- Study coordinators will provide extensive training in the use of the daily diary. Participants will receive symptom and medication logs to be filled out daily.
- The baseline peak inspiratory flow rate will be determined with an inspiratory flow meter (In-Check DIAL, Clement Clarke International, Harlow UK) using the resistance of a Diskus inhaler (similar to that of an Ellipta device).
- Adjust medications to assure stability
    - Patients will be switched to Anoro Ellipta 1 puff daily. Inhalers will be purchased through UTMC pharmacy purchasing team and stored by the study coordinator. The study coordinator will dispense the Run-in inhaler. Those receiving inhaled corticosteroids or oral prednisone will be allowed to continue them at a stable dose. Patients may use albuterol and/or ipratropium for rescue therapy
    - Patients receiving supplemental oxygen will be allowed to participate if their oxygen requirements have been stable over 8 weeks
    - Oral theophylline will be discontinued but oral roflumilast will be continued at a stable dose

Baseline Study Visit 2 (within one week of screening/start of Run-in Visit) ± two days*:

*If a patient has taken study medication within 48 hours of their first Visit 2 pulmonary function test, or rescue medication within 6 hours of their first Visit 2 pulmonary function test, the visit will be rescheduled. If a patient is unable to come to the study site for Visit 2 due to illness or inclement weather, the visit will be rescheduled. The run-in period will be extended for one week. The study coordinator will assess the patients' compliance by phone prior to the run-in extension if the patient is ill or unable to come to the study site. Compliance will be assessed in person prior to the run-in extension whenever possible. The patient will be instructed to continue the DPI and diary completion until the next visit. This will not be considered a protocol deviation.

Pre-Dosing

- Patients will return one week post their screening visit
- Medical history and concurrent medications will be reviewed
- Adverse Events will be reviewed
- Symptom and medication logs will be reviewed to assure stability of COPD.
    - Participants must show ≥80% compliance in filling out the daily logs to continue in the study.
    - Patients < than 80% compliant will be considered screen failures. They will resume their previous medications, and will be instructed to follow up with their PCP as needed.
- The following questionnaires will be administered before study drug is administered
    - CAT score

- BDI
- SGRQ

- Vital signs (heart rate, respiratory rate, temperature, blood pressure and SpO2) will be recorded prior to study
- Pulmonary function will be measured in a body plethysmograph before drug administration (baseline)
- Physical examination and vital signs will be recorded
- Patients that meet all eligibility criteria will be randomized

Participants will be randomized 1:1 to receive either active drugs by DPI or nebulizer as a one-time administration. We will generate treatment assignments with a pseudo-random-number generator with randomly permutated blocks that will ensure balance between the numbers of subjects assigned to each treatment.

Treatment Groups

(Group A) Anoro Ellipta (Umeclidinium/Vilanterol; GSK Research Triangle Park, NC) 1 puff and nebulized Revefenacin Placebo (manufactured by The RiteDose Corporation, South Carolina, USA) and Formoterol Placebo (sterile normal saline) study drug arm ***-OR-***
(Group B) Revefenacin 175 µg and formoterol 20 µg by nebulizer (Theravance Biopharma, South San Francisco, CA) and 1 puff of placebo DPI study drug arm.

- ❖ The nebulizer will always be administered first, and the DPI will be given at the end of the nebulizer treatment. Time 0 will be at the end of the DPI treatment.
- ❖ Study treatments will occur within the same time range in the morning (7:00 -11:00am) and evening (7:00 - 11:00pm) to minimize diurnal variation.
- ❖ We will make all attempts to conduct the first study visit within 7±2 working days of the screening/enrolment visit.

Post-Dosing

- Vital signs (heart rate, respiratory rate, temperature, blood pressure and SpO2) will be recorded at approximately 1, 2, 4, and 6 hours after drug administration prior to performing the pulmonary function measurements.
- Pulmonary Function Measurements (by staff at the UT Pulmonary Function Laboratory): Every attempt will be made to perform repeated pulmonary function testing in a body plethysmograph before drug administration and at approximately 1, 2, 4, and 6 hours after each treatment. If patients become fatigued, or are unable to finish testing, the RRT will notify the coordinator and the reason for stopping prematurely will be clearly documented in the source document. Patients will continue in the study. This will not be considered a protocol deviation.

The following parameters will be assessed:

- FVC
- FEV1
- FEV1/FVC
- FEV3 FEV6
- FEF25%-75%
- Residual volume
- Total lung capacity

- Inspiratory capacity
- Airway resistance
- Modified Borg Dyspnea Index

- Training
  - Additional Diary training
    - Daily assessment of symptoms (CAT score)
    - Medication logs
  - Study drug/device use training (please see below)
  - Importance of medication compliance training
  - Study visits schedule review and scheduling
- Participants will continue with assigned treatment and placebo for 12 weeks
  - Morning dose
    - Group A: Anoro Ellipta + Nebulized Revefenacin Placebo and Formoterol Saline Placebo
    - Group B: Placebo DPI + Nebulized Revefenacin + Formoterol
  - Evening dose
    - Group A: Nebulized Formoterol Saline Placebo
    - Group B: Nebulized Formoterol

Phone Visit 1 Week 4

(Telephone call 4 weeks post first dose ± 2 days)

- Telephone monitoring by study coordinator to review symptom and medication logs
- Administer TDI
- Assess for side effects and rescue medication use

Phone Visit 2 Week 8

(Telephone call 8 weeks post first dose ± 2 days)

- Telephone monitoring by study coordinator to review symptom and medication logs
- Administer TDI
- Assess for side effects and rescue medication use

Study Visit 3

(In-person visit 12 weeks post first dose ± 2 days*)

* If a patient has taken study medication on the morning of their first Visit 3 pulmonary function test, or rescue medication within 6 hours of their first Visit 3 pulmonary function test, the visit will be rescheduled. If a patient is unable to come to the study site for Visit 3 due to illness or inclement weather the visit will be rescheduled. This will not be considered a protocol deviation.

Pre-Dosing

- Medical history and concurrent medications will be reviewed
- Adverse Events will be reviewed
- Diary will be reviewed
- The following questionnaires will be administered before study drug is administered
  - CAT score
  - TDI

- SGRQ

- Vital signs (heart rate, respiratory rate, temperature, blood pressure and SpO2) will be recorded prior to study dosing.
- Pulmonary function will be measured in a body plethysmograph before drug administration (baseline)
- Physical examination and vital signs will be recorded
- Medication compliance, collection, and reconciliation

Post-Dosing

- Vital signs (heart rate, respiratory rate, temperature, blood pressure and SpO2) will be recorded at approximately 1, 2, 4, and 6 hours after drug administration prior to performing the pulmonary function measurements
- Pulmonary Function Measurements (by staff at the UTMC Pulmonary Function Laboratory): Every attempt will be made to perform repeated pulmonary function testing in a body plethysmograph before drug administration and at approximately 1, 2, 4, and 6 hours after each treatment. If patients become fatigued, or are unable to finish testing, the RRT will notify the coordinator and the reason for stopping prematurely will be clearly documented in the source document. Patients will continue in the study. This will not be considered a protocol deviation.
  The following parameters will be assessed:
  - FVC
  - FEV1
  - FEV1/FVC
  - FEV3 FEV6
  - FEF25%-75%
  - Residual volume
  - Total lung capacity
  - Inspiratory capacity
  - Airway resistance
  - Modified Borg Dyspnea Index

End of Study Visits:

At the end of the study, patients will be given the choice of delivery systems for long-acting bronchodilators depending on their ability to use various devices, preference, and insurance coverage under the guidance of their treating physicians. Patients who end participation before the 12-week period will be scheduled for early termination visit assessments. We will record the reason for dropping out from the study.

12. Reasons for withdrawal/unblinding:

Patients may be withdrawn if they are non-compliant, require different treatment options to manage their COPD, or develop a serious adverse event (SAE) or an acute exacerbation of COPD that necessitates removal from the study. All adverse events meeting IRB reporting criteria will be reported to the IRB. Unblinding will be permitted for life-threatening complications.

13. Ethical and safety issues:

Principles of Good Clinical Practice (GCP) will be followed. Patients may withdraw from the study without any penalty. An independent Data Safety Monitor will be designated to monitor patient safety. All adverse events reported per the IRB and FDA guidelines will be reviewed by the Data Safety Monitor.

14. Device Training:

We will employ device-use training videos developed by National Jewish health for each device used in this protocol (including nebulizers). The videos can be viewed at: https://www.nationaljewish.org/treatment-programs/medications/asthma-medications/devices/instructional-videos. These videos are also available for viewing on YouTube.

After coordinators administer device-use training they will use the "teach-to-goal" method [41] to confirm that subjects are using the proper technique, via placebo devices, at the time of enrolment in the study. Study coordinators will provide on-site training to participants. The subject will have access to the online training videos. We expect that this will make the findings of our study more generalizable to current clinical practice.

15. Study Therapies

Group A: DPI

The Anoro Ellipta inhaler (GSK) contains:
Umeclidinium 62.5 mcg
Vilanterol 25 mcg

Patients will receive a single inhalation from the device. A matching inhaler without any active drug will be used as placebo. We chose Anoro Ellipta DPI because it is commercially available, has the same class of bronchodilators (LAMA/LABA) as revefenacin and formoterol and is commonly used by patients with COPD. Furthermore, patients can be easily trained in using the Ellipta device.[42] Moreover, it is equally effective compared to other commercially available LAMA/LABA combinations.[43]

Group B: Nebulizer treatment

Participants will receive nebulizer treatments with revefenacin 175 mcg and formoterol 20 mcg with re-usable nebulizers (Pari LC Sprint with Pari Trek S compressors). The Pari-Trek nebulizer and Compressor combination delivers fast-efficient aerosol treatments in 5-6 minutes, and has proved effective in other clinical trials, including pivotal trials for approval of revefenacin (https://www.rxlist.com/yupelri-drug.htm#indication). The two drug solutions are compatible physio-chemically and they will be mixed in the nebulizer and administered together. The Placebo Revefenacin being supplied has been manufactured by The RiteDose Corporation, South Carolina, USA and contain all revefenacin ingredients, other than the active ingredient. The Formoterol Placebo used will be sterile 2.5 ml (0.9 % NaCL) saline vials for inhalation with the nebulizer. Nebulizers will be supplied by the study team.

Study coordinators are all familiar with the Ellipta DPI, nebulizer and compressor and have used these devices in previous studies. However, they will receive training in the use of the devices and their ability to instruct study subjects in proper device technique will be verified.

Blinding

Treatment assignment will be blinded in this trial.

Packaging, labeling, and re-supply

All medications will be supplied pre-packaged and labeled and will provide enough medication to treat each study participant for 12 weeks. Run-in medication will be relabeled before it is dispensed to ensure that no identifiable packaging will allow patients to distinguish between active medication and placebo if enrolled into the treatment phase of the study.

Storage conditions

All clinical trial supplies will be stored in a locked, secure cabinet and/or refrigerator and will be kept in their original packaging under the recommended storage conditions and may only be dispensed to trial subjects according to protocol.

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions defined by the manufacturer. Where necessary, a temperature log will be maintained to make certain that the drug supplies are stored at the correct temperature. The study team will receive the investigational drugs delivered by the manufacturer.

The unblinded coordinator will maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and the return to the manufacturer or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational products and trial patients.

The unblinded coordinator and/or study coordinator should return the unused and collected investigational drugs (including empty boxes) to the manufacturer after the trial.

Upon completion of the trial, the unblinded coordinator and/or study coordinator submits a copy of the investigational drug reconciliation log to the manufacturer.

Other Medications:

Additional maintenance long-acting bronchodilator therapy with other pMDIs, DPIs, or SMIs will not be permitted. Patients in either group may employ *albuterol pMDIs* for rescue. We will permit use of *nebulized albuterol and or ipratropium* only for relief of acute symptoms not relieved by use of short-acting bronchodilator pMDIs in either group. We will instruct patients not to switch from use of inhalers to nebulizers for maintenance therapy or vice versa. We will instruct patients to inform the investigators if a change in therapy becomes necessary. We will also monitor each patient's treatment by daily diaries, during monthly telephone calls and at each clinic visit. All patients will continue to be under the care of their regular treating physicians.

16. Pre-Pulmonary Function Testing Restrictions

Patients will be instructed to stop their run-in or study medication prior to testing for the following time intervals:

Albuterol	6 hours prior to Baseline/Visit 2, and Visit 3 pulmonary testing
Ipratropium	6 hours prior to Baseline/Visit 2, and Visit 3 pulmonary testing
Run-in DPI	48 hours prior to Baseline/Visit 2 pulmonary testing
Study Drug	No morning dose of study medication for Visit 3

Caffeine and caffeine containing beverages should not be consumed on the days of treatment visits.

17. Quality assurance procedures:

We will develop a workable, detailed, protocol and Regulatory Binder for use by the investigators and clinic staff. This binder will serve as a reference and training guide for all project procedures and policies. Other

quality assurance procedures to be used are: 1) staff training prior to beginning the study on forms, procedures, protocol, and randomization 2) at the end of the final study visit (Study Visit 3), subjects will be asked which treatment they believe they received during the treatment period. Responses will then be used to calculate a "blinding index" and a formal statistical test suggested by Bang and colleagues[44] will be applied to assess the degree of blinding. The same tests will be administered to the study personnel.

18. Sample size:

We anticipate no more than 15% attrition over a 12-week period, leaving at least 60 patients who will complete all aspects of the trial.[45]

19. Data analysis:

The data will be codified according to the data dictionary. Clinical data will be checked for coding errors using frequency statistics. Statistical assumptions will be tested before undertaking any inferential analyses. Frequency statistics will be conducted on all categorical variables. For each continuous within-subjects observation of IC, residual lung volume (baseline, one [1] hour, two [2] hours, four [4] and six [6] hours), the distribution of values at each time point will be checked for normality using skewness and kurtosis statistics. For the primary outcome of IC, the Area Under the Curve (AUC) for each treatment group across the within-subjects observations will be calculated using the trapezoid method. For the secondary outcomes (residual volume, etc.), paired-samples *t*-tests will be used to compare within-subjects observations, given that the statistical assumption of normality is met. If normality is violated, Wilcoxon signed rank tests will be used for within-subjects comparisons. Statistical significance will be assumed at an alpha value of 0.05 and all analyses will be conducted using SPSS Version 25 (Armonk, NY: IBM Corp.).

20. Risks to the Subjects:

We will conduct the study in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Enrollment will be open to subjects ≥40 years old, of any race, sex, or ethnic background who meet pre-defined inclusion and exclusion criteria and are free of contraindications to participate in the trial. These methods are designed to determine general health status, ability to understand informed consent and to cooperate with study procedures, and presence of medical conditions, habits, or medication usage that would otherwise interfere with the study. No vulnerable special populations will be studied, no women who are pregnant or are trying to get pregnant will be enrolled, and no children will be enrolled in this project. No subpopulation will be targeted or excluded from recruitment. No invasive procedures are planned for the purpose of this study. Participants in the study will receive compensation for their time (up to $370), but this level of payment is commensurate with the time and effort of participation in the study, and hence is at a level that we do not consider to be "coercive." Otherwise, there are no immediate benefits to patients for participating in this study.

<u>Risks from lung function testing</u>:
Patients will be asked to spend 10-20 minutes in a plethysmograph (box) several times during each of the two study visits. Patients may feel claustrophobic in the box, and may experience dizziness, weakness, and/or fatigue from repeated testing.

<u>Risk from the study medications</u>:
The medicines used in this study are "standard," in that they are routinely used in patients with COPD, have undergone years of clinical use and investigation, and have been fully approved by the FDA for use in this patient population. However, like all medications, potential side-effects have been noted, including (but not

limited to) minor and serious allergic reactions, changes in blood pressure, headache, upper respiratory infection, arrhythmia, hyperglycemia, nausea, fatigue, and nervousness. Participants in this study will be monitored for side-effects and will be encouraged to report any side effects to study personnel.

Risk from loss of confidentiality:
Loss of confidentiality is possible because study data will not be collected anonymously. Throughout the study, measures to ensure the privacy of information on study subjects will be maintained. All project investigators and staff have been certified for training in the use of human subjects in research and have received training in HIPAA regulations. Subjects and staff will be informed of the confidentiality of information and assured that data will be used only for statistical purposes and group analyses in which the individual cannot be identified.

All subjects will have assigned code numbers. All completed forms will be kept in locked files in locked rooms to which only project personnel have access. In addition to measures to ensure confidentiality is not breached from the use or storage of hard copies (discussed above), electronic files will be available to only key study personnel only on the server and designated PCs. Both the computers and the electronic files will be username/password protected. PCs will be kept in locked rooms. Server computer security is maintained 24 hours a day.

21. Anticipated Problems and Pitfalls:

1) Challenges with recruitment can arise in a clinical study. However, we care for a large population of patients with COPD and do not anticipate problems with recruitment or with unexpected side effects or complications.

2) There can be imbalances in treatment groups according to disease severity. However, we will ensure that study subjects meet eligibility criteria for enrollment and assess the balance of severity among treatment groups.

3) Variability in baseline pulmonary function could affect the response. However, we will assess baseline values of pulmonary function at the study visit and account for any imbalance in analyses as needed to help ensure comparability between the two groups.

22. Anticipated Outcomes and Deliverables:

The anticipated start date will be January 2, 2023. The first 2 months of the study involves finalizing the manual of operations, forms, data entry screens, and other study materials. During this time, IRB approval will be obtained, staff trained, and pre-test procedures and refinements carried out. The last patients to complete the clinical protocol will do so at the 16 month point of the study so that data entry, editing and analysis will be completed within the following 2 months. The anticipated completion date will be July 1, 2024. Scholarly output will subsequently appear in several forms, including print (articles published in high impact medical journals, abstract and poster presentations at national meetings, policy briefs, and institutional newsletters); internet (university and professional organization websites, and various social media venues); and face-to-face interactions with various COPD support groups and other meetings of senior citizens.

23. Adverse Events and Serious Adverse Events

Adverse Event Definitions

We do anticipate that this patient population may have COPD exacerbations during the study that result in hospitalizations. We will follow the standard guidelines for the reporting of AEs and SAEs.
An adverse event (AE) is any untoward medical occurrence that may present itself during the course of a research study. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the patient's participation in the research study, regardless of the suspected cause.

Unexpected Adverse Event

An unanticipated or unexpected adverse event is a medical occurrence whose nature, severity or frequency is not consistent with existing information regarding the risk profile of the study procedure.

Serious Adverse Event

A serious adverse event (SAE) is a medical condition that results in one of the following:

- Death
- Is life threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Creates persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent one of the outcomes noted above.

Life threatening: an SAE considered life threatening refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Adverse Event Assessment and Documentation

AEs that are considered possibly, probably or definitely related to the study procedure will be recorded in the CRFs. AEs will be assessed starting with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the patient's condition is stable.

All AEs will be characterized by the following:

- AE name
- Start and Stop dates
- Relationship to study procedure
- Severity
- Action taken
- Outcome

Relationship

The investigators will assess the AEs and using their clinical judgment will assign an attribution to the AE using the following categories:

- Unrelated – The AE is clearly NOT related to the study procedure
- Unlikely – The AE is doubtfully related to the intervention

- Possibly – The AE may be related to the study procedure
- Probably – The AE is likely related to the study procedure
- Definitely – The AE is clearly related to the study procedure

Severity

The severity of the AEs should be graded by the investigator as follows:

- Mild – Transient discomfort; no prescribed medical intervention/therapy required and does not interfere with daily activities.
- Moderate – Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; medical intervention/therapy required.
- Severe – Discomfort and limitation in daily activities, assistance required; medical intervention/therapy required.

Action Taken

The action taken in response to the AE should be reported using the following categories:

- None
- Procedure or physical therapy
- Withdrawn from study due to AE
- Hospitalization
- Prescription drug therapy
- Non-prescription drug therapy
- Other (specify)

Outcome

The clinical outcome of an AE should be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e., continuing at time of study discontinuation)
- Death
- Unknown/lost to follow-up
- Other

Reporting

All SAEs will be documented in the CRFs. SAEs will be reported to the local IRB per the following guidelines:

Adverse event reports will only be submitted to the local IRB if they are determined by the principal investigator to be: Unanticipated, Serious, and Possibly, Probably or Definitely related to a research study procedure.

SAEs meeting these criteria (except for deaths) must be reported to the IRB within 5 working days of the study team's notification of occurrence. Deaths that are unanticipated and are possibly, probably or definitely related to a research study procedure must be reported to the IRB within 24 hours of notification of occurrence.

Any relevant follow-up information regarding the SAE should be submitted to the IRB as soon as it becomes available and/or upon request.

SAE reports to the IRB must include the following: subject identifier, adverse event or problem description, the event relationship to the test article or underlying condition, seriousness assessment, whether the event was anticipated or unanticipated, type of report (initial or follow-up), date of injury, whether the intervention was stopped, and, if so, whether it was re-started, and whether the event provides new risk information that alters the risk-benefit assessment and/or should be added to the informed consent disclosure.

24. Patient Recruitment and Informed Consent

Recruitment

The study team will recruit from the UTMC pulmonary function lab and other treating physicians within the community. Pulmonary staff (IRB approved team members) will inform potential patients of the study. If interested, study team members will discuss the study with them in person. If patients are interested but cannot be spoken with while on campus, the study team will present them with the IRB approved "Contact Form". If they sign and date the form and provide their phone number and email, the study team will contact them via phone or email.

Informed Consent

Informed consent will be conducted by study team members. The potential subject will be given an IRB approved ICF to read. They will be given ample time to read the consent, and all of their questions will be answered by the study team prior to signing. After all questions have been answered, the potential subject will sign the consent and then a copy will be given to them for their personal records. The original will be filed in their research record.

Withdrawal of Consent

Patients may withdraw from the study at any time. Patients should make every attempt to complete the study as specified. Investigators should encourage patient treatment compliance and adherence. All deviations from the planned treatment schedule will be documented.

25. Study Management

The PI and study team has the site resources, time availability, and the patient population needed to complete this protocol under FDA, ICH, and GCP guidelines within the defined study timeline. Research that is subject to regulation, as defined in 46.102, must be reviewed and approved, by an institutional review board (IRB) that operates in accordance with regulation requirements of this policy. Per 21 CFR part 50 Investigator must obtain legal informed consent if human participants are being included within research and meet certain guidelines.

The PI is ultimately responsible for the conduct of the trial; however, he will delegate authority to appropriate members of the research team. The PI will ensure the following:

- Study team complies with be GCP and other regulatory requirements.
- The study team allows monitoring and auditing by regulating institutions.
- Ensures person delegated trial responsibilities are qualified and trained appropriately.

- Ensure that study team members have sufficient time to properly conduct and complete the trial within the agreed trial period.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
- Ensure record keeping and record retention in accordance with 21 CFR 50.
- Ensures compliance with, GCP guidelines and other local regulatory requirements.
- Will maintain a list of research team members and delegated duties.
- Assures protocol compliance.
- Reports protocol non-compliance appropriately.
- Obtains IRB approval of the trial.
- Followings regulations and guidelines to protect subject rights, safety, and welfare.
- Controls the accountability of the investigational product(s).
- Ensures accurate case histories and records all observations and other data pertinent to the clinical trial on each subject.

26. Protocol Deviations

A protocol deviation is failure to follow procedures specified in the approved research protocol, which include (but are not limited to), deviations from study inclusion/exclusion criteria, or failure to follow criteria for subject follow-up, withdrawal, or timely monitoring procedures. Protocol deviations must be reported to the IRB by the PI within 5 working days from the day the investigator becomes aware of the event.

Protocol deviation reports to the IRB must include the subject identifier, date of deviation, impact on the subject's safety, and the plan for preventing the deviation in the future (if applicable).

27. Data Quality Assurance

A quality assurance audit/inspection of this study may be conducted by the overseeing IRB or by regulatory authorities. The quality assurance auditor will have access to all study records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

28. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. For eCRFs, all data must be derived from source documents.

Direct Access to Source Data and Documents

The PI will permit study-related monitoring, audits, IRB review and regulatory inspection, providing direct access to source data/documents.

29. Completion of Trial

When the trial is completed, the PI will inform the IRB and funding institution of the completion in writing.

30. SUMMARY

Inhalers are generally recommended for maintenance therapy in patients with stable COPD, mainly due to their convenience and, otherwise, presumed equivalence to nebulizers in terms of effectiveness; the use of nebulizers in this setting is often discouraged. However, recent investigations, especially those that include

patient perceptions as an outcome measure, suggest bronchodilator therapy with nebulizers may be more effective than inhalers in reducing dyspnea symptoms and improving quality of life in many patients. Clearly, well-designed comparative efficacy trials with LABA/LAMA combinations administered by inhalers vs. nebulizers are needed to evaluate the role of nebulizers for maintenance therapy in patients with stable COPD. The present study seeks to address this important gap in knowledge.

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