# Nebulizer versus Dry Powdered Inhalers for COPD

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**Title:**

**Preliminary study for comparison of triple therapy nebulizer versus dry powdered inhaler for care transitions in COPD**

**Abstract:**

Drugs used to treat COPD are available primarily in hand held inhaler devices that deliver dry powder (DPI), a soft mist or a metered dose of spray (MDI). The frail, arthritic elderly are often prescribed DPI rather than MDI or soft mist devices, because they require less coordination. DPIs however require the ability to inhale against a resistance with a peak inspiratory force (PIF) more negative than -60 L/min to break the dry powder into respirable particles. Preliminary data suggests that suboptimal PIF's are common during an acute exacerbation of COPD, affecting 48% of hospitalized patients, thus placing them at risk for treatment failure and possibly hospital readmission. Use of nebulizers to administer respiratory medications may avoid the hazards of insufficient dosing that can result from use of DPI however they are cumbersome, expensive and the variety of drugs available in a nebulizer format is limited. We *hypothesize* that patients treated in hospital and discharged on respiratory medications administered by nebulizers will exhibit better symptom control and lower COPD and all cause hospital readmission rates compared with patients treated with respiratory medications delivered by DPI. We aim to demonstrate that 1) patients treated and discharged on nebulized bronchodilators will have fewer readmissions to hospital at 30 and 90 days compared to the group utilizing DPI 2) that the nebulizer group will demonstrate a longer duration of time till hospital readmission for COPD and all cause readmission compared to the group utilizing DPI and 3) the nebulizer group will demonstrate better symptom control compared to the group utilizing DPI. This non-blinded feasibility (pilot) study will enroll 100 patients hospitalized for an exacerbation of COPD who are $\geq$ 40 years of age, have a clinical diagnosis of COPD defined by FEV1/FVC or FEV1/SVC < 70% on bedside or previous baseline spirometry and FEV1/FVC or FEV1/SVC < 70% on clinic visit < 2 weeks from hospital discharge and have smoked $\geq$ 10 pack years. The study will consist of 3 outpatient visits (Transitional Care Visit [3-14 days], Visit #2 [30 +/- 5 days], and Visit #3 [90 +/- 5 days after discharge]). Visit #2 and #3 are for study purposes, the Transitional Care Visit is standard of care. Study endpoints will include 30- and 90-day hospital readmission,

time until COPD and all-cause readmission, number of unscheduled clinic or ER visits, and mortality. COPD Assessment Test (CAT), Modified Medical Research Council (mMRC) dyspnea score, Saint George Respiratory Questionnaire (SGRQ), and patient preference will be assessed during each outpatient visit. The Montreal Cognitive Assessment (MOCA) test and spirometry variables will be measured at the bedside during hospitalization and at Visit #3 after hospital discharge.

**Background:**

COPD (Chronic obstructive pulmonary disease) is a disorder that is estimated to affect 6% of adults[1] and is largely caused by cigarette smoking.[2] Patients with COPD have a disproportionate prevalence of comorbidities compared with smokers without COPD, with arthritis being the most common of the co-morbidities.[3] Because COPD is more common in the elderly with a prevalence of 12% in individuals 65 years of age and older[1], many COPD patients may also suffer dementia and other disorders of cognition that may affect their disease management. COPD is characterized by acute exacerbations or flares of the disease that account for 50-75% of the annual $50 billion cost of COPD in the US.[4] Many drugs used to treat COPD have also been shown to decrease exacerbation frequency,[5-8] thus reducing costs. These drugs are most effective when used in combination[9,10] and are available primarily in hand held devices that include dry powder inhalers (DPI), a soft mist and metered dose inhalers (MDI). The frail, arthritic elderly are often prescribed DPI rather than MDI or soft mist devices, because they require less coordination. DPIs however require the ability to inhale against a resistance with a force more negative than -60 L/min to break the dry powder into respirable particles and deliver them to the site of action in the lower respiratory tract.[11] In addition to an adequate peak inspiratory flow rate (PIFR), also required for reliable delivery of a DPI is an initial inhalational blast and suitable inhalational duration. Preliminary data suggests that suboptimal PIFs are common during an acute exacerbation of COPD affecting 48% of hospitalized patients. This places patients at risk for treatment failure and possibly leads to hospital readmissions, a significant socioeconomic burden.[12] Use of nebulizers to administer respiratory medications may avoid the hazards of insufficient medication delivery that can result from use of DPI in a population characterized by suboptimal PIFs, frailty, and arthritis.

**Hypothesis and aims:**

We *hypothesize* that patients treated in hospital and discharged on respiratory medications administered by nebulizers will exhibit better quality of life (QoL), symptom control and lower COPD and all cause hospital readmission rates compared with patients treated with respiratory medications delivered by DPI

We *aim to demonstrate* that:

1) patients treated and discharged on nebulized bronchodilators will have fewer readmissions to hospital at 30 and 90 days compared to the group utilizing DPI

2) the nebulizer group will demonstrate a longer duration of time until hospital readmission for COPD and all cause readmission compared to the group utilizing DPI

3) the nebulizer group will demonstrate better QoL (measured by the SGRQ – Saint George Respiratory Questionnaire) and symptom control (as measured by the CAT & mMRC) compared to the group utilizing DPI.

## Study Design

This will be a non-blinded feasibility (pilot) study and therefore it is not formerly powered. The study will consist of enrollment during hospitalization and 3 outpatient visits.

**Enrollment:** Patients will be identified, qualified, enrolled and consented by the respiratory therapy navigator (RTN) such that they will receive study medication prior to hospital discharge. Once hospitalized patients are stable for transition to long term COPD medications (triple therapy) the patients will be randomized in 1:1 ratio to 1 of 2 arms, a nebulizer arm or a DPI arm. Before discharge the following assessments will be performed; Montreal cognitive assessment test (MOCA) and SGRQ.

**Visit 1:** Patients will return for their standard of care post hospital discharge visit 3- 14 days after date of discharge. As part of that visit they will be evaluated by both a physician and a respiratory therapist. The following tests are part of that visit: PIF, spirometry, mMRC and CAT. The respiratory therapist study coordinator will also check patient preference for nebulizer vs. DPI using a Likert scale and administer the SGRQ. The study coordinator will also determine and record if the patient has had an unscheduled physician appointment, urgent care, ER or inpatient visits for COPD or any other condition since discharge.

**Visit 2:** The 30+/-5 day visit will include PIF, spirometry, mMRC, CAT and patient preference for nebulizer vs. DPI. The study coordinator will also determine and record if the patient has had an unscheduled physician appointment, urgent care, ER or inpatient visit for COPD or any other condition since the last visit.

**Visit 3:** The end of study visit (90+/- 10 days) will include PIF, spirometry, mMRC, CAT, patient preference for nebulizer vs. DPI, MOCA, SGRQ and collection of unused study drugs and equipment. The study coordinator will also determine and record if the patient has had an unscheduled physician appointment, urgent care, ER or inpatient visit for COPD or any other condition since the last visit.

Patients (n=100) will be randomized to therapy groups regardless of PIF. The patients will be counselled and educated regarding their assigned medications and delivery devices (nebulizers vs. DPIs) and disease state management during hospitalization and at outpatient visits by the

RTN according to the current standard of care. Patients will be randomized by the Investigational Drug Service pharmacy. The patients will be discharged on therapy and given all meds and equipment needed for the first 30 days of the study. All COPD controller medications and nebulizer equipment will be made available to the patient free of charge for the duration of the study (90 days). All medications will be provided by the funding pharmaceutical agency to eliminate bias. Inhalational medication costs can vary widely (from 10 to $1000/month) dependent upon the preferred product of the insurer thus allowing the insurer to influence the medication or delivery device and therefore possibly introduce bias in this protocol.

**Treatment Arms:**

**Nebulizer Arm:** Subjects will receive a long-acting $B_2$-agnoist (LABA; *Brovana,* twice daily), corticosteroid (ICS; *Pulmicort,* twice daily) and a short-acting anti-cholinergic (SAMA; *Atrovent,* three times a day).

**DPI Arm:** Subjects will receive a LABA/ICS *(Advair Diskus,* twice daily*)* **plus** a long-acting anticholinergic *(*LAMA-*Spiriva Handihaler,* once daily).

**Eligibility:**

Patients hospitalized for an exacerbation of COPD will be eligible if all of the following criterial are met:

*Inclusion:*

- ≥ 40 years of age
- Clinical diagnosis of COPD
- Smoking history ≥ 10 pack years
- Lung Function- FEV1/FVC or FEV1/SVC < 70% on bedside spirometry or previous baseline and FEV1/FVC or FEV1/SVC < 70% on clinic visit < 2 weeks from discontinuation
- Able to give informed consent

Patients will be excluded for any of the following reasons:

*Exclusion:*

- Dementia
- to active cancer with an anticipated survival of < 6 months
- End stage cardiovascular disease with an ejection fraction of < 20%
- Inability to attend outpatient visits
- Active Schizophrenia (actively hallucinating, combative)

Pregnancy; subjects will be excluded if female and are not post-menopausal for at least one year. Since there is no possible benefit from participating in this protocol for a pregnant woman, we

will exclude pregnant women. If a subject is found to be pregnant during the 90-day study period, they will be excluded from the study and their data not used for study purposes.

*Study Endpoints:*

- Number of patients readmitted within 30 days of hospital D/C
- Number of days until COPD or all cause hospital readmission
- Number of patients readmitted within 90 days of hospital D/C
- PIF measured with in check device set on DPI (Advair Diskus) at the bedside during hospitalization and at every study visit
- COPD Assessment Test (CAT) during each visit
- Modified Medical Research Council (mMRC)
- Mortality
- Number of Unscheduled clinic or ER visits
- Patient preference for nebulizer or DPIs
- Spirometry variables measured at the bedside during hospitalization, visit #1 (<14 days) and visit #3 (90 +/- days) after hospital discharge
- Patient reported readmissions at outside hospital, or outpatient/ED treatment for AECOPD
- QoL measured by SGRQ

*Demographic data:*

- Name/Study ID number
- DOB/Age
- Smoking status (current/former)
- Pack year
- Wood stove exposure (years)
- Gender
- BMI
- Charlson Comorbidity Index
- Cognitive function measured by the Montreal Cognitive assessment (MoCA) measured at randomization and on first & last post discharge clinic visit
- Presence or absence of chronic respiratory failure defined as needing supplemental O2 and required flow rates
- Date of index admission
- Date of index discharge
- LOS for index admit
- Days on mechanical ventilation for index admit
- Days on NIV for COPD (not for Obstructive Sleep Apnea) for index admit
- ICU days for index admit

- Dates of readmission (all cause and COPD)
- D/C date for readmission
- # of readmission/90 days

Data capture will be done exclusively within Wake Forest's REDCap database. Please see attachments for database schemata and collection forms. There is an additional form within REDCap to collect readmission or adverse events that are obtained at a subject visit, or if a patient contacts a study member via telephone number provided.

Statistical methods:

This research project is primarily a feasibility project. The sample size will be 50 participants in each treatment group. We expect that we will be able to follow 90% or more of the participants for 90 days. With this sample size we will be able to estimate the retention percentage in each group with a standard error of 4%. We will be able to estimate the percentages of the dichotomous outcomes with a standard error of 7% and for continuous outcomes with a standard error of 0.15 times its standard deviation.

We will compare summary statistics of the outcome variables to get a preliminary estimate of the possible effect sizes to be expected in a larger trial. The percent of patients readmitted within 30 and 90 days of hospital discharge, 90-day mortality, and other dichotomous outcomes will be compared between the two groups using Fisher's Exact test. The number of days until readmission and until death will be compared by Kaplan-Meier curves and tested using the log-rank test. The number of unscheduled clinic or ER visits will be compared using Poisson Regression. Continuous outcome measures when there is no baseline value will be compared and tested using the two sample t-test. When a baseline value of the outcome is available, analysis of covariance using the baseline value as covariate will be used. Spirometry variables measured at baseline and post randomized visits 1 and 3 will be analyzed by repeated measures analysis of covariance with the baseline value being a covariate. A statistician from the Wake Forest University Department of Biostatisticial Sciences (Tim Morgan, Ph.D; no conflicts of interest) will analyze and perform statistical tests for this study. Jill Ohar, the P.I., will be excluded from data collection and will not have access to REDCap database.

## Subject Recruitment Methods

Patients will be identified, consented, and enrolled by the respiratory therapy navigator (RTN) during the usual course of care they provide to inpatients that are admitted for a COPD exacerbation and utilize the attached informed consent form. The RTN, in the usual course of care, assesses the patient, and per protocol/standing order, prescribes chronic/long-term inhalation therapies, which may include nebulizers or dry powder inhalers (DPI). Once hospitalized patients are stable for transition to long term COPD medications, the patients will be

randomized in 1:1 ratio to 1 of 2 arms, a nebulizer arm or a DPI arm by the investigational drug service pharmacy. The patients will receive medication education as part of usual care provided to COPD exacerbation patients prior to hospital discharge. Inclusion criteria include a clinical diagnosis of COPD, age >/= 40 years, smoking history >/= 10 pack years, spirometry findings consistent with COPD and ability to give informed consent. Patients will be excluded for dementia, active cancer or schizophrenia, end stage cardiovascular disease, or inability to attend outpatient clinic visits. No recruitment flyers or advertisements will be utilized. No penalty or loss of benefits will occur as a result of either not participating or withdrawing at any time.

Vulnerable or special classes of subjects will not be included in this study. Patients who are cognitively or psychologically impaired will be excluded based on study exclusion criteria (dementia, schizophrenia, and by inability to attend clinic visit). Patients will also be enrolled during hospitalization and the RTN will be aware, during usual daily care of any possible impairment and will not enroll those with possible impairment or vulnerable to coercion. The RTN will utilize medical records in their standard practice to identify COPDE exacerbation patients admitted to the hospital and follow them throughout the hospitalization. The RTN will identify and screen patients based on the study inclusion and exclusion criteria during standard of practice evaluation. A limited waiver of HIPAA is requested to utilize PHI to identify potential subjects who will be approached for participation in the study. The RTN will access and use only the minimum amount of PHI necessary to review eligibility criteria. This includes, but is not limited to patient's past medical history and evaluation of their COPD diagnosis (e.g. smoking pack years, prior pulmonary function testing results). Confidentiality and privacy will be protected prior to ascertaining desire to participate by only accessing the minimal amount of information required to screen patients for eligibility. This is expected to be information that is accessed in the usual care delivered by the RTN to the screening population. No information regarding screening will be collected by the RTN, unless enrolled and randomized, and therefore will not need to be destroyed if a patient declines participation in the study.

## Informed Consent

Signed informed consent will be obtained from each subject. Informed consent will be obtained by the RTN, or another member of the study team if the RTN is unavailable to obtain consent. Informed consent will be obtained while the subject is still admitted to the hospital. The subject will therefore be able to be randomized to a treatment arm and receive education regarding the medication delivery device, as is part of the usual care provided to this patient population prior to hospital discharge.

## Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could

directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study by deletion of electronic files and shredding of any paper files, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured in a REDCap Database, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Research sponsor will have access to finalized study data, but not individual subject records. All accessible data will be de-identified and not contain PHI.

**Data and Safety Monitoring**

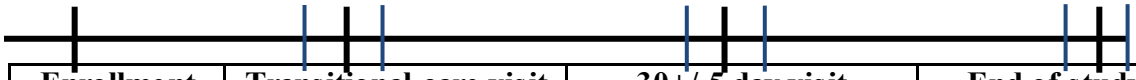
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. The principal investigator or study coordinator will report all events or risks to the IRB in a timely manner.

**Reporting of Unanticipated Problems, Adverse Events or Deviations**

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

**Figure 1. Study Schemata**

Randomization prior to discharge



| Enrollment | Transitional care visit (3-14 days post D/C) | 30+/-5 day visit | End of study visit (90+/- 10 days) |
|---|---|---|---|
| Demographics<br>PIF<br>CCI<br>MOCA<br>SGRQ | •PIF<br>•Spirometry<br><br>•mMRC<br>•CAT<br>•SGRQ<br>•Patient preference | •PIF<br><br><br>•mMRC<br>•CAT<br>•SGRQ<br>•Patient preference | •PIF<br>•Spirometry<br>•MOCA<br>•mMRC<br>•CAT<br>•SGRQ<br>•Patient preference<br>•Clinical Outcomes<br>•Collect study medication and equipment |
| | •Navigator to ask patient about all:<br>Unscheduled MD visits<br>Urgent Care visits<br>Emergency Room visits<br>Hospital admittance for all causes & COPD | •Navigator to ask patient about all:<br>Unscheduled MD visits<br>Urgent Care visits<br>Emergency Room visits<br>Hospital admittance for all causes & COPD | •Navigator to ask patient about all:<br>Unscheduled MD visits<br>Urgent Care visits<br>Emergency Room visits<br>Hospital admittance for all causes & COPD |

CCI: Charleson Comorbidity index
MOCA: Montreal Cognitive Assessment
SGRQ: Saint George Respiratory Questionnaire
mMRC: Modified Medical Research Council Dyspnea Scale
CAT: COPD Assessment Test
PIF: Peak Inspiratory Flow

References

1. Chronic obstructive pulmonary disease among adults--United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(46):938-943.

2. From the Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2015; http://www.goldcopd.org. Accessed March 8, 2015.

3. Pleasants RA, Ohar JA, Croft JB, Liu Y, Kraft M, Mannino DM, et al. Chronic obstructive pulmonary disease and asthma-patient characteristics and health impairment. *COPD*. 2014;11(3):256-266.

4. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res*. 2013;5:235-245.

5. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.

6. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685-694.

7. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med*. 2008;102(8):1099-1108.

8. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1(3):210-223.

9. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64(3):450-504.

10. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther*. 2010;23(4):257-267.

11. Mahler DA, Waterman LA, Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus(R) dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2013;26(3):174-179.

12. Loh CH, Lovings T, Ohar JA . Low Inspiratory Flow Rates Predict COPD and All Cause Readmissions. *ATS* Abstract;2016;In press.Appendix

Attachments:

1. REDCap data collection form schemata
2. Copies of Questionnaires/Surveys
    a. MOCA
    b. CAT
    c. MMRC
    d. SGRQ
    e. Patient Preference
3. Consent form