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October 7, 2019

Clinical Protocol

A Study for the Assessment of the Benefits of a Novel Mesh Nebulizer in the Treatment of Patients with Stable COPD

Protocol # SRC-RDD-InnospireGo-2018-10458

Written By: _____
Sara Garbin Date
Clinical Development Scientist, SRC Clinical Development

Approved By:
_____
Ketah Doty Date
Senior Clinical Research Associate, SRC Clinical Operations

Approved By:
_____
Jeff Jasko Date
Senior Data Manager, Q&R Reg. & Clin. Aff. - Biostatistics/DM

Sponsored by

Respironics, Inc., a Philips Healthcare Company
1740 Golden Mile Hwy,
Monroeville, PA 15146
USA

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Protocol Number: SRC-RDD-InnospireGo-2018-10458

Author(s): Sara Garbin, Chuck Cain, Dirk Von Hollen, Cheryl Nickerson

Study Sponsor:

Philips Respironics Inc.
1740 Golden Mile Highway
Monroeville, PA 15146
724.387.7500

Site(s):
Jefferson Associates in Internal Medicine
575 Coal Valley Road, Suite 511
Clairton, PA 15025
Phone: 412-466-6161

Principal Investigator:
Michael I. Mallinger, MD
575 Coal Valley Road, Suite 511
Clairton, PA 15025
Phone: 412-466-6161
412-606-2924 (24-hour number)
E-mail: mallmimd01@gmail.com

Collaborator(s)
Consolidated Clinical Trials, Inc.
4232 Northern Pike, Suite 102
Pittsburgh, PA 15146
Phone: 412-273-9100

Philips Respironics, Inc. Contact Information

Study Monitor(s):

Ketah Doty, RN, BSN, OCN
Senior Clinical Research Associate
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-7921
Mobile: 412-738-6281
Email: ketah.doty@philips.com

Reporting of Adverse Events or Adverse Device Effects

Report the occurrence of a serious adverse event or serious adverse device effect to Philips Respironics within 24 hours of the occurrence.

Ketah Doty, RN, BSN, OCN
Senior Clinical Research Associate
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-7921
Mobile: 412-738-6281
Email: ketah.doty@philips.com

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Protocol Approvals

Investigator Agreement

As Investigator of the study entitled "A Study for the Assessment of the Benefits of a Novel Mesh Nebulizer in the Treatment of Patients with Stable COPD" Protocol # SRC-RDD-InnospireGo-2018-10458, I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the IRB (the "Protocol"); all applicable laws and regulations; Good Clinical Practice and the Declaration of Helsinki; and any IRB or FDA conditions of approval;

(ii) await IRB approval for the Protocol before obtaining informed consents;

(iii) ensure that all requirements for informed consent are met and not let any subject participate in the Study before obtaining that subject's informed consent;

(iv) not make modifications to the Protocol as supplied to me by Respironics, Inc. (the "Sponsor"), without first obtaining the written approval of the Sponsor;

(v) provide the Sponsor with accurate financial information as required by FDA regulations;

(vi) supervise all testing of investigational devices that involves any Study subject;

(vii) maintain Study documentation for the period of time as required by FDA regulations;

(viii) will supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

Investigator Signature: _____ **Date**:_____

Printed Name: _____

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Protocol Revisions

Revision Level	Changes Made to Protocol	Date	By
0.0	Initial release	15Apr2019	C. Cain, K. Doty, S. Garbin, J. Jasko, C. Nickerson, D. Von Hollen
1.0	Updated inclusion/exclusion criteria, added collection of height and weight, clarified study procedure details	19Apr2019	S. Garbin
2.0	Revised inclusion criteria to allow use of albuterol alone; updated study procedures and potential side effects to reflect use of albuterol; added site contact information	17Jun2019	S. Garbin
3.0	Updated site information, investigator name and contact information; revised instruction in the nebulizer satisfaction assessment	1Oct2019	S. Garbin

Glossary

6MWT	6-Minute Walk Test
ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRQ-SR	Chronic Respiratory Disease Questionnaire Self-Report
DPI	Dry Powder Inhaler
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
mMRC	Modified Medical Research Council (dyspnea scale)
PI	Principal Investigator
PIF	Peak Inspiratory Flow
pMDI	Pressurized Metered Dose Inhaler
QC	Quality Control
SAE	Serious Adverse Event
US	United States
USADE	Unanticipated Serious Adverse Device Effect

Protocol Synopsis

Title	A Study for the Assessment of the Benefits of a Novel Mesh Nebulizer in the Treatment of Patients with Stable COPD
Background	Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease that results in airflow obstruction. Affecting more than 5% of adults, COPD is the third leading cause of death in the United States.[1, 2] Manifestations of COPD may include dyspnea, poor exercise tolerance, chronic cough (with or without sputum production), wheezing, respiratory failure or cor pulmonale.[1] GOLD states that pharmacologic treatment should be individualized and guided by the severity of symptoms, risk of exacerbations, side effects, comorbidities, drug availability and cost, and the patient's response, preference and ability to use various drug delivery devices.[3] Their final point regarding preference and ability to use various drug delivery devices may be related, in part, to the issues that patients with COPD have in using pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) correctly.[4] Administration of nebulized therapy to patients with COPD avoids many of these issues because the aerosol is typically inhaled using the patients usual breathing cycle, and inhalation maneuver, coordination and moderate to high flows are not required for inhalation of the aerosolized drug.[5] Use of nebulized therapy may therefore be preferred over inhaler therapy in some situations.[6-8] In the US a nebulized combination of short acting beta$_2$-agonists and anti-muscarinic drugs is widely prescribed to patients with COPD discharged from hospital after an exacerbation.[9] A nebulizer breaks up medical solutions into small droplets suspended in air (aerosol) so that they may be delivered to the patient's airways for respiratory therapy. Jet nebulizers have been the standard delivery system for aerosolized medications. From the perspective of medication delivery to the lungs, jet nebulizers are relatively inefficient and require an external pressurized gas source to operate. There also is limited control of the dose delivered to the patient.[10] A vibrating mesh nebulizer is composed of a liquid reservoir with a piezo mesh disk mounted on one side of it, and a piezo mesh driver circuit board with batteries. The piezo mesh disk consists

	of a metallic plate with thousands of precision formed holes surrounded by a piezoelectric material. The piezoelectric material vibrates at a very high rate of speed. As a result of rapid vibration, solution is drawn through the holes in the piezoelectric material to form droplets of consistent size that are delivered at a low velocity to be inhaled directly into the lungs.[11] Devices that use a vibrating mesh or plate with multiple apertures to generate aerosol create aerosols with a high fine particle fraction and they have a significantly higher efficiency of delivering drugs to the lung than conventional jet or ultrasonic nebulizers. The aerosol is generated as a fine mist and no baffling system is required. Vibrating mesh devices are portable, battery-operated (operation with alternating current is optional in some devices), and they efficiently aerosolize solutions and suspensions with minimal residual volume (volume of liquid remaining in the nebulizer at the end of nebulization).[12] Philips Respironics has developed a new handheld mesh nebulizer (InnoSpire Go), which has recently been cleared for use by the Food and Drug Administration.
Study Design	This will be a randomized open-label cross-over trial to investigate the potential benefits to the patient of using the InnoSpire Go over one month, compared to one month's use of their usual jet nebulizer.
Objectives	Primary Objective: The primary objective of this study is to assess device preference in stable ambulatory COPD patients.
	Secondary Objective: The secondary objective of this study is to evaluate the treatment effect of InnoSpire Go on quality of life.
	Exploratory Objectives: The exploratory objectives of this study are to: • Evaluate the treatment effect of InnoSpire Go on physical activity • Assess effects of InnoSpire Go on symptom scores • Assess device satisfaction based on specific elements of the device's operation and handling • Evaluate use of the device • Evaluate the safety of the InnoSpire Go device
Endpoints	Primary Endpoint: • Difference in overall device preference after 30 days of device use ○ Measure: Nebulizer Satisfaction Questionnaire, question 8

	Secondary Endpoint:
	• Change in quality of life scores after 30 days of device use compared to baseline
	  ○ Measure: Chronic Respiratory disease Questionnaire – Self-Report (CRQ-SR)
	Exploratory Endpoints
	• Difference in total distance walked
	  ○ Measure: 6-Minute Walk Test (6MWT)
	• The change in the modified Borg score following 6MWT, where the visit's post-nebulizer Borg score will be used as the baseline for this endpoint)
	  ○ Measure: Borg
	• The change in the modified Borg score following nebulizer use, where the visit's pre-nebulizer Borg score will be used as the baseline for this endpoint)
	  ○ Measure: Borg
	• Difference in modified Borg score from pre-nebulizer to post-6MWT
	  ○ Measure: Borg
	• Difference in device confidence after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 1
	• Difference in perceived effect of the device after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 2
	• Difference in difficulty of device assembly/disassembly after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 3-1
	• Difference in difficulty of cleaning and regular care after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 3-2
	• Difference in overall ease of handling or usability after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 3-3
	• Difference in overall burden of use after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 3-4

	• Difference in medication delivery confidence after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 4
	• Difference in overall satisfaction after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 5
	• Difference in likelihood of recommendation after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 6
	• Difference in perception of fit with lifestyle needs after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 7
	• Difference in average ease of use score after 30 days of device use
	  ○ Measure: Nebulizer Preference Questionnaire, average of scores from questions 3-1 through 3-4
	• Time in mouth (treatment time = first insert of mouthpiece to last removal of mouthpiece)
	  ○ Video recording
	• Time to fill (open disposable nebulizer, dispense ampule, close or reassemble)
	  ○ Video recording
	• Amount of fluid nebulized (pre- and post-weight of nebulizer)
	  ○ Nebulizer cup/reservoir weights
	• Time to sputter
	  ○ Video recording
	• Incidence of Unanticipated Serious Adverse Device Effects (USADEs) and Serious Adverse Events (SAEs)
	  ○ Measure: Side Effects and Adverse Event Assessment

Study Population	Up to 25 stable ambulatory COPD patients who are currently prescribed jet nebulizer albuterol treatment or albuterol/ipratropium bromide combination will be included in this study. The goal is to have 20 participants complete the study.
Inclusion Criteria	1. Patients ≥ 40 years of age. 2. Diagnosis of COPD. 3. Currently using only a mouthpiece with their nebulizer system. 4. FEV1 ≥ 30% predicted (pre- or post-bronchodilator). 5. mMRC grade ≥ 1. 6. Use of a jet nebulizer for the administration of albuterol or combination albuterol/ipratropium for the past 6 months. 7. Willing to use the same compressor/nebulizer system throughout the study.

	8. Willing to refrain from using the jet nebulizer system when using the InnoSpire Go. 9. Prescribed nebulizer combination albuterol/ipratropium (single or multiple vials) with self-report of at least daily use or prescribed nebulizer albuterol with self-report of at least twice daily use. 10. Willing to permit audio and video recording during the visit. 11. Willing and able to follow instructions and complete all activities required by the trial, including phone calls. 12. Able to read and understand English.
Exclusion Criteria	1. Unable to complete 6MWT or, if patient is not currently prescribed oxygen, persistent oxygen desaturation ≤ 88% on the 6MWT. 2. Exacerbation of COPD requiring hospitalization (defined as hospital admission, urgent care visit, or emergency room visit) in the last 3 months. 3. Prescribed non-selective beta blockers. 4. Prescribed additional ipratropium bromide via nebulizer or inhaler or any other nebulized treatments via the subject's jet nebulizer. 5. Patients currently in assisted living or nursing home. 6. Diagnosis of asthma, parenchymal lung disease other than COPD, bronchiectasis, tuberculosis, cor pulmonale, clinically significant obstructive urinary disease, narrow-angle glaucoma, unstable angina, depression, anxiety, or other serious medical condition that, in the opinion of the investigator, would interfere with the patient's participation in the trial. 7. History of thoracotomy. 8. Myocardial infarction within the last 6 months. 9. Participation in any other therapeutic clinical trial in the previous 4 weeks.
Phase	Post-market study
Sites/Facilities	Consolidated Clinical Trials, Inc. 4232 Northern Pike, Suite 102 Pittsburgh, PA 15146
Enrolling Participants:	COPD patients
Description of Study Intervention:	General purpose vibrating mesh nebulizer
Study Duration	Approximately 6 months

Participant Duration	Approximately 60 days

Background Information

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease that results in airflow obstruction. Affecting more than 5% of adults, COPD is the third leading cause of death in the United States.[1, 2] Manifestations of COPD may include dyspnea, poor exercise tolerance, chronic cough (with or without sputum production), wheezing, respiratory failure or cor pulmonale.[1]

GOLD states that pharmacologic treatment should be individualized and guided by the severity of symptoms, risk of exacerbations, side effects, comorbidities, drug availability and cost, and the patient's response, preference and ability to use various drug delivery devices.[3]

Their final point regarding preference and ability to use various drug delivery devices may be related, in part, to the issues that patients with COPD have in using pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) correctly.[4] Administration of nebulized therapy to patients with COPD avoids many of these issues because the aerosol is typically inhaled using the patients usual breathing cycle, and inhalation maneuver, coordination and moderate to high flows are not required for inhalation of the aerosolized drug.[5] Use of nebulized therapy may therefore be preferred over inhaler therapy in some situations.[6-8] In the US a nebulized combination of short acting beta$_2$-agonists and anti-muscarinic drugs is widely prescribed to patients with COPD discharged from hospital after an exacerbation.[9]

A nebulizer breaks up medical solutions into small droplets suspended in air (aerosol) so that they may be delivered to the patient's airways for respiratory therapy. Jet nebulizers have been the standard delivery system for aerosolized medications. From the perspective of medication delivery to the lungs, jet nebulizers are relatively inefficient and require an external pressurized gas source to operate. There also is limited control of the dose delivered to the patient.[10]

A vibrating mesh nebulizer is composed of a liquid reservoir with a piezo mesh disk mounted on one side of it, and a piezo mesh driver circuit board with batteries. The piezo mesh disk consists of a metallic plate with thousands of precision formed holes surrounded by a piezoelectric material. The piezoelectric material vibrates at a very high rate of speed. As a result of rapid vibration, solution is drawn through the holes in the piezoelectric material to form droplets of consistent size that are delivered at a low velocity to be inhaled directly into the lungs.[11]

Devices that use a vibrating mesh or plate with multiple apertures to generate aerosol create aerosols with a high fine particle fraction and they have a significantly higher efficiency of delivering drugs to the lung than conventional jet or ultrasonic nebulizers.

The aerosol is generated as a fine mist and no baffling system is required. Vibrating mesh devices are portable, battery-operated (operation with alternating current is optional in some devices), and they efficiently aerosolize solutions and suspensions with minimal residual volume (volume of liquid remaining in the nebulizer at the end of nebulization).[12]

Philips Respironics has developed a new handheld mesh nebulizer (InnoSpire Go), which has recently been cleared for use by the Food and Drug Administration.

Description of the Intervention Studied

The InnoSpire Go (see Figure 1) is a handheld, single patient use, vibrating mesh nebulizer system designed to aerosolize liquid medications for respiratory disease. The device operates continuously once initiated and automatically switches off once the medication has been delivered. The device may be used in pediatric and adult populations, as permitted by the prescribed medication, and is suitable for use in home environments or hospital/clinic settings.

FIGURE 1

Study Design Rationale

Study Objectives and Purpose

Primary Objective	Primary Endpoint
To assess device preference in stable ambulatory COPD patients	• Difference in overall device preference after 30 days of device use ○ Measure: Nebulizer Satisfaction Questionnaire, question 8
Secondary Objective	**Secondary Endpoint**

To evaluate the treatment effect of InnoSpire Go on quality of life	• Change in quality of life scores after 30 days of device use compared to baseline ○ Measure: Chronic Respiratory disease Questionnaire – Self-Report (CRQ-SR)
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the treatment effect of InnoSpire Go on physical activity	• Difference in total distance walked ○ Measure: 6-Minute Walk Test (6MWT)

To assess effects of InnoSpire Go on symptom scores	• The change in the modified Borg score following 6MWT, where the visit's post-nebulizer Borg score will be used as the baseline for this endpoint)
	  ○ Measure: Borg
	• The change in the modified Borg score following nebulizer use, where the visit's pre-nebulizer Borg score will be used as the baseline for this endpoint)
	  ○ Measure: Borg
	• Difference in modified Borg score from pre-nebulizer to post-6MWT
	  ○ Measure: Borg

To assess device satisfaction based on specific elements of the device's operation and handling	• Difference in device confidence after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 1
	• Difference in perceived effect of the device after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 2
	• Difference in difficulty of device assembly/disassembly after 30 days of device use
	  ○ Measure: Nebulizer Satisfaction Assessment, question 3-1
	• Difference in difficulty of cleaning and regular care after 30 days of device use

	○ Measure: Nebulizer Satisfaction Assessment, question 3-2 • Difference in overall ease of handling or usability after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 3-3 • Difference in overall burden of use after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 3-4 • Difference in medication delivery confidence after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 4 • Difference in overall satisfaction after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 5 • Difference in likelihood of recommendation after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 6 • Difference in perception of fit with lifestyle needs after 30 days of device use ○ Measure: Nebulizer Satisfaction Assessment, question 7 • Difference in average ease of use score after 30 days of device use ○ Measure: Nebulizer Preference Questionnaire, average of scores from questions 3-1 through 3-4
To evaluate use of the device	• Time in mouth (treatment time = first insert of mouthpiece to last removal of mouthpiece) ○ Video recording • Time to fill (open disposable nebulizer, dispense ampule, close or reassemble) ○ Video recording

	• Amount of fluid nebulized (pre- and post-weight of nebulizer)
	  ○ Nebulizer cup/reservoir weights
	• Time to sputter
	  ○ Video recording

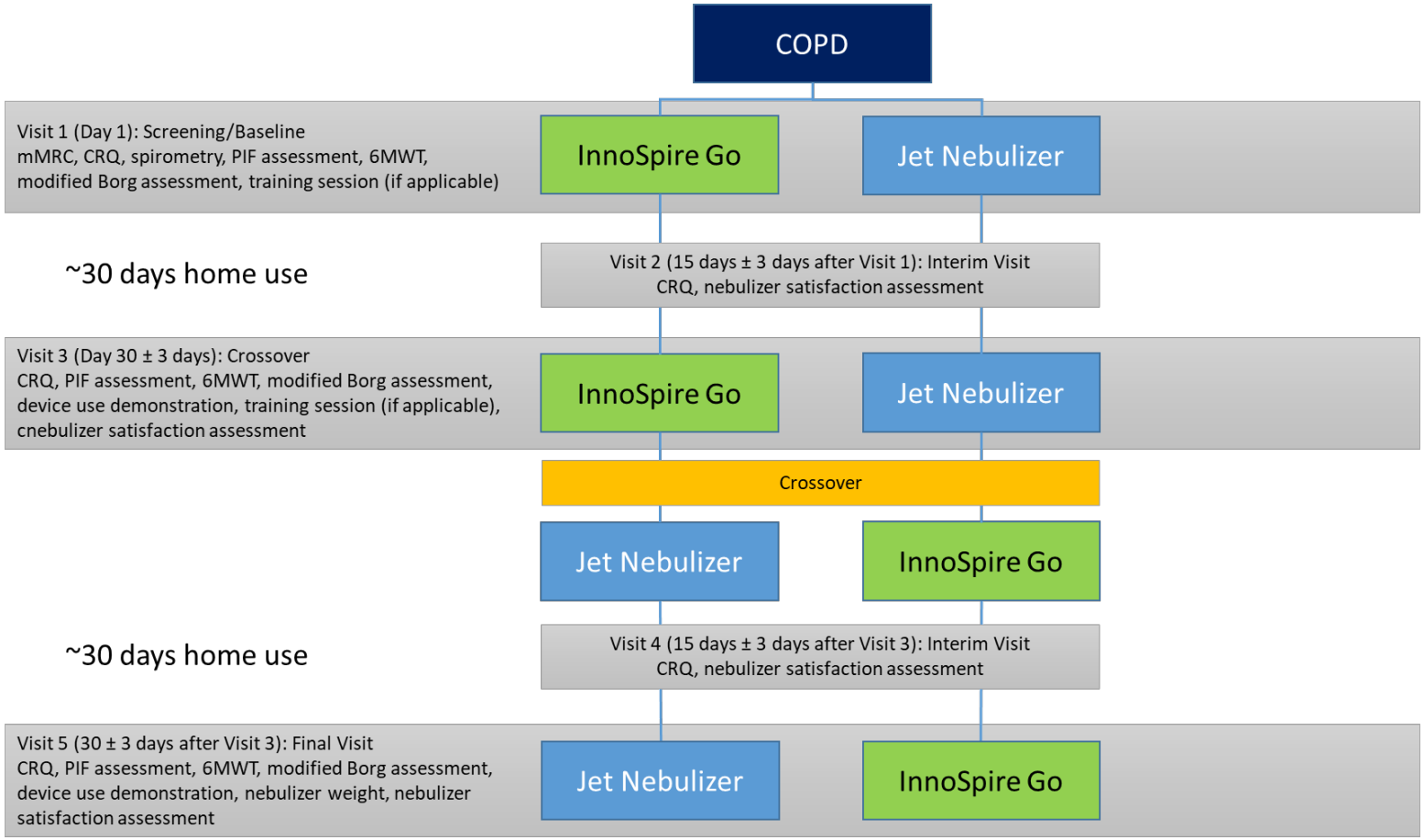
To evaluate the safety of the InnoSpire Go device	• Incidence of Unanticipated Serious Adverse Device Effects (USADEs) and Serious Adverse Events (SAEs) ○ Measure: Side Effects and Adverse Event Assessment

Study Design

This will be a randomized open-label cross-over trial to investigate the potential benefits to the patient of using the InnoSpire Go over one month, compared to one month's use of their usual jet nebulizer.

Up to 25 stable ambulatory COPD patients who are currently prescribed jet nebulizer albuterol treatment or albuterol/ipratropium bromide combination will be included in this study. The goal is to have 20 participants complete the study.

Figure 2


COPD
Visit 1 (Day 1): Screening/Baseline
mMRC, CRQ, spirometry, PIF assessment, 6MWT,
modified Borg assessment, training session (if applicable)
InnoSpire Go
Jet Nebulizer
~30 days home use
Visit 2 (15 days ± 3 days after Visit 1): Interim Visit
CRQ, nebulizer satisfaction assessment
Visit 3 (Day 30 ± 3 days): Crossover
CRQ, PIF assessment, 6MWT, modified Borg assessment,
device use demonstration, training session (if applicable),
cnebulizer satisfaction assessment
InnoSpire Go
Jet Nebulizer
Crossover
Jet Nebulizer
InnoSpire Go
~30 days home use
Visit 4 (15 days ± 3 days after Visit 3): Interim Visit
CRQ, nebulizer satisfaction assessment
Visit 5 (30 ± 3 days after Visit 3): Final Visit
CRQ, PIF assessment, 6MWT, modified Borg assessment,
device use demonstration, nebulizer weight, nebulizer
satisfaction assessment
Jet Nebulizer
InnoSpire Go

Schedule of Events

Procedures	Pre-Screening	Visit 1 (Day 1) Screening/Baseline	Visit 2 (15 days ± 3 days after Visit 1) Interim Visit	Visit 3 (Day 30 ± 3 days) Crossover	Visit 4 (15 days ± 3 days after Visit 3) Interim Visit	Visit 5 (30 days ± 3 days after Visit 3) Final Visit
Recruitment	X					
Informed Consent		X				
Inclusion/Exclusion Criteria Review		X				
Demographics		X				
Medical History		X				
Height and Weight		X				
Concomitant Medication		X	X	X	X	X
Device Photograph		X				
Modified Medical Research Council Dyspnea Scale		X				
Chronic Respiratory Disease Questionnaire Self-Report		X	X	X	X	X
Spirometry		X				
Peak Inspiratory Flow Assessment		X		X		X
Vital Signs		X		X		X
6-Minute Walk Test		X		X		X
Modified Borg Assessment*		X		X		X
Device Use Demonstration (Audio/Video)				X		X
Nebulizer Weight				X		X
Training Session		X†		X§		
Side Effects and Adverse Event Assessment			X	X	X	X
Nebulizer Satisfaction Assessment			X	X	X	X

*Borg assessment will be performed up to three times at each designated visit (see visit procedures below).
†For participants randomized to InnoSpire Go in the first treatment arm.
§For participants randomized to InnoSpire Go in the second treatment arm.

Screening Procedures:

Participants will be contacted by designated study site staff. Participants may be pre-screened through medical records over the phone to assess potential eligibility. Participants that are interested will be scheduled for a screening visit at the clinical office.

Visit 1 – Screening/Baseline:

Once the participant arrives, the study will be explained in full detail. If the participant agrees, he/she will be consented into the study and the participant will be given a copy of the informed consent. After the consent is signed, the following procedures will be performed:

Demographics

Demographic data will be collected from standard sources.

Medical History

Information related to the patient's medical history, including COPD history.

Height and Weight

Participants' height and weight will be collected.

Concomitant Medication

Prescription history will be collected. Participants will be asked to bring all inhaled medications to this visit. Their self-reported use of either albuterol or combination albuterol/ipratropium will also be documented.

mMRC

Dyspnea ratings will be collected using the Modified Medical Research Council (mMRC) dyspnea scale.

CRQ-SR

The participant will complete the CRQ-SR[13, 14] (Appendix 1) to assess disease-related quality of life.

Pulmonary Function Tests

Spirometry will be performed at Visit 1. Participants must have an $FEV_1 \geq 30$ to be eligible for participation. Site staff will document the number of hours since the participant's last use of bronchodilators.

Additionally, peak inspiratory flow (PIF) will be measured using In-Check inspiratory flow device. The highest of three attempts should be recorded.

Vital Signs

Heart rate, blood pressure and SpO_2 will be collected before 6MWT is performed.

6-Minute Walk Test

A 6MWT will be performed according to international guidelines.[15, 16] Parameters measured during this test include total distance walked and Borg[17-19] dyspnea scale pre- and post-test. SpO_2 will be continuously measured using a pulse oximeter.

Modified Borg Assessment

The modified Borg assessment (Appendix 2) will be performed before and after 6MWT.

Inclusion/Exclusion Criteria Review

Site staff will review inclusion/exclusion criteria to determine participant eligibility. Only eligible participants will be randomized.

Device Photograph

Participants will be asked to bring their current jet nebulizer system to the visit. Study staff will take a photograph of the compressor, handset, and associated labels, if available.

Randomization

Participants will be randomly assigned to either their current jet nebulizer or the InnoSpire Go device for the first 30 days of treatment.

Training Session

Participants randomized to InnoSpire Go in the first treatment arm will be trained on the use and cleaning of the device before being sent home. These participants will be asked to refrain from using their own jet nebulizer system during this 30-day period.

Visit 2 – Interim Visit:

Participants will be asked to return to the research center 15 days ± 3 days after Visit 1.

Side Effects and Adverse Event Assessment

Participants will be asked about any side effects or adverse events (AEs) since the last visit.

Concomitant Medications

Participants will be asked about any changes in their medication since the last visit.

CRQ-SR (Follow-Up)

Participants will complete the follow-up CRQ-SR (Appendix 3) to assess disease-related quality of life since the previous visit.

Nebulizer Satisfaction Assessment

Participant satisfaction with the device used in the first treatment arm will be assessed. See Appendix 4 for assessment details.

Visit 3 – Cross-over:

Participants will be asked to return to the research center within 30 days ± 3 days after Visit 1. They will be instructed to bring the first assigned study device and their prescribed albuterol or combination albuterol/ipratropium medication for the demonstration.

CRQ-SR (Follow-Up)

Participants will complete the follow-up CRQ-SR to assess disease-related quality of life since the previous visit.

Concomitant Medications

Participants will be asked about any changes in their medication since the last visit.

Device Use Demonstration

Participants will be asked to assemble their device and administer their next scheduled dose in the clinic to demonstrate their use of the device before completing the 6MWT. Site staff will verify that the demonstration does not conflict with patient's prescribed

dosage. All demonstrations will be video recorded to provide information on nebulizer use in post-study analysis.

Nebulizer Weight

The nebulizer cup/reservoir alone will be weighed with the medication before device use and after device use to capture residual medication. This process will take place during video recording.

PIF

Peak inspiratory flow will be measured using the In-Check inspiratory flow device. The highest of three attempts should be recorded.

Vital Signs

Blood pressure and SpO_2 will be collected after nebulizer use but before 6MWT is performed. Heart rate will be collected before nebulizer use, after nebulizer use, immediately after and approximately 15 minutes after the 6MWT.

Modified Borg Assessment

The modified Borg assessment will be performed three times (i.e., before and after nebulizer use and after 6MWT). The post-nebulizer Borg assessment should be performed at least 15 minutes after the completion of the nebulizer treatment.

6-Minute Walk Test

A 6MWT will be performed after nebulizer has been used and all post-nebulizer assessments (i.e., vital signs and modified Borg) have been completed.

Nebulizer Satisfaction Assessment

Participant satisfaction with the device used in the first treatment arm will be assessed.

Training Session

Participants randomized to InnoSpire Go in the second treatment arm will be trained on the use and cleaning of the device before being sent home. These participants will be asked to refrain from using their own jet nebulizer system during this 30-day period.

Visit 4 – Interim Visit:

Participants will be asked to return to the research center 15 days ± 3 days after Visit 3. Participants will complete procedures outlined in Visit 2.

Visit 5 –Final Visit:

Participants will return to the clinical facility 30 days (± 3 days) after Visit 3 completion. They will be instructed to bring the second assigned study device and their prescribed albuterol or combination albuterol/ipratropium medication for the demonstration. Participants will complete the procedures outlined in Visit 3. Participants will need to return all study equipment at this visit.

Participants will be discharged from the study following completion of study procedures.

Consent for Participation

Consent forms describing in detail the study intervention, study procedures and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. An Independent Review Board will review consent forms. After approval, the participants will be asked to read, review and sign the document. The investigator or Investigator's representative will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and/or friends or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any study procedures being done. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date). The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Selection and Withdrawal of Subjects:

Inclusion Criteria

1. Patients ≥ 40 years of age.
2. Diagnosis of COPD.
3. Currently using only a mouthpiece with their nebulizer system.
4. FEV_1 ≥ 30% predicted (pre- or post-bronchodilator).
5. mMRC grade ≥ 1.
6. Use of a jet nebulizer for the administration of albuterol or combination albuterol/ipratropium for the past 6 months.
7. Willing to use the same compressor/nebulizer system throughout the study.
8. Willing to refrain from using the jet nebulizer system when using the InnoSpire Go.
9. Prescribed nebulizer combination albuterol/ipratropium (single or multiple vials) with self-report of at least daily use or prescribed nebulizer albuterol with self-report of at least twice daily use.

10. Willing to permit audio and video recording during the visit.
11. Willing and able to follow instructions and complete all activities required by the trial, including phone calls.
12. Able to read and understand English.

Exclusion Criteria

1. Unable to complete 6MWT or, if patient is not currently prescribed oxygen, persistent oxygen desaturation ≤ 88% on the 6MWT.
2. Exacerbation of COPD requiring hospitalization (defined as hospital admission, urgent care visit, or emergency room visit) in the last 3 months.
3. Prescribed non-selective beta blockers.
4. Prescribed additional ipratropium bromide via nebulizer or inhaler or any other nebulized treatments via the subject's jet nebulizer.
5. Patients currently in assisted living or nursing home.
6. Diagnosis of asthma, parenchymal lung disease other than COPD, bronchiectasis, tuberculosis, cor pulmonale, clinically significant obstructive urinary disease, narrow-angle glaucoma, unstable angina, depression, anxiety, or other serious medical condition that, in the opinion of the investigator, would interfere with the patient's participation in the trial.
7. History of thoracotomy.
8. Myocardial infarction within the last 6 months.
9. Participation in any other therapeutic clinical trial in the previous 4 weeks.

Withdrawal

The term "discontinuation" refers to the participant's premature withdrawal from the study prior to completing all procedures. Participants may be discontinued from the study for any of the following reasons:

- If in the investigator's judgement, continuation in the study may prove harmful to the participant. Such a decision may be precipitated by AEs, including fever, nausea, rash, changes in vital signs, or the development of a new medical condition. The investigator will be solely responsible for making medical/safety decisions regarding the participant's continued participation in the study.
- Non-compliance with protocol requirements, including concomitant medication requirements
- At the request of the participant
- Exacerbation resulting in hospitalization

The study team will document whether or not each participant completed the study. If study treatment or assessments were discontinued for any participant, the reason will be recorded. Participants who are discontinued will not be replaced.

The goal is to have 20 participants successfully complete the study.

Discontinuation of Study Intervention

If a participant requests to stop using the device it does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol unless the participant does not wish to return and complete the follow-up visits. If a clinically significant side effect is identified (including, but not limited to negative changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational device, whether or not related to the investigational device will be reported as an AE. See Assessment of Safety section for additional definitions and AE management.

Treatment of Subjects

Intended Use

InnoSpire Go is intended to be used as a general purpose mesh nebulizer used to aerosolize commonly prescribed liquid inhalation drugs for respiratory disease in children and adults. It is to be used by, but not limited to, patients with asthma, COPD and cystic fibrosis.

Contraindications

InnoSpire Go is not be used by patients that are unconscious or not breathing spontaneously.

Monitoring

Remote monitoring will be conducted for this study. Data that is directly entered into EDC will not be verified. 100% of the remaining data will be verified among 10% of the study participants' records.

This study will be monitored in compliance with Code of Federal Regulations (CFR) for clinical research; namely, 21 CFR Parts 50, 54, 56 and 812 and others as applicable. The purpose of such monitoring is to ensure that the rights and wellbeing 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 (ICH) Good Clinical Practice (GCP), and with applicable regulatory requirement(s). Monitoring visits will be performed periodically and will be conduct by trained clinical research

professionals. The monitoring process includes initial subject qualifications, periodic contact with the subject, and a final review once the study is complete.

It has been determined that this study does not require a Data Safety Monitoring Board (DSMB).

Unscheduled Visits

Unscheduled calls and/or visits will be documented in the participant study file upon occurrence. Participants may be asked to receive additional phone calls in order to evaluate a technical or device issue and on an as needed basis.

Assessment of Performance

Device performance will be assessed based on the endpoints described in the Study Objectives and Purpose section.

Assessment of Safety

Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unanticipated Serious Adverse Device Effect

A USADE is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Severity of Event

The following guidelines will be used to describe AE 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".

Relationship to Study Intervention

All AEs 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 judgement. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Adverse Event Assessment and Follow-Up

Adverse events will be collected on an ongoing basis following signing of informed consent. Detailed information regarding the event will be recorded on the appropriate form in the electronic case report form (eCRF), where the Investigator will determine the severity of the event, 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. Follow-up data to ascertain the existence of residual effects from the event will be obtained. Serious adverse events must be reported to the sponsor within 24 hours of discovering the occurrence of the SAE. The research staff is required to complete and submit the sponsor's standard SAE form detailing the event. Reports should be directed to:

Ketah Doty, RN, BSN, OCN
Senior Clinical Research Associate
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-7921
Mobile: 412-738-6281

Email: ketah.doty@philips.com

Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

The study investigator will complete an SAE/Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to local regulatory authorities and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect to local regulatory authorities.

Device Deficiencies

All device deficiencies, use or user errors, and equipment failures will be documented. Use or User errors will be captured as part of the source documentation. Device deficiencies and equipment failures will be kept on a separate log. The serial numbers and type of deficiency/failure will be captured. Unanticipated device deficiencies that lead to SAE's will be reviewed with the principal investigator (PI) and reported to the IRB as required.

Statistical Methods

Determination of Sample Size

The study plans to randomize up to 25 participants with a goal of having 20 participants complete the study. The sample size is based on project timelines and budgetary constraints.

General Considerations

The primary analysis will be include all randomized participants. Descriptive data tables will be provided for all variables of interest. Continuous data will be presented by mean, standard deviation, median, minimum, and maximum observation. Data will be presented in the untransformed and transformed format (if applicable) for each continuous variable. Categorical data will be presented as frequencies and percentages. All formal statistical analyses will be performed using either SAS® or SPSS® software. Significance tests will be conducted at a two-sided significance level of $p < 0.05$.

There are no statistical criteria for terminating the study. No sensitivity analysis will be completed, and any deviations to the original statistical plan will be noted in the analysis report.

Participant Disposition

Participant disposition, including the total number of participants enrolled, completed, early terminations and withdrawals, will be presented. A listing will be provided with the reasons for discontinuation.

Primary Analysis

Continuous ratings that are collected at only one interval per device will be examined using either a paired t-test or the non-parametric Wilcoxon Singed-Ranks test, depending on the distribution of the paired differences. Mixed Models with repeated measures may be used for endpoints collected at multiple intervals per device.

Categorical ratings that are provided for each device will be analyzed using the McNemar test; if there are more than two levels for these ratings, they will need to be grouped into two levels for this analysis.

Categorical preference endpoints that are answered at the final visit (e.g., “Which device do you prefer?”) will be analyzed with a One-sample Binomial Test that compares the observed proportion to a 50/50 split.

Treatment Compliance and Missing Data

Any discontinued participants or protocol deviations will be tracked and reported in data listings. If a participant discontinues a device after the 15-day assessment, their ratings will be carried forward to the 30-day interval for the intent-to-treat analysis. This imputation will only be necessary for participants that complete at least the 15-day assessment for both devices. If a participant discontinues before providing ratings for both devices, they will be excluded from the analysis.

Safety Analysis

Safety evaluations will be performed by recording clinical adverse events at the time originally reported, and they will be followed at regular intervals until resolution, or until the study is completed, whichever comes first. Adverse events will be provided in data listings.

Interim Analysis

Preliminary results will be assessed after 10 participants complete the study, but the sample size will not be adjusted based on these interim outcomes.

Direct Access to Source Data/Documents

Only site clinical study staff and approved Philips staff working with the research will know the identity of the participants. All information recorded by the study team and provided for analysis will be given a study ID number. A unique source record will be created for each study participant.

Privacy rules and requirements according to federal and state governing regulations will be implemented. Except when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records. For records disclosed outside the Institution conducting this study, participants will be assigned a unique code number. The key to the code will be kept by the investigators. Data will be managed by study number and analyzed anonymously. The study record will include documentation of the informed consent form review process, HIPAA completion according to site policies, and applicable medical history. The Sponsor will have access to these source records.

In addition, participants' records including sensitive information and/or identifying information, may be inspected by the IRB, government agencies, and/or competent authorities, in the course of carrying out their duties.

All data will be kept confidential and in a secure location if on paper or on a secure server or device. Only approved study personnel will have access to study related documents. Approved study personnel are trained on privacy, HIPAA and data protection laws.

In addition, participant records may be reviewed in order to meet federal and state regulations. Reviewers may include representatives from the FDA or similar government authorities in other countries where the device is being used, and Philips Respironics for the purposes of the following side effects, and to gather additional information related to the study, and the IRB. Participant permission for review of confidential information is granted by signing the associated informed consent. Philips Respironics will ensure that it follows all applicable state and federal data protection regulations.

Data may be reviewed by any Philips research team, in any location, for purposes as outlined above, made available via a secure Philips site.

Case Report Forms

Study related eCRFs and source documentation will be collected and maintained by the sponsor, will be kept confidential, and stored in a secure location if on paper or on a secure server or protected device. Only staff delegated by the PI will have the ability to enter in, or make changes to, the eCRFs and source documents.

Quality Control and Quality Assurance

Each 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. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The clinical monitor(s) will verify that the clinical trial is conducted and data are generated, tests are completed and documented (recorded), and reported in compliance with the

protocol and ICH GCP. Monitoring will be completed in accordance with FDA US CFR and ICH-E6 GCP Section 6, as applicable.

The investigational site will provide direct access to all source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Ethics
This study will be submitted and reviewed by an IRB. All participants will be consented prior to completing the trial. The Primary Investigator will review all AEs as it relates to the study device.

All the information collected as part of this study will be kept confidential. All information collected for this study will be kept in a secured area or stored in a password protected computer, if digital. Results of the study-related tests, medical history and information obtained from the questionnaires will be reported to the study sponsor (Philips Respironics, Inc.). Philips Respironics may use participant study data for research or regulatory purposes. Investigators may use participant study data to prepare research publications or presentations at meetings. No personally identifiable information will be used in any reports, meeting presentations, or publications of this study.

Data Handling and Recordkeeping
Hard copies of the study will be kept on site for at least 2 years after study completion. The sponsor will maintain study records indefinitely. Records will be stored at Iron Mountain, a secure information management services company.

Financing and Insurance
If the participant is injured during the course of the trial and as a direct result of this trial, they should contact the Principal Investigator. The participant will be directed to seek clinically appropriate medical care for that injury. However, we cannot guarantee that the medical care and treatment will be provided without charge or that it will be paid for by the participants insurance company, and the costs incurred may ultimately be the participant's responsibility.

Registration on ClinicalTrials.gov or other applicable registry
This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Risk and Benefit Analysis
Potential Risks and Discomforts
Adverse effects of nebulizer use are usually minor and manageable. All AEs encountered, will be recorded on data sheets that are part of the eCRF.

The risks of using the InnoSpire Go device are minimal. Use of nebulizer devices themselves do not have any known side effects. Side effects are generally associated with the medication being nebulized. The medications used in this study will be albuterol sulfate and combination ipratropium bromide/albuterol sulfate, which is a commonly prescribed medication for COPD patients.

Reported side effects of albuterol sulfate or combination ipratropium bromide/albuterol sulfate include tremors, dizziness, nervousness, headache, insomnia, nasal congestion, tachycardia, hypertension, bronchospasm, cough, bronchitis, wheezing, chest or body pain, diarrhea, dyspepsia, nausea, muscle cramps, bronchitis, lung disease, pharyngitis, pneumonia, urinary tract infection, constipation and voice alterations.[20, 21]

The use of albuterol sulfate and ipratropium bromide singly or in combination has also been associated with precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, mydriasis, exacerbation of COPD symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, sinusitis, back pain, urticaria, angioedema, rash, oropharyngeal edema, arrhythmias (including atrial fibrillations, supraventricular tachycardia, extrasystoles) and metabolic acidosis.[20, 21]

There are minimal risks of using the device and should they occur during the course of the study, they will be recorded. Other more serious AEs are distinctly unusual in the outpatient setting but will be recorded if they occur. Serious adverse events and device-related AEs will be reported to the IRB per their policy. Patients may find InnoSpire Go to be less comfortable than their previous nebulizer, but this is not a real medical risk.

Thus, we believe that although there may be discomforts associated with the use of this device and study related procedures, the risks are minimal.

We believe that the risks and discomforts associated with this study are minimal.

The following measures will be taken to minimize risk to patients

- Physicians and staff will receive adequate training on the use of the device.
- Patients will be closely monitored throughout the trial.
- Reported AEs will be reviewed regularly throughout the study and appropriate medical measures will be taken to resolve the AEs.

Potential Benefits

Although participation in this trial will not result in any direct benefit to the subject, they will be contributing to generalizable data that will help improve device design and function.

Compensation for Research-Related Activities

Participants will only be compensated for the activities that they complete. Participants' compensation will be paid according to the following schedule.

Activity	Payment Amount

Visit 1	$100
Visit 2	$25
Visit 3	$50
Visit 4	$25
Visit 5	$50

Publication

It is the intent that these data will be used/considered for a submission to peer-reviewed publication, white paper or scientific abstract.

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Appendix 1: Chronic Respiratory Disease Questionnaire-Self Report
Document attached.

Appendix 2: Borg Assessment
Document attached.

Appendix 3: Chronic Respiratory Disease Questionnaire-Self Report (Follow-Up)
Document attached.

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Appendix 4: Nebulizer Satisfaction Assessment

No.	Questions (select one)	0	1	2	3	4	5	6	7	8	9	10
1	How confident are you in using the device?	Not at all confident										Very confident
2	How does this device affect your shortness of breath?	Much worse										Much better
3	Please tell us about any difficulties you experienced when using the device											
3-1	Device assembly and disassembly?	Very difficult										Very easy
3-2	Device cleaning and regular care	Very difficult										Very easy
3-3	Overall ease of handling or usability for a treatment	Very difficult										Very easy
3-4	Overall burden (filling, taking treatment and cleaning)	Very difficult										Very easy
4	How confident are you the device delivered all your medication?	Not at all confident										Very confident
5	Please rate your overall satisfaction with the device	Very dissatisfied										Very satisfied
6	Would you recommend the device to others (i.e., family, friends) that are prescribed a nebulizer?	Very unlikely										Very likely

No.	Questions (select one)	0	1	2	3	4	5	6	7	8	9	10
7	How well does the device fit your lifestyle needs?	Not well at all										Very well
	To be asked at Visit 5 only											
8	Which nebulizer do you prefer?	Jet/ Compressor	InnoSpire Go									