Clinical Study of the Vivatmo *pro*™ for Fractional Exhaled Nitric Oxide (FeNO) Monitoring in U.S. Asthmatic Patients Responding to Inhaled Corticosteroid (ICS) Treatment

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PROTOCOL REVISION HISTORY

Revision	Effective Date	Description of Revision
Version 1.0	11-May-2020	Initial Release
Version 2.0	25-September-2020	Revisions to modify inclusion and exclusion criteria to enhance enrollment of subjects with uncontrolled asthma.

PROTOCOL APPROVAL

	Name	Department / Affiliation	Signature	Date
Draft / Revision	Neil Mucci	GBC (CRO)		
Reviewer	Klaus Mueller	BHCS/PAT		
Approval	Carola Doeffinger	BHCS/QMM		

PROTOCOL SIGNATURE PAGE

Investigator's Signature

I have read and approve this protocol. My signature confirms my agreement that the study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the ICH Guideline for GCP, the CFR, and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____	_____
Name of Investigator	Date

LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ATS	American Thoracic Society
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical Laboratory Standards Institute
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
CV	Coefficient of Variation (relative standard deviation in %)
ERS	European Respiratory Society
FAS	Full Analysis Set
FeNO	Fractional Exhaled Nitric Oxide
FDA	Food and Drug Administration (U.S.)
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IFU	Instructions for Use
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
ISF	Investigational Site File
µL	Microliter
mL	Milliliter
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Case Excellence (UK)
NO	Nitric Oxide
OTC	Over-the-Counter
PI	Principal Investigator
POC	Point of Care
PPA	Positive Percent Agreement
SAE	Serious Adverse Event
SDV	Source Data Verification
SIV	Site Initiation Visit
TLC	Total Lung Capacity
TMF	Trial Master File
U.S.	United States
USB	Universal Serial Bus

STUDY SYNOPSIS

Name of Sponsor	Bosch Healthcare Solutions GmbH
Name of Device	Vivatmo *pro*™ (Bosch Healthcare Solutions GmbH)
Study Title	Clinical Study of the Vivatmo *pro*™ for Fractional Exhaled Nitric Oxide (FeNO) Monitoring of U.S. Asthmatic Patients Responding to Inhaled Corticosteroid (ICS) Treatment
Study Short Title	Vivatmo pro™ US Study
Study Type	Multi-center, open label, non-randomized, prospective, single cohort study
Number of Study Sites	6 clinical sites in the United States
Target Population	120 male and female asthma subjects from 7 to 80 years of age with uncontrolled asthma. Including: • ~40 subjects (~30%) from 7 to 17 years of age • ~80 subjects (~70%) from 18 to 80 years of age
Study Objectives	**Primary Objective:** To measure the impact of inhaled corticosteroid (ICS) treatment on fractional exhaled nitric oxide (FeNO) measured with the Vivatmo *pro*™ in adult and pediatric subjects with uncontrolled asthma as measured at visits before and after treatment. **Secondary Objectives:** • To compare changes according to the primary objective with those of spirometry (lung function), and asthma symptoms before and after treatment. • To evaluate the precision of repeat measurements made for each subject at a single visit. • To evaluate the success rate of the subject using the device.
Study General Design and Duration	This is a multi-center, competitive enrollment, dual-visit, point-of-care study to evaluate fractional exhaled nitric oxide (FeNO) measured with the Vivatmo *pro*™, spirometry, and asthma symptoms using an Asthma Control Questionnaire (ACQ) in adult and pediatric subjects. Subjects will be screened, enrolled and tested at Study Visit #1 and then prescribed inhaled corticosteroid (ICS) treatment as per routine clinical care. Subjects will return for Study Visit #2 in two weeks and repeat fractional exhaled nitric oxide

	(FeNO) measured with the Vivatmo *pro*™, spirometry, and complete an Asthma Control Questionnaire (ACQ). Results of the fist valid FeNO measurement made at each study visit (Visit #1 - pre-treatment and Visit #2 - post-treatment) will be analyzed in conjunction with recorded asthma symptoms and spirometry results. At least two FeNO measurements will be made at each visit allowing assessment of repeatability of the method under daily use conditions. Subject screening, recruitment, initial measurement, treatment, and follow up measurement are expected to take 3 months.
Study Endpoints	**Primary Endpoint:** The primary analysis variable will be the percent change of the fractional exhaled nitric oxide (FeNO) measurement made at Visit #1 compared to Visit #2 using the Vivatmo *pro*™. The first valid FeNO measurement made at each visit will be used for this comparison analysis. **Secondary Outcome Measures:** • The change in standard outcome measures (asthma symptoms and spirometry) between Visit #1 to Visit #2 • Repeatability as assessed by replicate FeNO measurements (N=2) at one or more visits. The first two valid FeNO measurements made for each subject at each visit will be used for this repeatability analysis. • Success rate (proportion of patients with successful measurement)
Subject Inclusion / Exclusion Criteria	See criteria starting on page 23.

Study Procedures	• Patients meeting study inclusion/exclusion criteria will be consented and will be enrolled in the study. • Subjects will be observed during each of two study visits according to routine clinical diagnosis and treatment standards for uncontrolled asthma patients and will have asthma symptoms recorded using a standardized Asthma Control Questionnaire (ACQ). • Subjects will have fractional exhaled nitric oxide (FeNO) and spirometry measured and documented at each visit. • All study subjects will be asked to perform two valid fractional exhaled nitric oxide (FeNO) measurements at each study visit using the Vivatmo *pro*™ with a limit of 10 total exhalation attempts per subject per visit. If only one valid measurement is taken, it will be used for comparative analysis. No repeatability data will be available for this subject. • One operator will guide each subject through the fractional exhaled nitric oxide (FeNO) measurements at each visit. • At the first visit, after all study assessments (FeNO, Spirometry, ACQ), subjects will receive therapy by prescription of inhaled corticosteroid (ICS) medication according to routine treatment standards. • Subjects will return after 2 weeks (14 days) of treatment for a repeat of measurements.
Statistical Analysis	**Analysis Population:** The Full Analysis Set (FAS) will be defined as all patients intended to receive a FeNO measurement. The Per Protocol Set will be defined as enrolled subjects without major protocol violations, with inhaled corticosteroid (ICS) treatment, and successfully completing at least one valid FeNO measurement at both Visit #1 and Visit #2 will be evaluated for the primary endpoint. **Definition of Measured Value:** For primary endpoint analysis the value of FeNO measurement will be derived as the result of the first valid measurement. For repeatability, the first and second valid FeNO measurements at each visit will be used. Repeatability will be the pooled result of pairwise analyses for repeatability to demonstrate precision (see below). **Descriptive Statistics:** Baseline characteristics, such as demographics, as well as analytical clinical data by visit will be summarized using descriptive statistical methods. Continuous data will be summarized using the mean, the median, standard

	deviation, and range (minimum and maximum value). Categorical values will be summarized using frequency counts and percentages. **Analysis of Primary Endpoint:** The change of FeNO values will be estimated in ANOVA with baseline values as the covariable and will be reported as percent change together with the 95%-confidence interval. In a sensitivity analysis, the first valid single measurement is used for the analysis. **Analysis of Secondary Endpoints:** The relationship between changes in FeNO-values and clinical assessments (spirometry, ACQ-questionnaire) will be assessed by Spearman's rank correlation. **Repeatability:** Repeatability will be estimated together with the 95%-confidence interval as pooled standard deviation (mean < 50 ppb) and CV (mean ≥ 50 ppb), respectively, using the residual variance component resulting from a random effects ANOVA (as used in CLSI EP05 guideline) with patient and visit as random factors. The resulting pooled repeatabilities are hereby estimated taking into account conditions of variability over sites and operators. **Success rates:** The success rates (proportion of patients with successful measurement within FAS) will be reported. The number of attempts necessary to obtain 2 valid replicate measurements will be tabulated in contingency tables by visit. **Sample Size:** Since the effect size of the change (mean change / standard deviation) is on the order of 1 (resulting in N=10 and 13 for power = 80% and 90%, respectively) and therefore large, the sample size is not determined by the primary objective but by the necessity to achieve representative data of FeNO measurement data over all age groups, measurement ranges (<, ≥ cut off) and sites. Thus, 120 subjects will be recruited.

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1. BACKGROUND AND INVESTIGATIONAL DEVICE

1.1. Background

According to the Centers for Disease Control (CDC) asthma has increased 28% in the last decade in the Unites States with the number of asthmatic individuals totaling 25 million adults (7.9% of the adult US population) and 6.1 million children (8.4% of US children). The National Institutes of Health (NIH) guidelines for the diagnosis and management of asthma strongly recommend long term anti-inflammatory therapy, such as oral or inhaled corticosteroids to reverse airway inflammation in an effort to prevent irreversible airway damage. The difficulty in diagnosing and managing asthma however lies primarily in the lack of available clinical technologies capable of assessing airway inflammation, an early and persistent component of asthma.

The medical community has expressed the need for objective and noninvasive measures of airway inflammation for diagnosing asthma and monitoring the effectiveness of and compliance with anti-inflammatory therapies. Because airway inflammation is a key pathophysiologic abnormality in asthma, there has been an emphasis on incorporating inflammatory biomarkers into the diagnosis and management of asthma.

Fractional exhaled nitric oxide (FeNO) as a noninvasive surrogate biomarker for airway inflammation can play a significant role in supporting asthma treatment and management decisions. Numerous studies have shown that fractional exhaled nitric oxide (FeNO) is well correlated with other markers of airway inflammation such as bronchial hyperresponsiveness, sputum eosinophils, bronchoalveolar lavage fluid eosinophilia, bronchial biopsy eosinophil score, and blood eosinophilia. Fractional exhaled nitric oxide (FeNO) levels have been shown to rise prior to asthma exacerbation and decrease with the use of anti-inflammatory medications in a dose dependent manner. Monitoring of fractional exhaled nitric oxide (FeNO) can help clinicians and patients with:

- Better self management [1]
- Better safety [1]
- Control of adherence [1]
- Improved asthma control [2]
- Optimized steroid dosage [3]
- Reduction of exacerbations [4]
- Reduction of hospitalization [5][6]
- Reduction of costs [5]

A new portable device using electrochemical sensors to measure fractional exhaled nitric oxide FeNO (Bosch Healthcare Solutions GmbH, Vivatmo *pro*™) has recently been developed. The aim of this study is to evaluate the performance of this new hand-held device.

1.2. Description of the Device

The nitric oxide test system called the Vivatmo *pro*™ (Bosch Healthcare Solutions GmbH, Waiblingen Germany) is a point-of-care (POC) breath gas analyzer that uses solid-state electrochemical technology to measure fractional exhaled nitric oxide (FeNO), a biomarker for airway inflammation, in human exhaled breath. Measurement of FeNO is a quantitative and

non-invasive method to evaluate an asthma patient's response to anti-inflammatory therapy, as well as an adjunct to establishing a clinical assessment of asthma. The Vivatmo *pro*™ measures expired nitric oxide (NO) in the range of 5 ppb to 300 ppb from a 10 second exhalation. The Vivatmo *pro*™ is suitable for children 7 to 17 years of age and adults 18 to 80 years of age.

Vivatmo *pro*™ is comprised of two components: a handheld wireless measurement unit with disposable mouthpiece (held and used by the patient) and a base station with touch screen interface and AC adapter. The handheld mouthpiece is a single-patient use, disposable component used up to 5 times in a single testing session before being disposed of and replaced. The device keeps track of the number of uses for each mouthpiece. The mouthpiece has an ergonomically designed interface for the patient to aid in creating a proper seal during the exhalation maneuver. Vivatmo *pro*™ uses solid state, sensor technology sensitive to NO compounds in parts per billion (ppb) in the handheld component with a pneumotachograph display in the base station. The solid state sensor in the handheld component is preceded by filters in the disposable mouthpiece that: (a) eliminate germs and protect against cross-contamination; (b) eliminate potential interfering molecules such as carbon monoxide (CO), ammonia (NH4), and methanol (CH_4O) by making them inactive; (c) convert breath NO to the NO_2 equivalent for measurement; and finally (d) dehumidify the breath sample. Vivatmo *pro*™ provides visual and audible feedback during the FeNO measurement process such that the user can modulate their breath speed within the optimal flow parameters as recommended by American Thoracic Society (ATS) and European Respiratory Society (ERS) standards.

To use the system the patient empties their lungs, inhales deeply to total lung capacity, and then slowly and evenly exhales through the Vivatmo *pro*™ mouthpiece of the handheld component for 10 seconds. Vivatmo *pro*™ tests the last three second fraction of a 10 second exhalation in order to report the average NO concentration in parts per billion (ppb). Results are processed and stored on the system using dedicated software. In order to verify the device's performance there are control procedures performed on a routine basis. Vivatmo *pro*™ also has an optional PC application for access and management of electronic testing records.

1.3. Intended Use

Vivatmo *pro*™ Nitric Oxide Test is a portable, non-invasive device to measure fractional exhaled nitric oxide (FeNO) in human breath. FeNO is increased in some airway inflammatory processes, such as asthma, and often decreases in response to anti-inflammatory treatment. Measurement of FeNO by Vivatmo *pro*™ is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FeNO levels. FeNO measurements are to be used as an adjunct to established clinical assessments. Vivatmo *pro*™ is suitable for children, approximately 7-17 years, and adults 18 years and older. Testing using the Vivatmo *pro*™ should only be done in a point-of-care healthcare setting under professional supervision. Vivatmo *pro*™ should not be used in critical care, emergency care or in anesthesiology.

1.4. Special Conditions for Use Statement

- Vivatmo *pro*™ should only be used as directed in the Vivatmo *pro*™ Instructions for Use (IFU).
- Vivatmo *pro*™ should not be used in critical care, emergency care, or in anesthesiology.
- Vivatmo *pro*™ results should not be used as a sole parameter for the diagnosis or screening of airway diseases.
- Vivatmo *pro*™ measurement procedure requires patient cooperation and patients must be capable of a complete breathing maneuver (exhalation) and cooperating with all necessary requirements for test performance.
- Vivatmo *pro*™ should not be used with infants or by children under 7 years of age.
- Patients should refrain from eating and drinking for 1 hour before exhaled NO measurement.
- Recent intake of nitrate rich foods, such as lettuce, spinach, beets, walnuts, peanuts, and animal organs, can lead to increased FeNO levels.
- Alcohol ingestion reduces FeNO levels in patients with asthma and healthy subjects.
- Patients should not smoke for 1 hour before measurement, and any short-term and long-term active and passive smoking history should be recorded. Smoking reduces FeNO levels.
- Vivatmo *pro*™ results obtained from patients who smoke should only be considered after accounting for the subject's smoking history and the potential impact on FeNO levels.
- When possible, perform serial FeNO measurements at the same time of the day.
- Regardless of displayed results clinicians must follow standard clinical care practices for symptoms of chest tightness, shortness of breath, and coughing or wheezing for decisions relative to treatment,
- For prescription use only.

1.5. Investigator Requirements

The study Principal Investigator (PI) and study staff must read this entire protocol and the Vivatmo *pro*™ Instructions for Use before beginning the clinical study. Site training on the study protocol, study subject management, instrument usage, and study data collection will be provided by the Sponsor and/or designated Contract Research Organization (CRO) at study outset.

2. STUDY OBJECTIVES

The objective of the study is to evaluate fractional exhaled nitric oxide (FeNO) measured with Vivatmo *pro*™, spirometry (lung function), and asthma symptoms in adult and pediatric subjects with uncontrolled asthma before and after inhaled corticosteroid (ICS) treatment.

2.1. Primary Objective

To measure the impact of inhaled corticosteroid (ICS) treatment on fractional exhaled nitric oxide (FeNO) measured with the Vivatmo *pro*™ in adult and pediatric subjects with uncontrolled asthma as measured at visits before and after treatment.

2.2. Secondary Objectives

- To compare changes according to the primary objective with those of spirometry (lung function), and asthma symptoms before and after treatment.
- To evaluate the precision within a series of repeat measurements made for each subject at a single visit.
- To evaluate the success rate of the subject using the device.

3. STUDY DESIGN

3.1. General Design

This is a multi-center, competitive enrollment, dual-visit, non-invasive, point-of-care study designed for "treatment monitoring and efficacy" to evaluate fractional exhaled nitric oxide (FeNO) measured with Vivatmo *pro*™, spirometry, and asthma symptoms as assessed by a standardized Asthma Control Questionnaire (ACQ) in adult and pediatric subjects with uncontrolled asthma.

Subjects will be screened, enrolled and tested at Study Visit #1, undergo fractional exhaled nitric oxide (FeNO) measurement with Vivatmo *pro*™, spirometry, and assessment of asthma symptoms using an Asthma Control Questionnaire (ACQ), and will then be prescribed an inhaled corticosteroid (ICS) treatment as per the standard of clinical care. Study subjects will return for Study Visit #2 two weeks (14 days) after their initial visit for repeat fractional exhaled nitric oxide (FeNO) measurement with Vivatmo *pro*™, spirometry, and assessment of asthma symptoms using an Asthma Control Questionnaire (ACQ).

3.2. Study Endpoints

Primary Endpoint

The primary analysis variable will be the percent change of the fractional exhaled nitric oxide (FeNO) measurement made at Visit #1 compared to Visit #2 using the Vivatmo *pro*™. The first valid FeNO measurement made at each visit will be used for this comparison analysis.

Secondary Outcome Measures:

- The change in standard outcome measures (asthma symptoms and spirometry) between Visit #1 to Visit #2
- Repeatability as assessed by replicate FeNO measurements (N=2) at one or more visits. The first two valid FeNO measurements made for each subject at each visit will be used for this repeatability analysis.
- Success rate (proportion of patients with successful measurement)

3.3. Number of Subjects

The study is designed to enroll patients that have clinically diagnosed signs and symptoms of uncontrolled asthma and who are candidates for inhaled corticosteroid (ICS) treatment. The study will enroll 120 male and female asthma subjects from 7 to 80 years of age. This will include a target of 40 pediatric subjects (approximately 30% of enrollment) from 7 to 17 years of age and a target of 80 adult subjects (approximately 70% of enrollment) from 18 to 80 years of age. This is estimated to be a sample size sufficient to demonstrate device performance in the intended use population of pediatric and adult patients.. The Sponsor may extend the overall enrollment goal and/or suspend enrollment of adult subjects in order to reach a minimum required number of enrolled pediatric subjects.

It is the goal of the study to include moderate to severe asthma patients to the maximum extent possible and as per the professional discretion of participating physician investigators. Enrollment should optimally include newly diagnosed asthma patients, but may also include those patients with a previous history or diagnosis of uncontrolled asthma who have not been using corticosteroids for at least 4 weeks prior to study Visit #1. Patients currently using a short-acting inhaled bronchodilator medication (also known as a "rescue inhaler") or leukotriene modifiers may be enrolled, but should not participate if they have used these medications within one hour of either study Visit #1 or study Visit #2 Vivatmo *pro*™ readings. Patients using inhaled corticosteroids, oral corticosteroids, or who are taking biologic immunotherapy medications should not be enrolled.

Measured FeNO levels from the subject population are expected to encompass the full Vivatmo *pro*™ measurement range from 5 ppb to 300 ppb. If a maximum range measurement goal of 270 ppb is not met by enrollment of 120 subjects then additional subjects may be enrolled until the maximum range measurement goal is met.

3.4. Number of Study Sites

The study will be conducted at 6 clinical sites in the United States. This will include specialized asthma clinics and practices optimally able to enroll both pediatric and adult subjects.

3.5. Duration of Study Subject Participation

Study subject participation will take approximately 50 minutes for visit #1 and 30 minutes for visit #2. At the first study visit subjects will be screened, consented, enrolled, assigned a Study Subject ID number (~10 minutes). Subjects will then be instructed on use of the Vivatmo *pro*™ (~10 minutes) and then undergo Vivatmo *pro*™ measurement (~10 mins), spirometry (~10 mins), and ACQ assessment and Case Report Form (CRF) questions (~10 mins). Vivatmo *pro*™ measurement, spirometry, ACQ assessment, and CRF questions will be repeated at the second study visit. At each study visit subjects will be asked to attempt up to 10 exhalation breaths to achieve 2 valid Vivatmo *pro*™ measurements (excluding exhalations for spirometry). Study timing does not include patient counseling for ICS prescription and recommended usage.

3.6. Overall Study Duration

Subject screening, recruitment, initial measurements, treatment, follow up measurements, and data collection are expected to take 3 months.

4. STUDY POPULATION

4.1. Asthma Patients who are Candidates for Study Enrollment and Inhaled Corticosteroid (ICS) Treatment

Potential study subjects may be recruited from those already scheduled for clinic visits. Subjects qualified for study participation should (1) have a confirmatory diagnosis of uncontrolled asthma made by a physician and (2) have not used inhaled corticosteroids or oral corticosteroids within 4 weeks prior to enrollment. Use of a short-acting inhaled bronchodilator, leukotriene modifier, or any rescue inhaler will be permitted before the study, but not within one hour of either Vivatmo *pro*™ study reading. Subjects may be prescribed or use a rescue inhaler if necessary during the study and between study Visit #1 and study Visit #2.

Eligible study subjects should be diagnosed with uncontrolled asthma and some degree of presumed lung inflammation. According to guidelines a diagnosis of uncontrolled asthma is established by determining that:

- Symptoms of recurrent airway obstruction are present, based on patient history and examination.
- Patient has symptoms of cough, recurrent wheezing, recurrent difficulty breathing, or recurrent chest tightness are present.
- Symptoms occur or worsen at night or with exercise, viral infection, exposure to allergens and irritants, changes in weather, hard laughing or crying, stress, or other factors.

Long term asthma management is assessed and monitored by:

- Assessing at each visit asthma control, proper medication usage, written asthma action plan, patient adherence, and patient concerns.
- Obtaining lung function measurements by spirometry at least every 1–2 years; more frequently for asthma that is not well controlled.
- Determining if therapy should be adjusted, maintained, stepped-up if needed, stepped-down, if possible.

To these general diagnostic procedures Vivatmo *pro*™ FeNO measurement will be added after taking full account of the uncontrolled asthma diagnosis and guidelines described above. Vivatmo *pro*™ FeNO results will not be used for diagnostic decisions or to confirm the presence of asthma.

Since asthma has varying severity that may impact Vivatmo *pro*™ results, sites should enroll subjects meeting study criteria in a sequential manner that does not introduce bias into the study design or results. Sites should avoid enrollment of subjects diagnosed with asthma who will not be prescribed inhaled corticosteroid (ICS) treatment, who are not able to fill their ICS prescription, or who may not comply with recommended ICS usage.

4.2. Subject Inclusion Criteria

Patients meeting the following criteria may be included:

1. Subject is 7 to 80 years of age.*

2. Subject is newly diagnosed or has a confirmed past diagnosis of uncontrolled asthma determined by a physician and as defined below:
   (a) Symptoms of cough, recurrent wheezing, recurrent difficulty breathing, or recurrent chest tightness are present.
   (b) Symptoms occur or worsen at night or with exercise, exposure to allergens and irritants, changes in weather, hard laughing or crying, stress, or other factors.

3. Has been identified as a candidate for inhaled corticosteroid (ICS) treatment and is willing and able to comply with the recommended ICS treatment plan.

4. Is willing and able to perform Vivatmo pro™ testing at initial and follow-up study visits.

5. Subject or legal guardian is willing and able to provide informed consent.

4.3. Subject Exclusion Criteria

Patients meeting the following criteria should be excluded:

1. Subject has used inhaled corticosteroids or oral corticosteroids within 4 weeks prior to enrollment; or subject has taken biologic immunotherapy medications.**

2. Subject has other current serious medical conditions (other than asthma) that may impair study participation and measurements unless deemed acceptable by the study site investigator including, but not limited to:
   (a) respiratory diseases,
   (b) cardiovascular diseases,
   (c) neuromuscular diseases, or
   (d) chest wall or spinal column deformities.

3. Subject is suffering from acute upper or lower respiratory infection including:
   (a) common cold,

(b) influenza, or
(c) pneumonia.

4. Subject is pregnant.

5. Subject is currently participating in another interventional pharmaceutical study or undergoing another asthma therapy.

6. Subject has engaged in any of the following within one hour prior to fractional exhaled nitric oxide (FeNO) measurement:
   (a) food and beverage (other than water) intake,
   (b) caffeine (coffee, tea, etc.) intake,
   (c) nicotine (including cigarettes, cigars, pipe, nicotine chewing gum, nicotine patch, snuff, vapor e-cigarettes, etc.) intake,
   (d) strenuous exercise, or
   (e) use of a short-acting inhaled bronchodilator, leukotriene modifier, or any rescue inhaler.

7. Subject has a history of prior or excessive alcohol use*** or drug abuse within last 12 months.

8. Subject has a familial or close relationship with study personnel (device instructors of administrators).

9. Subject is unwilling or unable to perform Vivatmo pro™ and spirometry testing (pulmonary function test) at initial and follow-up study visits and to comply with treatment plan.

10. Subject or legal guardian is unwilling or unable to provide informed consent.

Inclusion/Exclusion Notes:

(*) Including 30% pediatric cases (age 7 to 17) and 70% adult cases (age 18 to 80)

(**) Subjects undergoing a corticosteroid "wash-out" are not allowed.
Subjects on leukotriene modifiers (such as Singulair) prior to or during the study are allowed.
Antihistamine usage prior to and during the study is allowed.

(***) Excessive alcohol use defined as more than 2 alcoholic drinks per day (14 per week) for adult males and more than 1 alcoholic drink per day (7 per week) for adult females.

5. STUDY INSTRUMENTS AND SUPPLIES

5.1. Investigational Product Receipt, Accountability, and Storage

The investigational product in this study is the Vivatmo *pro*™ instrument. To ensure that the investigational product will not be used for any purpose other than what is stated in this protocol, the Principal Investigator (PI), or responsible party designated by the PI, will maintain an inventory record of all investigational products and consumables received, used, returned, or discarded. At the start of the study, material accountability (inventory) forms will be provided by Sponsor with detailed instructions. Material delivery dates, quantities used, and lot/batch/serial numbers will be tracked throughout the study.

5.2. Vivatmo *pro*™ Instrument Components, Consumables, and Supplies Provided by Sponsor

The following Vivatmo *pro*™ instrument components and consumables will be provided by the Sponsor to each participating clinical site:

- Vivatmo *pro*™ base station with AC power adapter
- Vivatmo *pro*™ handheld unit
- Vivatmo *pro*™ Oxycap Mouthpiece ("blue" on outside) for standard study measurements
- Vivatmo *pro*™ Level 0 Mouthpiece ("opaque/white" outside and "blue" inside) for instrument quality control measurements.
- Vivatmo *pro*™ owner´s manual
- Vivatmo *pro*™ software (for attached PC computer)
- USB printer (black and white)

5.3. Materials and Space Supplied by Clinical Site

Each participating clinical site will agree to provide the following:

- Designated space for Vivatmo *pro*™ set-up and conducting study subject testing
- Designated space for storage of Vivatmo *pro*™ consumables
- Spirometry test equipment (ATS/ERS compliant)
- PC computer (connected to internet and the Vivatmo *pro*™ for delivery of electronic measurement results and study data)
- Inhaled corticosteroid (ICS) prescription (covered under standard of clinical care and not reimbursed as part of the study)
- Secure storage for study records and study related documents

5.4. Vivatmo *pro*™ General Overview

Vivatmo *pro*™ device will be delivered to each participating clinic, set up, and calibrated by the Sponsor, or designated CRO, prior to or at the time of the study site initiation visit (SIV). Vivatmo *pro*™ instrument should be used at temperatures of 59°F to 81°F (15°C to 27°C) and 15% to 60% relative air humidity. Vivatmo *pro*™ device should be stored in conditions not to fall below or exceed 41°F to 104°F (5°C to 40°C) and 10% to 85% relative air humidity. Surfaces of the

Vivatmo *pro*™ base station and handheld unit should be wiped down regularly with 30% ethanol or disinfecting wipes containing up to 30 % alcohol. Protect all openings from ingress of moisture or liquid. Do not spray anything directly onto the device.

5.5. Vivatmo *pro*™ Base Station

The device base station will be set up for secure access by two or more administrators designated at each study site. The device hardware, firmware, and software version will be recorded at the time of set-up. The device will be connected to a USB printer and will also be connected to a PC computer with internet access (via USB cable, ethernet cable, or wifi) running the dedicated Vivatmo *pro*™ software application and which will be used for delivery of electronic study records. The USB printer may alternately be connected to the PC computer. The Vivatmo *pro*™ software will not be connected to any patient electronic medical record system for the study.

The Vivatmo *pro*™ base station has a 7 inch color touchscreen with 1024 x 600 pixels, weighs 3 lbs (1,350 g) and is 6.3 in x 8.4 in x 10.4 in (16.0 cm x 21.3 cm x 26.5 cm). It has the ability to store up to 15,000 patient measurements, print measurement results using a USB printer, and export electronic measurement data files (see study data management section below).

5.6. Vivatmo *pro*™ Handheld

Vivatmo *pro*™ cordless handheld component contains a lithium-ion battery that is recharged by placement on the base station. It is capable for 5,000 measurement attempts and synchronizes data to the base station. The cordless handheld stores 1,000 measurements. It performs measurements over an exhalation time of 10 seconds with FeNO measurements in the range 5 ppb to 300 ppb. The Vivatmo *pro*™ handheld has a startup time of 60 sec, a time-to-result of 5 sec, and a regeneration-time of 90 sec.

5.7. Vivatmo *pro*™ Mouthpiece

The study will use the disposable Vivatmo *pro*™ Oxycap Mouthpiece ("blue" on outside) for standard study measurements. The study will use the disposable Vivatmo *pro*™ Level 0 Mouthpiece ("opaque/white" outside and "blue" inside) for instrument quality control (QC) measurements.

The design of the mouthpiece allows the subject to close their lips around it in a relaxed and natural way resembling the mouthpiece of a flute. This supports velum closure and accurate device measurement. When using Vivatmo *pro*™ mouthpieces instrument operators should ensure the following:

- Check that disposable Vivatmo *pro*™ mouthpieces have not expired (expiration dates are printed on the packaging).
- Vivatmo *pro*™ mouthpieces should be unpackaged immediately prior to use and used within 15 minutes of opening.

- Each Vivatmo *pro*™ mouthpiece may be used for one patient performing a maximum of 5 exhalations. Replace the mouthpiece after every 5 exhalation attempts.
- Ensure that the Vivatmo *pro*™ mouthpiece fits on the handheld unit properly to avoid leakage of air around the edge of the disposable fitting, which may lead to a lower measurement result.
- Do not attempt to clean the disposable mouthpiece.
- Dispose of used mouthpieces in the waste for contaminated patient material.

5.8. Guidance for Vivatmo *pro*™ Calibration and Routine Quality Control (QC) Testing

Each Vivatmo *pro*™ device will be pre-calibrated prior to initial use for the study and no additional calibration will be needed during the study.

Quality Control (QC) testing should be performed by the designated device administrator (QC tester) on a routine basis and is recommended to be performed weekly or after every 50 measurements. The identity of the individual designated and performing QC testing is recorded within the device software and they must meet the following criteria:

- Be over 18 years of age;
- Be a non-smoker
- Have no ongoing cold or known airway disease
- Be expected to have stable FeNO values between 10 ppb and 40 ppb
- Preferably have no allergies or asthma

Quality Control (QC) testing is performed by:

- Making 4 measurements in 7 days using the Vivatmo *pro*™, with 1 measurement per day
- Confirming that the QC mean value from measurements on the first 3 days is between 5 ppb to 50 ppb, and
- Confirming that the QC measurement on the 4th day is within ±10 ppb from mean value

If the QC tester does not perform a QC test in 30 days, the qualification is suspended and the QC tester needs to re-qualify within the instrument software.

5.9. Vivatmo *pro*™ Instrument Support

Each site will be provided with a Vivatmo *pro*™ device and the necessary consumables to conduct the planned number of measurements. In the event that an instrument requires troubleshooting, the designated local study coordinator may contact the Study Manager, who will coordinate technical assessment and provide either verbal or written instructions.

6. STUDY PROCEDURES

6.1. Clinical Site Study Staff Training

At the initiation of the study the Sponsor, and/or designee, will visit each study site. The Sponsor will ensure that study staff are informed and understand the study requirements.

The Principal Investigator (PI) and designated study staff at each participating site will attend a training session conducted at a site initiation visit (SIV) or other appropriate training session. Training will include, but will not be limited to, procedures to select, prepare, and manage patients for the study; review of the study protocol, visit plan, and testing plan; review of device training and operation; and completion of the study Case Report Forms (CRFs).

Designated study staff should familiarize themselves with the Vivatmo *pro*™ user manual. All trained study personnel will sign a training log. No study staff will perform any study-related procedures prior to being trained and signing a training log.

6.2. Study Visit #1 Overview

Study Visit #1 will include patient screening, consent, enrollment, assignment of a Study Subject ID number, subject training on use of the Vivatmo *pro*™, Vivatmo *pro*™ measurement, spirometry, ACQ assessment, and Case Report Form (CRF) completion.

6.3. Study Visit #2 Overview

Study Visit #2 will be conducted at 14 days from study Visit #1 (14 to 21 days is the acceptable range). Study Visit #2 will include a subject training refresher (if necessary) on use of the Vivatmo *pro*™, Vivatmo *pro*™ measurement, spirometry, ACQ assessment, and Case Report Form (CRF) completion.

Study patients should be instructed to withhold (not take) their prescribed ICS (except rescue inhalers) the day that they come in for Study Visit #2.

6.4. Patient Screening and Consent

Subjects will optimally be selected from those already scheduled for clinic visits. Prior to study participation and the collection of any study data the PI, and designated study coordinator, will obtain informed consent from each subject who meets inclusion/exclusion criteria. The date of informed consent and confirmation of compliance with study inclusion/exclusion criteria will be recorded on the designated study CRF. Upon completion of consent subjects will be enrolled into the study and this will optimally occur after confirmation of a clinical diagnosis of asthma and prior to prescription of inhaled corticosteroid (ICS) treatment. Diagnosis of asthma may require spirometry measurement.

6.5. Guidance for Preparing and Training Study Subjects on Use of the Vivatmo *pro*™

Study Coordinators, designated testers, and study subjects should wash their hands prior to using the Vivatmo *pro*™ device for testing. The study coordinator should explain the test to the subject and demonstrate appropriate techniques. It is recommended that study coordinators train subjects (especially children) on proper grasping technique and exhalation technique prior to performing the first Vivatmo *pro*™ measurement. Training may involve practice with holding and positioning the handheld component and practicing a controlled exhalation using a "Flow Be" floating ball toy (where constant exhalation flow/rate causes a toy ball to be suspended in air), using a musical instrument, or other equivalent simulation. The test assumes a full inhalation before beginning.

The subject may need to be prompted or encouraged to ''blow" the air from their lungs. Enthusiastic coaching of the subject using appropriate body language and phrases, such as ''keep going'', may be required. Encouragement, detailed but simple instructions, lack of intimidation, and visual feedback from the instrument are important in helping children to perform the test.

It is helpful to observe the subject to check for distress and to observe the Vivatmo *pro*™ base station display during the test to help ensure correct effort. If the patient feels ''dizzy'' testing should be stopped. Well-fitting false teeth should not be routinely removed, since they preserve oropharyngeal geometry and results may generally be better with them in place. Correct patient performance (exhalation flow rate) is required for the measurement to be considered valid.

6.6. Guidance for Vivatmo *pro*™ Testing Procedure

Fractional exhaled nitric oxide (FeNO) measurements should be performed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) Guidelines. Study subjects should be tested while in the seated position, preferably using a chair with arms and without wheels, and without using a nose clip. Subjects should maintain good posture with head slightly elevated. Vivatmo *pro*™ measurements should be made prior to spirometry measurements. When possible perform serial Vivatmo *pro*™ measurements at the same time of the day.

Subjects should inhale to total lung capacity and then exhale into the mouthpiece of the Vivatmo *pro*™ handheld unit at a constant pressure and stable flow rate for 10 seconds guided by visual cues and auditory cues on the display of the Vivatmo *pro*™ base station. Results are processed using dedicated software and in approximately 5 seconds, the NO concentration is displayed on the device in parts per billion (ppb).

The exhalation may be repeated after a brief rest period until 2 acceptable measurements are obtained. A total of up to 10 exhalations may be performed in order to achieve 2 acceptable measurements. The Vivatmo *pro*™ mouthpiece should be changed after every 5 exhalation attempts and recorded appropriately on Study Case Report Form (CRF).

The Vivatmo *pro*™ measurements, spirometry measurements, and asthma control questionnaire information collection may be performed in any sequence at a given patient visit so long as they are all performed on the same day.

6.7. Guidance for Vivatmo *pro*™ Test Result Acceptance Criteria and Invalid Results

Vivatmo *pro*™ will indicate if each measurement is valid and acceptable or if it is invalid. If the first 2 exhalation measurements at a given study visit are valid then no additional measurements need be performed at that visit. A subject must produce each valid measurement within no more than 5 exhalation measurement attempts at a given study visit. If an exhalation measurement is invalid at a given study visit then exhalation measurement should be repeated at the visit with the subject performing up to a maximum of 10 exhalation measurements total (2 x 5) at the visit or until a total of 2 valid measurements are obtained. The Vivatmo *pro*™ mouthpiece should be changed after every 5 exhalation attempts

6.8. Guidance for Spirometry Testing

Electronic peak air flow spirometry testing will be performed at each study visit in accordance with ATS guidelines. Only ATS/ERS compliant electronic spirometers should be used and the same spirometer should be used on each study patient at each study visit. Participating clinical sites will use spirometers routinely used for clinical care. Spirometers will not be provided by the Sponsor to clinical sites participating in the study. Spirometry results at each study visit including fractional exhaled volume (FEV_1%), number of exhalations measured, make and model of spirometer, and spirometer reference standard used will be recorded in the designated study CRF.

6.9. Guidance for ACQ Data Collection

Subject responses to questions on the standardized Asthma Control Questionnaire (ACQ) will be obtained at any time during the study visit. This information will frequently be available prior to Vivatmo *pro*™ testing at the time of confirmation of a clinical diagnosis of asthma. ACQ responses will be recorded at each of the 2 study visits. ACQ responses will be recorded in the designated study case report form (CRF).

7. DATA COLLECTION, HANDLING AND RECORD KEEPING

7.1. Study Management Documentation and Logs

Participating clinical sites will maintain a Patient Screening Log and a Subject Enrollment Log. The Patient Screening Log should contain a nonconfidential (coded) listing of potential study patients screened at the clinic for study participation and identify those that were included in the study, those that were not included in the study, and the reasons why patients were not included (excluded). The Subject Enrollment log should identify enrolled study subjects and their assigned Study Subject ID.

7.2. Study Case Report Forms (CRFs)

In addition to instrument electronic report data, study Case Report Forms (CRFs) will be the primary data collection tool for the study and will constitute the original study record. The following study information will be collected using eCRFs/CRFs for each study subject:

CRF 1 - Consent and Demographics
CRF 2 - Current Asthma Prescription and Asthma History
CRF 3 - Other Medical Conditions and Medications
CRF 4 - Visit #1 - ACQ and Spirometry Results
CRF 5 - Visit #1 - Vivatmo *pro*^{TM} Results
CRF 6 - Visit #2 - ACQ and Spirometry Results
CRF 7 - Visit #2 - Vivatmo *pro*^{TM} Results

Data may be delivered via completion of electronic case report forms (eCRFS) directly into the online study database or by completion and delivery of PDF scans of completed hardcopy case report forms (CRFs). The PI, or designee, at each site must verify the accuracy and completeness of all recorded data by signing and dating all case report forms (eCRFs/CRFs) prior to submitting them. If a manual entry requires change, the correction will be made as follows:

- Draw a single line through the incorrect entry.
- Enter changed/corrected data ("white-out", erasure, or any form of obliteration of data is not permitted under any circumstances).

Neither the Sponsor nor its designee can interpret a blank answer as "none" or "N/A"; therefore, all fields must be completed. If data are not available, a straight line should be drawn through all applicable fields manually completed forms and unused pages, and dated and initialed to indicate there was no omission.

All supportive documentation must be clearly identified with the Study Subject ID number. Any personal information, including subject name, address, phone number, medical record number, or social security number must be removed or rendered illegible to preserve study subject confidentiality.

All records (e.g., regulatory documents, CRFs, study logs, data sheets) will be sent to the clinical monitor when requested. Unless otherwise instructed, original documents completed at the study site will remain in the Investigational Site File (ISF) while copies will be sent to sponsor, or designee, for the study Trial Master File (TMF).

The PI ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor as well as storage and security of the study files. Study ISF binders and CRF template forms will be provided by the sponsor.

7.3. Vivatmo *pro*^{TM} Instrument Data

The following instrument testing data will be reported to the sponsor or designee:

- Study Visit #1 - Vivatmo *pro*™ Test Results
- Study Visit #2 - Vivatmo *pro*™ Test Results

Instrument test results for each patient visit will be printed at the time of the visit (or immediately after) and stored in study data binder. Electronic exports of Vivatmo *pro*™ study results files will be emailed to the study sponsor or designee for uploading into study database.

Reports for the following will also be printed and stored in the study data binder and delivered electronically to the study Sponsor or designee.

- Vivatmo *pro*™ Initial Set-Up and Installation Information (as needed)
- Vivatmo *pro*™ QC results

7.4. Asthma Control Questionnaire (ACQ) and Spirometry Data

Asthma Control Questionnaire (ACQ) and Spirometry data for each patient visit will be recorded in the designated CRF. These CRFs will include:

- Study Visit #1 - ACQ Responses and Spirometry Testing Result
- Study Visit #2 - ACQ Responses and Spirometry Testing Result

7.5. Record Retention

All records pertaining to this study must be maintained by the PI in a condition suitable for inspection for whichever is the longer of:

- Two (2) years following FDA clearance to market of the investigational product;
- Two (2) years following termination or discontinuance of the entire clinical investigation; or
- Record retention policy of the investigational site and/or IRB/IEC.

7.6. Record Access

The PI and institution will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection (FDA or other regulatory authority) by providing direct access to study documents.

7.7. Study Training Manual

The study training manual will contain the following:

- Table of Contents
- Study Protocol
- Study Informed Consent Template
- Study Case Report Form Templates (CRFs)
- Screening Log Template
- Enrollment Log Template
- Study Material Accountability Log Template
- Study Deviation Report Template

7.8. The Investigational Site File (ISF)

The Investigational Site File (ISF) a.k.a. "Regulatory Binder" will contain the following:

- IRB approval of Study Protocol
- IRB approved Patient Informed Consent Template
- Completed and Signed Investigator Statement
- Completed and Signed Financial Disclosure Form 3454 or 3455
- Signed Clinical Site Agreement (Clinical Trial Agreement)
- All relevant and significant communications between sponsor, site and IRB, including all electronic and paper communications (e.g., emails, letters)
- Investigator notifications of protocol amendments and addenda
- IRB updates
- PI CV and Licenses
- PI GCP Certifications
- Site Staff Study Training Documentation

7.9. Data Binder

The study data binder will contain the following:

- Original completed Case Report Forms (CRFs)
- Printouts of the Vivatmo pro™ Test Result Data
- Printouts of Vivatmo pro™ Initial Set-Up and Installation Information
- Printouts of Vivatmo pro™ QC results

8. DATA ANALYSIS AND STUDY ENDPOINTS

8.1. Analysis Populations

The Full Analysis Set (FAS) will be defined as all patients intended to receive a FeNO measurement.

The Per Protocol Set will be defined as enrolled subjects without major protocol violations, with inhaled corticosteroid (ICS) treatment, and successfully completing at least one valid FeNO measurement at both Visit #1 and Visit #2 will be evaluated for the primary endpoint.

8.2. Descriptive Statistics

Baseline characteristics, such as demographic, as well as analytical clinical data by visit will be summarized using descriptive statistical methods. Continuous data will be summarized using the mean, the median, standard deviation, and range (minimum and maximum value). Categorical values will be summarized using frequency counts and percentages.

8.3. Analysis of Primary Endpoint

The change of FeNO values will be estimated in ANOVA with baseline values as the covariable and will be reported as percent change together with the 95%-confidence interval.

8.4. Analysis of Secondary Endpoints

The relationship between changes of FeNO-values and clinical assessments (spirometry, ACQ-questionnaire) will be assessed by Spearman's rank correlation.

Repeatability will be estimated together with the 95%-confidence interval as pooled standard deviation (mean of measurement pair < 50 ppb) and CV (mean of measurement pair ≥ 50 ppb), respectively, using the residual variance component resulting from a random effects ANOVA (as used in CLSI EP05 guideline) with patient and visit as random factors. . Technically, the CV is estimated as 100 x standard deviation applying the random effects ANOVA on ln-transformed values. The resulting pooled repeatability is hereby estimated taking in account conditions of variability over sites and operators.

The *success rates* (proportion of patients with successful measurement within FAS) will be reported. The number of attempts necessary to obtain 2 valid replicate measurements will be tabulated in contingency tables by visit.

9. COMPLIANCE WITH GOOD CLINICAL PRACTICES (GCP), ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

9.1. Adherence to Protocol, Good Clinical Practices (GPC), and Applicable Regulations

The study shall be conducted as described in this protocol, according to good clinical practices (GCP), in compliance with the principles set forth in the Declaration of Helsinki, and according to applicable U.S. Federal Regulations.

The PI shall ensure that all work and services described herein shall be conducted in accordance with the highest standards of medical and clinical research practice. The PI will provide copies of the protocol to all co-Investigators or other staff responsible for study conduct.

9.2. Institutional Review Board

The protocol, as well as the Informed Consent template, will be approved by a central IRB (WIRB - Western IRB, Puyallup, WA) prior to the start of the study.

The Institutional Review Board (IRB) will review and approve enrollment of subjects into this study. The PI shall obtain written confirmation from the IRB that the protocol and other applicable documents have been approved. The study cannot begin until approval is received.

If the study continues beyond the time period specified by the IRB, the PI would request a renewal of the study. The renewal application will include any applicable documents required for the duration of the study. The PI will obtain written confirmation from the IRB that the study has been renewed. The PI will inform the IRB when the study has been terminated and obtain written confirmation from the IRB/IEC of the study closure.

9.3. Subject Protections

It is the responsibility of the PI to assure that informed consent is obtained from each subject or legal guardian in accordance with current regulations. The content of the informed consent will conform to current ICH and FDA guidelines for the protection of human subjects, and/or to the specific IRB requirements. The informed consent form must be in English, signed and dated by the subject, or legal guardian, and Investigator, or designee.

Each subject will be given verbal and written information describing the nature and duration of the study. This will take place under conditions where the subject, and/or legal guardian, has adequate time to consider the potential risks associated with his/her participation in the study. All subjects' questions must be answered adequately to ensure that they have the information they require to make an informed decision about participation in the study. The signed informed consent form will be filed in a study Investigational Site File (ISF) along with all other Case Report Forms (CRFs).

No subject names, medical record numbers, or other personally identifying information will be used as part of the study or transmitted to the sponsor or designee. Case Report Forms (CRFs) will not contain any confidential information linking the date or outcome result to a subject. Only the study site will have the information that links a subject to his/her identifying information. Subjects will only be referred to by using their unique Subject ID number.

9.4. Confidentiality

This study protocol, study, documentation, and all other information generated, will be held in strict confidence by the PI and their representatives. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by the Sponsor.

9.5. Monitoring

The Study Manager and Clinical Monitor, as representatives of the Sponsor, have the obligation to follow this study closely. The Study Manager and/or Clinical Monitor will visit the study facility/site as needed, in addition to maintaining necessary contact by telephone, tele/video-conference, e-mail, facsimile, and/or letter communication. Monitoring of this study will entail review of the required study documents, such as Case Report Forms (CRFs), investigational testing results, quality control test results, staff training records, and other activities as deemed necessary during monitoring visits.

9.6. Study Deviations

All effort must be made to avoid deviations from the protocol, regulations, or GCPs. If a deviation occurs, it must be reported to the study Sponsor, or designee, and recorded by site personnel in a deviation report describing the deviation and corrective/preventative actions; which is kept with the ISF and a copy provided to the sponsor, or designee, for the TMF. The study manager will determine whether the site's IRB/IEC must be informed

9.7. Serious Adverse Event (SAE) Reporting

A significant adverse event (SAE) is one that has a serious adverse effect on the health or safety of a study subject, or causes any medical problem, life-threatening problem, or death of the study subject.

All SAEs should be recorded by the PI and reported by the PI to the Sponsor, or designee, and to the IRB within 24 hours after the PI becomes aware of the SAE. The Sponsor will collect adverse event information and may report serious and unanticipated adverse events to the FDA.

9.8. Risks

There are no known direct risks to patient health.

9.9. Potential Benefits

There is no guaranteed of benefit to a subject for participation in this study. Subjects are to be treated for their asthma per their physician's standard of care.

9.10. Compensation

Subjects may be offered a gift card, (worth no more than $25 per visit) for study participation. Sites may be compensated for time and effort completing study tasks.

All study instruments and supplies will be provided to the participating sites at no charge. Subject medications will not be covered by the Study Sponsor.

9.11. Quality Assurance Audit

In the event that PI is contacted by a Regulatory Agency in relation to this study, the PI will notify the Sponsor immediately. The PI or designee must be available to respond to reasonable requests and audit queries made during an audit process. The PI must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspectional Observations, and warning letters).

9.12. Publication Policy

The data and results from this study are the sole property of the Sponsor. The Sponsor will have the right to access and use all data and results generated during the clinical study. The PI will not use the study related data without the written consent of the Sponsor for any purpose other than for study completion or for generation of publication material. The Sponsor must approve all material for publication prior to submission.

9.13. ClinicalTrials.Gov

This study will be posted on clinicaltrials.gov (www.clinicaltrials.gov).

REFERENCES

1. *Systematic meta-review of supported self-management for asthma: a healthcare perspective.* Pinnock, Hilary, et al. 2017, BMC Medicine, Vol. 15, p. 64.

2. *Current evidence and future research needs for FeNO measurement in respiratory diseases.* Bjermer, Leif, et al. s.l. : Elsevier, February 2014, Respiratory Medicine, Vol. 108, pp. 830-841.

3. *Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial.* Hashimoto, Simone, et al. 6, June 2011, Thorax, Vol. 66, pp. 514-520.

4. *Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates.* Donohue, James F and Jain, Neal. 7, July 2013, Respiratory Medicine, Vol. 107, pp. 943-52.

5. *Symptom- and fraction of exhaled nitric oxide–driven strategies for asthma control: A cluster-randomized trial in primary care.* Honkoop, Persijn J, et al. 3, March 2015, The Journal of Allergy and Clinical Immunology, Vol. 135, pp. 682-88.

6. *Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial.* Powell, Heather, et al. 9795, September 2011, The Lancet, Vol. 378, pp. 983-990.

APPENDIX - Asthma Guidance and Reference Documents

1. **ACQ** - Asthma Control Questionnaire
   https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php

2. **ATS / ERS Guidelines** - Standardization of Lung Function Testing - American Thoracic Society / European Respiratory Society Task Force
   https://www.thoracic.org/statements/resources/pfet/PFT2.pdf

3. **NEAPP Guidelines** - National Asthma Education and Prevention Program Guidelines (2002)
   https://www.nhlbi.nih.gov/files/docs/guidelines/asthmafullrpt_archive.pdf

4. **NICE Asthma Guidelines** - National Institute for Health and Care Excellence (UK)

   a. Diagnosis and Monitoring of Asthma in Adults, Children and Young People, NICE Guideline, No. 80.1
      https://www.ncbi.nlm.nih.gov/books/NBK469773/

   b. Chronic Asthma: Management, NICE Guideline, No. 80
      https://www.ncbi.nlm.nih.gov/books/NBK469772/

5. **NHLBI Guidelines** - Guidelines for the Diagnosis and Management of Asthma (EPR-3) National Heart, Lung, and Blood Institute
   https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma