CONFIDENTIAL

HEALTH OUTCOMES STUDY PROTOCOL

UNIQUE IDENTIFIER	HO-17-17827 / 207223
FULL TITLE	Enabling Innovative Respiratory Real World Evidence Generation: Sensor and EHR Integration Pilot Study
ABBREVIATED TITLE	PPD Sensor Pilot
FINAL PROTOCOL APPROVED	October 16, 2017
SPONSORSHIP	Supported
DIVISION	Pharma
BUSINESS UNIT	Research & Development
DEPARTMENT	US VEO
STUDY ACCOUNTABLE PERSON	PPD
CONTRIBUTING AUTHORS	PPD PPD

INDICATION	Asthma and COPD

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Version Date	Document Type	Change(s) since last version
10-16-2017	Original	n/a
2-22-2018	Amendment 01	Revisions: 1. Added statement regarding the data captured from devices being for research use only 2. Updates subject identification to include study provider referral 3. Added collection of height and weight at Visit 1

		4. Added details regarding the 2 step process for full data integration

Description: PPD sensor pilot
Unique Identifier: HO-17-17827 / 207223

SPONSOR SIGNATORY

PPD

3/8/2018
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Date

Description: PPD Sensor Pilot

Unique Identifier: HO-17-17827 / 207223

Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: Paul Simonelli, MD PhD

PPD

20-MAY-2019

Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Unique Identifier	HO-17-17827 / 207223
Abbreviated Title	PPD Sensor Pilot
Rationale	This is a pilot study exploring the opportunity for accessing data directly from electronic health records (EHR) and integrating with data from various sensors and mobile devices. The goal is to assess how to scale these methods for use in interventional trials.
Objectives (Primary, Secondary)	• To assess how the use of EHR may be beneficial in recruiting populations for future clinical trials, • To evaluate how representative the consented, study population is when compared to the eligible population, • To develop a monitoring dashboard for integration of data from various sources, • To evaluate patient experience, data quality and consistency with novel, patient-data collection methods: o Mobile spirometry o Sensor for monitoring rescue medication use o Sensor for monitoring maintenance medication use o Physical activity monitor o Electronic patient reported outcomes (ePROs) • To assess the relationships between EHR-based healthcare utilization (ambulatory care visits and hospitalizations for COPD or asthma exacerbations) and lab measures (specified below) with patient data remotely collected via methods outlined in previous bullet.
Study Design	A prospective study that will include two cohorts of patients (COPD and asthma) identified via EHR database analyses recruited from sites of usual care. Participants will attend two visits at 0 and 6 months and data will be collected via sensors and mobile devices between the visits.
Study Population and Sampling Methods	Eligibility Criteria Inclusion Criteria All patients will be selected based on the following criteria. **Inclusion Criteria for COPD cohort:** To be eligible to participate in this study, a subject must meet all of the following criteria: • Provide signed and dated informed consent form. • Be willing to comply with all study procedures and be available for the duration of the study. • Age ≥ 40

	• Diagnosed with COPD, defined as COPD listed on the patient's problem list and one of the following: o At least one inpatient hospitalization with a COPD diagnosis listed as the primary or secondary diagnosis (J41.x, J42.x, J44.x [chronic bronchitis], J43.9 [emphysema] or J44.9 [Chronic obstructive pulmonary disease, unspecified]) in the last 12 months *OR* o At least one emergency room encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months *OR* o At least two encounters of any combination of the following (each must be a distinctly different event with different dates of service): • an outpatient encounter with a diagnosis of COPD exacerbation (J44.1), Acute bronchitis (J20.x), or bronchitis (J40) listed as the primary or secondary diagnosis in the last 12 months, *OR* • an urgent care encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months • At least one order for an inhaled COPD medication during the prior year. • 12+ months of data available in the integrated EHR data prior to date of screening. **Inclusion Criteria for Asthma cohort** • Provide signed and dated informed consent form. • Be willing to comply with all study procedures and be available for the duration of the study. • Age ≥ 18 • Diagnosed with asthma, defined as asthma listed on the patient's problem list and one of the following: o At least one inpatient hospitalization with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR* o At least one emergency room encounter with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR* o At least two urgent care encounters, with different dates of service, with an asthma diagnosis (J45.x)

	listed as the primary or secondary diagnosis in the last 12 months *OR* ○ At least three or more prescriptions or prescription refills in the past 12 months for any combination of the following: an inhaled glucocorticoid with or without a second controller (Montelukast, Theophylline, a long-acting beta agonist [LABA] alone), or a combination drug with a LABA and an inhaled glucocorticoid • 12+ months of data available in the integrated EHR data prior to date of screening **Exclusion Criteria (screening question) for COPD cohort** • Inability/Unwillingness to use the required devices, or • Inability to read and understand English **Exclusion Criteria (screening question) for Asthma cohort** • Inability/Unwillingness to use the required devices, or • Inability to read and understand English, or • Diagnosis of COPD listed on problem list
Data Source	Integrated EHR records (primary and specialty care) are the key source for retrospective analysis and for identifying patients. Digital data collection from patient reports, devices, and sensors over six months are the key source for the prospective analysis. The full data integration will be accomplished in two stages.
Data Analysis Methods	• Spirometry ○ Change from baseline in FEV1 • Activity ○ Median/mean steps per day ○ Median/mean daily activity level based on vector magnitude units (VMUs) • PROactive total score and difficulty domain score (C-PPAC) • E-RS:COPD symptoms Exacerbations (COPD cohort only) ○ EXACT-defined events • HCRU ○ Median/mean number of primary care visits for COPD/asthma conditions ○ Median/mean number of secondary care visits (inpatient, urgent care and ED visits) for COPD/asthma conditions ○ Median/mean number of all primary care visits ○ Median/mean number of all secondary (inpatient, urgent care and ED visits) care visits

	○ Summary of new prescriptions for any COPD/asthma treatments ○ Number of days in hospital for COPD/asthma ○ Number of albuterol inhalers (adjusted to equivalence of 200 actuations) prescribed • ePRO ○ Mean change from baseline in CAT (COPD cohort) ○ Mean change from baseline in ACT (asthma cohort) All PRO data will be collected via electronic platform Further details and exploratory analyses describing patterns of cohort and individual changes will be described in the full statistical and analysis plan. All analyses will be performed using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA). These will be described in more detail in the full statistical analysis plan.
Sample Size and Power	This study aims to evaluate the patient experience with new data collection methods and the association between new methods and the EHR-defined variables regarding disease severity and healthcare resource utilization, therefore no comparisons or hypothesis testing will be performed. In order to collect adequate information about the feasibility of these new data collection methods, approximately 200 PPD patients from the integrated delivery network (IDN) will participate in the study (100 in each group COPD and asthma). If we assume a dropout rate of at most 25%, we will have complete data on at least 150 patients, which will be sufficient to address feasibility of the new collection methods in two different cohorts. In addition, since this is a pilot study to assess feasibility of an interventional study that would use the data capture methods, a formal power calculation is not required.
Limitations	Participants included in this study will be selected from among those within the PPD IDN, therefore may not be representative of a sample of all COPD and asthma patients from the US. There will likely be a selection bias based on which patients are willing to participate in a study with multiple devices and due to established inclusion/exclusion criteria. Medication use and activity will be monitored using sensors so there is a risk that the patient's behavior may be altered.

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ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse event
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
EHR	Electronic Health Records
ERS-COPD	Evaluating Respiratory Symptoms in COPD
ePROs	Electronic patient reported outcomes
PPD	PPD
IDN	Integrated Delivery Network
IRB	Institutional Review Board
PACDC	Phenomic Analytics Clinical Data Core
VMUs	vector magnitude units

1 INTRODUCTION/BACKGROUND

Electronic health records (EHR) are becoming more common in clinical practice in the United States. This study aims to assess the feasibility of collecting increasing amounts of clinical study data from patients (e.g. sensor and web/app based methods) and their EHR to facilitate more efficient and meaningful research with acceptable quality.

2 OBJECTIVES

2.1 General Objective

To recruit small cohorts (n=100 each) of chronic obstructive pulmonary disease (COPD) and asthma patients from their usual healthcare environment to gain experience with novel, digital data collection methods combined with EHR extraction to explore feasibility of larger real-world studies. Overall, we hope to assess how the use of EHR may be beneficial in recruiting populations for future clinical trials.

2.2 Specific Objectives

- To evaluate how representative the consented, study population is when compared to the eligible population.
- To develop a monitoring dashboard for integration of data from various devices
- To evaluate patient experience, data quality and consistency with novel, patient-data collection methods:
    - Mobile spirometry
    - Sensor for monitoring rescue medication use
    - Sensor for monitoring maintenance medication use
    - Physical activity monitor
    - Electronic patient reported outcomes (ePROs) – monthly CAT (COPD cohort), ACT (asthma cohort)
        - monthly PROactive – using the C-PPAC
        - For COPD only: EXACT PRO daily symptoms [ERS-COPD]
- To assess the relationships between EHR-based healthcare utilization (ambulatory care visits and hospitalizations for COPD or asthma exacerbations) and lab measures (specified below) with patient data remotely collected via methods outlined in previous bullet, for example.
    - EHR spirometry
    - Blood WBC, eosinophils, neutrophils (number and %)
    - Other blood biomarker samples if available (e.g. fibrinogen, CRP, periostin, sRAGE etc)

2.3 Information regarding devices

All the data collected from the devices in this study listed above (i.e. mobile spirometry and actigraphy) are for research use only. This means that the data cannot be used for clinical patient management or as a primary clinical outcome measure.

3 RESEARCH METHODOLOGY

3.1 Study Design

This is a prospective study that will include two cohorts of patients (COPD and asthma) identified via EHR database analyses, study provider referral (COPD and asthma diagnoses with and without specialist confirmation), or recruited from sites of usual care. Participants will attend two visits with study team members at 0 and approximately 6 months, as most data will be captured either remotely via sensors and devices provided by GSK to the patients or via a data pull of EHR data. At the baseline visit, study team members will obtain written informed consent, distribute study devices, and provide instruction for proper use of study devices and platforms. Approximately six months later, at the second visit, the patient will return study devices. Patients will then be called to complete an exit interview to provide relevant feedback on the study.

3.2 Study Population

3.2.1 Eligibility Criteria

3.2.1.1 Inclusion Criteria

All patients will be selected based on the following criteria in EHR.

Inclusion Criteria for COPD cohort:

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Provide signed and dated informed consent form.
- Be willing to comply with all study procedures and be available for the duration of the study.
- Age ≥ 40
- Diagnosed with COPD, defined as COPD listed on the patient's problem list and one of the following:
    - At least one inpatient hospitalization with a COPD diagnosis listed as the primary or secondary diagnosis (J41.x, J42.x, J44.x [chronic bronchitis], J43.9 [emphysema] or J44.9 [Chronic obstructive pulmonary disease, unspecified]) in the last 12 months *OR*
    - At least one emergency room encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - At least two encounters of any combination of the following (each must be a distinctly different event with different dates of service):
        - an outpatient encounter with a diagnosis of COPD exacerbation (J44.1), Acute bronchitis (J20.x), or bronchitis (J40) listed as the primary or secondary diagnosis in the last 12 months, *OR*
        - an urgent care encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months
- At least one order for an inhaled COPD medication during the prior year

- 12+ months of data available in the integrated EHR data prior to date of screening

Inclusion Criteria for Asthma cohort

- Provide signed and dated informed consent form.
- Be willing to comply with all study procedures and be available for the duration of the study.
- Age ≥ 18
- Diagnosed with asthma, defined as asthma listed on the patient's problem list and one of the following:
    - At least one inpatient hospitalization with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - At least one emergency room encounter with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - at least two urgent care encounters, with different dates of service, with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - At least three or more prescriptions or prescription refills in the past 12 months for any combination of the following: an inhaled glucocorticoid with or without a second controller (Montelukast, Theophylline, a long-acting beta agonist [LABA] alone), or a combination drug with a LABA and an inhaled glucocorticoid
- 12+ months of data available in the integrated EHR data prior to date of screening

Exclusion Criteria (screening question) for COPD cohort

- Inability/Unwillingness to use the required devices, or
- Inability to read and understand English

Exclusion Criteria (screening question) for Asthma cohort

- Inability/Unwillingness to use the required devices
- Inability to read and understand English
- Diagnosis of COPD listed on problem list

3.2.2 Sampling

PPD located in PPD has a service area that is largely rural, mostly Caucasian, remarkably stable population (i.e., a very low out-migration rate), and a higher percentage of elderly patients (aged 65+) than the national average. PPD catchment area is one of the oldest and sickest in the nation in terms of multiple co-morbidities.
Patients will be selected based on the criteria previously described.

3.3 Study Visits

3.3.1 Recruitment

The study team will utilize three recruitment methods. The first method is to have a Phenomic Analytics Clinical Data Core (PACDC) data broker identify potential participants through a data pull of EHR data or by review of PPD clinical dashboard. The second method is for study providers to refer eligible patients to the study team. The third method will have a study team member review the pulmonary clinics schedules and identify eligible patients. Potential subjects will be invited to participate.

3.3.2 Baseline Visit

A baseline clinic visit will be scheduled with interested patients and a study team member. At the visit, the potential participants will be informed of all pertinent details, risks, and benefits of the study via the study consent form. A study team member will answer any patient questions and patients will be given adequate time to consider participation. Written informed consent will be obtained using the study consent form. After consent, the participant will receive study devices and training on proper use of the devices. Patient vitals including height and weight will be collected by study staff. Participants will complete a baseline questionnaire. Data will be collected remotely from the devices and platforms for six months.

3.3.3 Six Month Visit

After six months (+/- 2 weeks), a second visit will be scheduled with the participant and a study team member. At the second visit, the participant will return the study devices and will complete an exit interview to obtain relevant feedback from the patient's perspective on the study. Exit interviews will be performed by PPD personnel.

3.4 Study Duration

3.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 6 months.

3.4.2 Approximate Duration of Study

200 patients will be enrolled over an eight-month period, including 100 in the asthma cohort and 100 in the COPD cohort. Each patient will be followed for approximately six months after consent and enrollment into the study.

3.5 Data Source / Data Collection

Integrated EHR records (primary and specialty care) are the key source for retrospective analysis and for identifying patients. Digital data collection from patient reports, devices, sensors, and EHR records over six months are the key sources for the prospective analysis. The full data integration will happen in two stages and a summary of variables to be extracted in each stage is included in Section 6.4. The study database will be housed on a third-party vendor's secure network. In the initial data integration stage and at the baseline visit, the study

team member will manually enter patient information (including name, MRN, date of birth, gender, ethnicity, date of consent, height, and weight) into the study portal built into the study tablet. The information entered into the study portal will calibrate the predictive formulas in the study devices and flow to the study database on the third-party vendor's secure network. Patients will then take the study devices home and use them as instructed. Data from the study devices, including the mobile spirometry device, the sensors for rescue and maintenance medications, activity monitors, and the ePRO platform will flow directly to the database on Vendor A's network. During stage one of the data integration, no EPIC data will be sent to the study database on the third-party vendor's secure network.

During stage two of the data integration, EHR data will be extracted and combined with device data in the database housed on Vendor A's network. Vendor A will de-identify the study database and send the data set to Vendor B. PPD staff will administer a study Exit Interview at the follow-up visit asking participants to provide feedback on the study, the study devices, and ePRO platform.
PPD data is part of the mini-sentinel monitoring system which means their data set meets standard criteria for data integrity and quality.

3.6 Endpoints

We will be measuring the following:

- Spirometry
- Activity (Steps and daily activity)
- Patient experience of physical activity
- COPD symptoms Exacerbations (COPD cohort only)
- Rescue and maintenance medication use
- Primary care and secondary care visits specific to each cohort and in general,
- Number of days in hospital, new prescriptions, number of albuterol inhalers specific to each cohort
- CAT (COPD cohort) and ACT (asthma cohort)
- Exit Interviews

3.7 Sample Size/ Power Calculation

This study aims to evaluate the feasibility of measuring patient experience with new data collection methods and the association between new methods and the EHR-defined variables regarding disease severity and healthcare resource utilization, therefore no comparisons or hypothesis testing will be performed. In order to collect adequate information about the feasibility of these new data collection methods, approximately 200 PPD PPD patients will participate in the study (100 in each group COPD and asthma). If we assume a dropout rate of at most 25%, we will have complete data on at least 150 patients, which will be sufficient to address feasibility of the new collection methods in two different cohorts. In addition, since this is a pilot study to assess feasibility of an interventional study that would use the data capture methods, a formal power calculation is not required.

4 DATA ANALYSIS CONSIDERATIONS

Descriptive statistics will be presented as frequency and percentages, means and standard deviations, medians and interquartile range (IQR), and for categorical variables, normally distributed and non-normally distributed continuous variables, respectively. Spearman correlations will also be assessed between endpoints. The following will be analyzed over the study period:

- Spirometry (mobile and clinic)
  - Change from baseline in FEV1
- Activity
  - Median/mean steps per day
  - Median/mean daily activity level based on vector magnitude units (VMUs)
- PROactive total score and subdomains Symptoms
- E-RS:COPD symptoms Exacerbations (COPD cohort only)
  - EXACT-defined events
- HCRU
  - Median/mean number of primary care visits for COPD/asthma conditions
  - Median/mean number of secondary care visits (inpatient, urgent care and ED visits) for COPD/asthma conditions
  - Median/mean number of all primary care visits
  - Median/mean number of all secondary (inpatient, urgent care and ED visits) care visits
  - Summary of new prescriptions for any COPD/asthma treatments
  - Number of days in hospital for COPD/asthma
  - Number of albuterol inhalers (adjusted to equivalence of 200 actuations) prescribed
- ePRO
  - Mean change from baseline in CAT (COPD cohort)
  - Mean change from baseline in ACT (asthma cohort)

All analyses will be described in more detail in the full statistical analysis plan.

5 LIMITATIONS

Participants included in this study will be selected from among those within the PPD PPD (IDN), therefore may not be representative of a sample of all COPD and asthma patients from the US. There will likely be a selection bias based on which patients are willing to participate in a study with multiple devices. Medication use and activity will be monitored using sensors so there is a risk that the patient's behavior may be altered.

6 STUDY CONDUCT, MANAGEMENT & ETHICS

6.1 Ethics Committee/IRB Approval

The study will be submitted for Institutional Review Board (IRB) review.

6.2 Informed Consent

All participants will provide signed and dated informed consent prior to initiation of any study activities via the study consent form.

6.3 Data Protection

All data collected in this study will be strictly confidential in accordance with all appropriate legislation. Data from study devices and ePROs will be encrypted and automatically transmitted to Vendor A. The portal that the study staff will enter patient information into during stage one of the data integration, including dates, participant names, MRNs, date of birth, gender, and ethnicity will be reviewed and approved by PPD EHR data, including PHI such as names, dates, and MRNS, will be encrypted and sent to Vendor A via a PPD approved, secure portal. Vendor A's Insight Platform maintains a HITRUST certification to protect patient data. Vendor A will integrate the data from study devices, ePROs, and PPD on their secure network. Vendor A will de-identify the integrated study data set and transfer the de-identified data set to Vendor B.

Study staff will be instructed to maintain complete confidentiality of all collected data. Patient files will be kept on secure servers. The final study report will not contain any patient identifying information. Participants will be assigned a unique participant number in the final data set to ensure confidentiality and anonymity. Interview transcripts will be identified by this unique participant number and will not have any identifiers associated with the individual.

6.4 Personally Identifiable Information (PII)

The final data set will be de-identified and will not contain PHI. However, Vendor A will have access to participant names, dates, date of birth, and MRNs to integrate data from multiple data sources including study device data, ePRO, EHR data, and Exit Interview transcripts. Vendor A will remove PHI elements from the dataset. PHI accessed for recruitment will only be seen by PPD staff. The final data set, housed by Vendor B, will be de-identified.

The data in the table below, including relevant dates, will be collected. The table also outlines who will have access to each type of data during each stage of data integration.

Stage One – Data Integration				
	PPD	GSK	Vendor A	Vendor B
Names	X		X	
Medical record number	X		X	
Telephone number	X			
Date of birth/date of death	X		X	
Height and weight	X	X	X	X
Information relevant to all encounters, admissions/discharges, clinical procedures, medications administered, problem list entries, and lab values	X			
Baseline demographic variables of patients (age, sex, ethnicity, tobacco use, comorbidities)	X		X	
Clinical outcomes and procedural related complications	X			
Information from study devices, sensors, and electronic platforms	X	X	X	X
Information gather from patient interviews at study visits	X	X	X	X

Stage Two – Data integration				
	PPD	GSK	Vendor A	Vendor B
Names	X		X	

Medical record number	X		X	
Telephone number	X			
Date of birth/date of death	X		X	
Height/ Weight	X	X	X	X
Information relevant to all encounters, admissions/discharges, clinical procedures, medications administered, problem list entries, and lab values	X	X	X	X
Baseline demographic variables of patients (age, sex, ethnicity, tobacco use, comorbidities)	X	X	X	X
Clinical outcomes and procedural related complications	X	X	X	X
Information from study devices, sensors, and electronic platforms	X	X	X	X
Information gather from patient interviews at study visits	X	X	X	X

Records of data generated in the course of the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

6.5 Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

While this study does not involve the direct solicitation of adverse experience information, it is possible that participants could spontaneously describe potential adverse events that occurred during the course of their normal clinical care.

As part of the site orientation process, study team members will be trained in the recognition of potentially-reportable adverse events.

If an AE (serious or non-serious) or product complaint is reported spontaneously by a subject during the course of the study and the subject associates the AE with any specifically named GSK product, the following AE reporting process will be completed:

- The site staff will complete the AE reporting form (including the patient study ID number, their age and sex, the patient's description of the adverse event, and the product the patient named).

The site staff will transmit the report to the GSK study team within 24 hours of being made aware of the AE.

Patients will be asked about adverse events related to the use of the devices provided during the study (mobile spirometer, device sensor, activity monitor and tablet) at regular intervals via the study provided tablet. These data will not be monitored in real time and patients will be educated on the need to contact their physician directly should they have any medical concern.

7 EXTERNAL INVOLVEMENT

7.1 Third Party Suppliers

- Accenture (device integration, EHR integration)

  Accenture, LLP
  1160 West Swedesford Road
  Berwyn, PA, 19312
  USA

- Medidata (ePRO, data and visualization platform)

  Medidata Solutions, Inc.
  350 Hudson Street, 9th Floor
  New York, NY 10014
  USA

- ActiGraph (activity monitors)

  49 East Chase Street.
  Pensacola, FL 32502
  USA

- Propeller Health (sensors for MDI and DPI)

  634 West Main Street, Suite 102
  Madison, WI 53703
  USA

- MIR (mobile spirometry)

5462 S. Westridge Drive
New Berlin, WI 53151
USA

7.2 External Expert/Health Care Professionals (Consultants & Research PIs)

PPD MD, PhD.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent and HIPAA Authorization

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

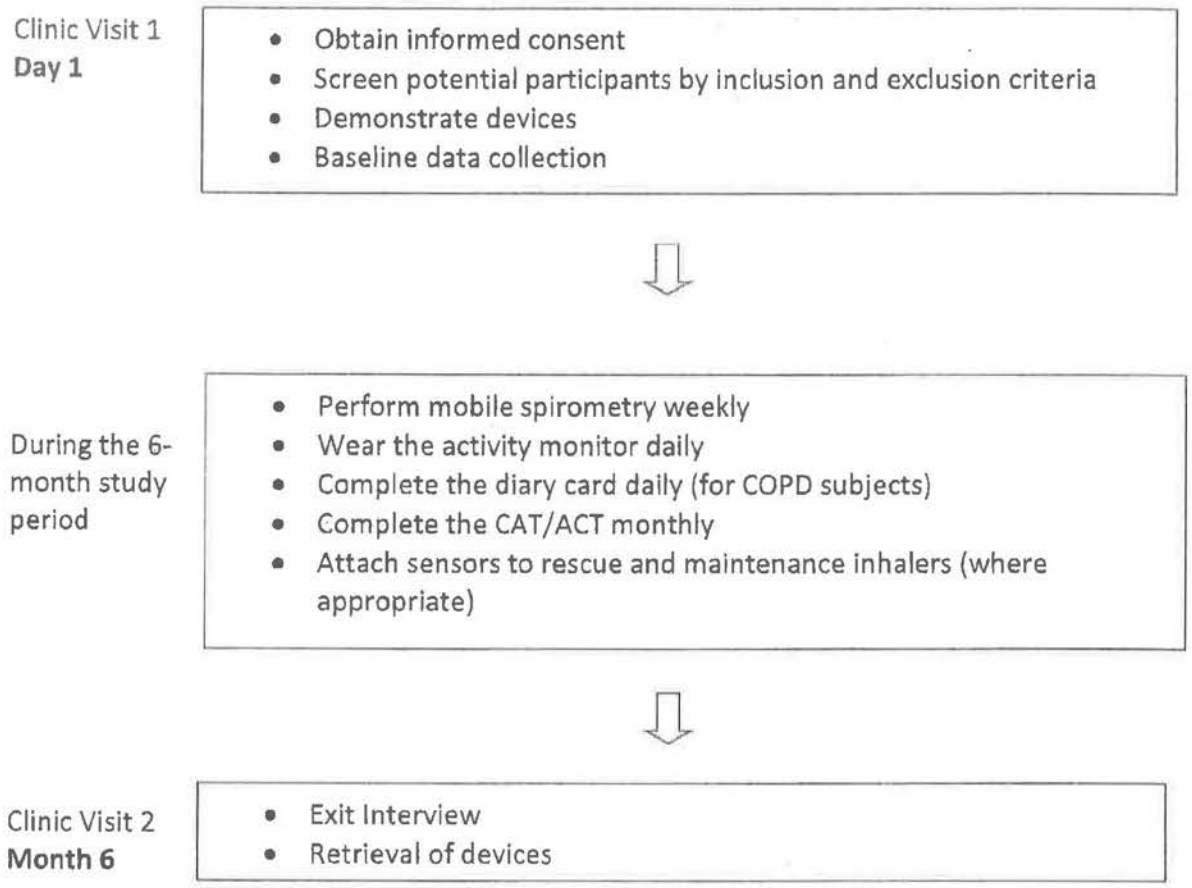
We are requesting a partial waiver of HIPAA authorization for pre-screening and contacting patients about the study will be requested by the IRB to allow the identification of potentially eligible participants from the medical record.

8.2 Protection of Human Subjects Against Risks

There is a risk of loss of confidentiality as PHI will be collected as part of the study. To minimize this risk, hard copy data will be stored in a locked environment that is only accessible only to the study team members and electronic data will be stored on a secure network (either PPD or Vendor A's HITRUST certified network). The portal into which study staff will enter patient information, including PHI, during visit one and stage one of the data integration will be reviewed and approved by the PPD EHR data, including PHI, will be sent to Vendor A through a secure portal approved by PPD governance during stage two of the data integration process. Vendor A will de-identify the dataset before sending the data set to Vendor B. All data transmissions will be encrypted. Only aggregate data without personal identifiers will be included when presenting results or submitting manuscripts for publication.

All subjects will be trained on the use of each device - it is important that all instructions be followed to minimize potential risks due to misuse.

Appendix 1. Schematic of a Prospective Study:



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CONTRIBUTING AUTHORS	PPD PPD – others TBD

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Version Date	Document Type	Change(s) since last version
Enter original protocol FPA	Original	n/a

Description: PPD sensor pilot
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SPONSOR SIGNATORY

PPD

PPD

Martin Marciniak,
VP CEVEO

October 16, 2017
Date

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Investigator Name:

_____

_____ _____

Investigator Signature Date (DD-MMM-YYYY)

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	  ○ Sensor for monitoring rescue medication use
	  ○ Sensor for monitoring maintenance medication use
	  ○ Physical activity monitor
	  ○ Electronic patient reported outcomes (ePROs)
	• To assess the relationships between EHR-based healthcare utilization (ambulatory care visits and hospitalizations for COPD or asthma exacerbations) and lab measures (specified below) with patient data remotely collected via methods outlined in previous bullet.

Study Design	A prospective study that will include two cohorts of patients (COPD and asthma) identified via EHR database analyses recruited from sites of usual care. Participants will attend two visits at 0 and 6 months and data will be collected via sensors and mobile devices between the visits.
Study Population and Sampling Methods	All patients will be selected based on the following criteria. **Inclusion Criteria for COPD cohort:** To be eligible to participate in this study, a subject must meet all of the following criteria: • Provide signed and dated informed consent form. • Be willing to comply with all study procedures and be available for the duration of the study. • Age ≥ 40 • Diagnosed with COPD, defined as COPD listed on the patient's problem list <u>and</u> one of the following: ○ At least one inpatient hospitalization with a COPD diagnosis listed as the primary or secondary

	diagnosis (J41.x, J42.x, J44.x [chronic bronchitis], J43.9 [emphysema] or J44.9 [Chronic obstructive pulmonary disease, unspecified]) in the last 12 months *OR* ○ At least two outpatient encounters with a diagnosis of COPD exacerbation (J44.1), Acute bronchitis (J20.x), or bronchitis (J40) listed as the primary or secondary diagnosis, with different dates of service in the last 12 months *OR* ○ At least one emergency room encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months *OR* ○ At least two urgent care encounters with different dates of service, with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months • At least one order for an inhaled COPD medication during the prior year. • 12+ months of data available in the integrated EHR data prior to date of screening. **Inclusion Criteria for Asthma cohort** • Provide signed and dated informed consent form. • Be willing to comply with all study procedures and be available for the duration of the study. • Age ≥ 18 • Diagnosed with asthma, defined as asthma listed on the patient's problem list and one of the following: ○ At least one inpatient hospitalization with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR* ○ At least one emergency room encounter with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR* ○ At least two urgent care encounters, with different dates of service, with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR* ○ At least three or more prescriptions or prescription refills in the past 12 months for any combination of the following: an inhaled glucocorticoid with or without a second controller (Montelukast, Theophylline, a long-acting beta agonist [LABA]

	alone), or a combination drug with a LABA and an inhaled glucocorticoid • 12+ months of data available in the integrated EHR data prior to date of screening **Exclusion Criteria (screening question) for COPD cohort** • Inability/Unwillingness to use the required devices, or • Inability to read and understand English **Exclusion Criteria (screening question) for Asthma cohort** • Inability/Unwillingness to use the required devices, or • Inability to read and understand English, or • Diagnosis of COPD listed on problem list
Data Source	Integrated EHR records (primary and specialty care) are the key source for retrospective analysis and for identifying patients. Digital data collection from patient reports, devices, and sensors over six months are the key source for the prospective analysis

Data Analysis Methods	• Spirometry
	  ○ Change from baseline in FEV1
	• Activity
	  ○ Median/mean steps per day
	  ○ Median/mean daily activity level based on vector magnitude units (VMUs)
	• PROactive total score and difficulty domain score (C-PPAC)
	• E-RS:COPD symptoms Exacerbations (COPD cohort only)
	  ○ EXACT-defined events
	• HCRU
	  ○ Median/mean number of primary care visits for COPD/asthma conditions
	  ○ Median/mean number of secondary care visits (inpatient, urgent care and ED visits) for COPD/asthma conditions
	  ○ Median/mean number of all primary care visits
	  ○ Median/mean number of all secondary (inpatient, urgent care and ED visits) care visits
	  ○ Summary of new prescriptions for any COPD/asthma treatments
	  ○ Number of days in hospital for COPD/asthma
	  ○ Number of albuterol inhalers (adjusted to equivalence of 200 actuations) prescribed
	• ePRO
	  ○ Mean change from baseline in CAT (COPD cohort)
	  ○ Mean change from baseline in ACT (asthma cohort)

	All PRO data will be collected via electronic platform Further details and exploratory analyses describing patterns of cohort and individual changes will be described in the full statistical and analysis plan. All analyses will be performed using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA). These will be described in more detail in the full statistical analysis plan.
Sample Size and Power	This study aims to evaluate the patient experience with new data collection methods and the association between new methods and the EHR-defined variables regarding disease severity and healthcare resource utilization, therefore no comparisons or hypothesis testing will be performed. In order to collect adequate information about the feasibility of these new data collection methods, approximately 200 PPD patients from the integrated delivery network (IDN) will participate in the study (100 in each group COPD and asthma). If we assume a dropout rate of at most 25%, we will have complete data on at least 150 patients, which will be sufficient to address feasibility of the new collection methods in two different cohorts. In addition, since this is a pilot study to assess feasibility of an interventional study that would use the data capture methods, a formal power calculation is not required.
Limitations	Participants included in this study will be selected from among those within the PPD IDN, therefore may not be representative of a sample of all COPD and asthma patients from the US. There will likely be a selection bias based on which patients are willing to participate in a study with multiple devices and due to established inclusion/exclusion criteria. Medication use and activity will be monitored using sensors so there is a risk that the patient's behavior may be altered.

TABLE OF CONTENTS

ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse event
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
EHR	Electronic Health Records
ERS-COPD	Evaluating Respiratory Symptoms in COPD
ePROs	Electronic patient reported outcomes
PPD	PPD
IDN	Integrated Delivery Network
IRB	Institutional Review Board
PACDC	Phenomic Analytics Clinical Data Core
VMUs	vector magnitude units

1 INTRODUCTION/BACKGROUND

Electronic health records (EHR) are becoming more common in clinical practice in the United States. This study aims to assess the feasibility of collecting increasing amounts of clinical study data from patients (e.g. sensor and web/app based methods) and their EHR to facilitate more efficient and meaningful research with acceptable quality.

2 OBJECTIVES

2.1 General Objective

To recruit small cohorts (n=100 each) of chronic obstructive pulmonary disease (COPD) and asthma patients from their usual healthcare environment to gain experience with novel, digital data collection methods combined with EHR extraction to explore feasibility of larger real world studies. Overall, we hope to assess how the use of EHR may be beneficial in recruiting populations for future clinical trials.

2.2 Specific Objectives

- To evaluate how representative the consented, study population is when compared to the eligible population.
- To develop a monitoring dashboard for integration of data from various devices
- To evaluate patient experience, data quality and consistency with novel, patient-data collection methods:
    - Mobile spirometry
    - Sensor for monitoring rescue medication use
    - Sensor for monitoring maintenance medication use
    - Physical activity monitor
    - Electronic patient reported outcomes (ePROs) – monthly CAT (COPD cohort), ACT (asthma cohort)
        - monthly PROactive – using the C-PPAC
        - For COPD only: EXACT PRO daily symptoms [ERS-COPD]
- To assess the relationships between EHR-based healthcare utilization (ambulatory care visits and hospitalizations for COPD or asthma exacerbations) and lab measures (specified below) with patient data remotely collected via methods outlined in previous bullet, for example.
    - EHR spirometry
    - Blood WBC, eosinophils, neutrophils (number and %)
    - Other blood biomarker samples if available (e.g. fibrinogen, CRP, periostin, sRAGE etc)

3 RESEARCH METHODOLOGY

3.1 Study Design

This is a prospective study that will include two cohorts of patients (COPD and asthma) identified via EHR database analyses (COPD and asthma diagnoses with and without specialist confirmation), recruited from sites of usual care. Participants will attend two visits with study team members at 0 and approximately 6 months, as most data will be captured either remotely via sensors and devices provided by GSK to the patients or via a data pull of EHR data. At the baseline visit, study team members will obtain written informed consent, distribute study devices, and provide instruction for proper use of study devices and platforms. Approximately

six months later, at the second visit, the patient will return study devices and complete an exit interview to provide relevant feedback on the study.

3.2 Study Population

3.2.1 Eligibility Criteria

3.2.1.1 Inclusion Criteria

All patients will be selected based on the following criteria in EHR.

Inclusion Criteria for COPD cohort:

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Provide signed and dated informed consent form.
- Be willing to comply with all study procedures and be available for the duration of the study.
- Age ≥ 40
- Diagnosed with COPD, defined as COPD listed on the patient's problem list and one of the following:
    - At least one inpatient hospitalization with a COPD diagnosis listed as the primary or secondary diagnosis (J41.x, J42.x, J44.x [chronic bronchitis], J43.9 [emphysema] or J44.9 [Chronic obstructive pulmonary disease, unspecified]) in the last 12 months *OR*
    - At least two outpatient encounters with a diagnosis of COPD exacerbation (J44.1), Acute bronchitis (J20.x), or bronchitis (J40) listed as the primary or secondary diagnosis, with different dates of service in the last 12 months *OR*
    - At least one emergency room encounter with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - At least two urgent care encounters with different dates of service, with a COPD diagnosis (J41.x, J42.x, J44.x, J43.9, J44.9) listed as the primary or secondary diagnosis in the last 12 months
- At least one order for an inhaled COPD medication during the prior year
- 12+ months of data available in the integrated EHR data prior to date of screening

Inclusion Criteria for Asthma cohort

- Provide signed and dated informed consent form.
- Be willing to comply with all study procedures and be available for the duration of the study.
- Age ≥ 18
- Diagnosed with asthma, defined as asthma listed on the patient's problem list and one of the following:
    - At least one inpatient hospitalization with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*
    - At least one emergency room encounter with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*

- at least two urgent care encounters, with different dates of service, with an asthma diagnosis (J45.x) listed as the primary or secondary diagnosis in the last 12 months *OR*
- At least three or more prescriptions or prescription refills in the past 12 months for any combination of the following: an inhaled glucocorticoid with or without a second controller (Montelukast, Theophylline, a long-acting beta agonist [LABA] alone), or a combination drug with a LABA and an inhaled glucocorticoid

- 12+ months of data available in the integrated EHR data prior to date of screening

Exclusion Criteria (screening question) for COPD cohort

- Inability/Unwillingness to use the required devices, or
- Inability to read and understand English

Exclusion Criteria (screening question) for Asthma cohort

- Inability/Unwillingness to use the required devices
- Inability to read and understand English
- Diagnosis of COPD listed on problem list

3.2.2 Sampling

PPD located in PPD has a service area that is largely rural, mostly Caucasian, remarkably stable population (i.e., a very low out-migration rate), and a higher percentage of elderly patients (aged 65+) than the national average. PPD catchment area is one of the oldest and sickest in the nation in terms of multiple co-morbidities. Patients will be selected based on the criteria previously described.

3.3 Study Visits

3.3.1 Recruitment

Potential participants will be identified by a Phenomic Analytics Clinical Data Core (PACDC) data broker through a data pull of EHR data or by review of PPD clinical dashboard. Potential subjects will be invited to participate.

3.3.2 Baseline Visit

A baseline clinic visit will be scheduled with interested patients and a study team member. At the visit, the potential participants will be informed of all pertinent details, risks, and benefits of the study via the study consent form. A study team member will answer any patient questions and patients will be given adequate time to consider participation. Written informed consent will be obtained using the study consent form. After consent, the participant will receive study devices and training on proper use of the devices. Participants will complete a baseline questionnaire. Data will be collected remotely from the devices and platforms for six months.

3.3.3 Six Month Visit

After six months (+/- 2 weeks), a second visit will be scheduled with the participant and a study team member. At the second visit, the participant will return the study devices and will complete an exit interview to obtain relevant feedback from the patient's perspective on the study. Exit interviews will be performed by PPD personnel.

3.4 Study Duration

3.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 6 months.

3.4.2 Approximate Duration of Study

200 patients will be enrolled over an eight-month period, including 100 in the asthma cohort and 100 in the COPD cohort. Each patient will be followed for approximately six months after consent and enrollment into the study.

3.5 Data Source / Data Collection

Integrated EHR records (primary and specialty care) are the key source for retrospective analysis and for identifying patients. Digital data collection from patient reports, devices, sensors, and EHR records over six months are the key sources for the prospective analysis. A summary of variables to be extracted is included in Section 6.4. The study database will be housed on a third-party vendor's secure network. Data from the study devices, including the mobile spirometry device, the sensors for rescue and maintenance medications, activity monitors, and the ePRO platform will flow directly to the database on Vendor A's network. EHR data will be extracted and combined with device data in the database housed on Vendor A's network. Vendor A will de-identify the study database and send the data set to Vendor B. Participants will provide PPD staff with feedback on the study, the study devices, and ePRO platform during the study Exit Interview.
PPD data is part of the mini-sentinel monitoring system which means their data set meets standard criteria for data integrity and quality.

3.6 Endpoints

We will be measuring the following:

- Spirometry
- Activity (Steps and daily activity)
- Patient experience of physical activity
- COPD symptoms Exacerbations (COPD cohort only)
- Rescue and maintenance medication use
- Primary care and secondary care visits specific to each cohort and in general,
- Number of days in hospital, new prescriptions, number of albuterol inhalers specific to each cohort
- CAT (COPD cohort) and ACT (asthma cohort)
- Exit Interviews

3.7 Sample Size/ Power Calculation

This study aims to evaluate the feasibility of measuring patient experience with new data collection methods and the association between new methods and the EHR-defined variables regarding disease severity and healthcare resource utilization, therefore no comparisons or hypothesis testing will be performed. In order to collect adequate information about the feasibility of these new data collection methods, approximately 200 PPD PPD patients will participate in the study (100 in each group COPD and asthma). If we assume a dropout rate of at most 25%, we will have complete data on at least 150 patients, which will be sufficient to address feasibility of the new collection methods in two different cohorts. In addition, since this is a pilot study to assess feasibility of an interventional study that would use the data capture methods, a formal power calculation is not required.

4 DATA ANALYSIS CONSIDERATIONS

Descriptive statistics will be presented as frequency and percentages, means and standard deviations, medians and interquartile range (IQR), and for categorical variables, normally distributed and non-normally distributed continuous variables, respectively. Spearman correlations will also be assessed between endpoints. The following will be analyzed over the study period:

- Spirometry (mobile and clinic)
  - Change from baseline in FEV1
- Activity
  - Median/mean steps per day
  - Median/mean daily activity level based on vector magnitude units (VMUs)
- PROactive total score and subdomains Symptoms
- E-RS:COPD symptoms Exacerbations (COPD cohort only)
  - EXACT-defined events
- HCRU
  - Median/mean number of primary care visits for COPD/asthma conditions
  - Median/mean number of secondary care visits (inpatient, urgent care and ED visits) for COPD/asthma conditions
  - Median/mean number of all primary care visits
  - Median/mean number of all secondary (inpatient, urgent care and ED visits) care visits
  - Summary of new prescriptions for any COPD/asthma treatments
  - Number of days in hospital for COPD/asthma
  - Number of albuterol inhalers (adjusted to equivalence of 200 actuations) prescribed
- ePRO
  - Mean change from baseline in CAT (COPD cohort)

- Mean change from baseline in ACT (asthma cohort)

All analyses will be described in more detail in the full statistical analysis plan.

5 LIMITATIONS

Participants included in this study will be selected from among those within the PPD PPD (IDN), therefore may not be representative of a sample of all COPD and asthma patients from the US. There will likely be a selection bias based on which patients are willing to participate in a study with multiple devices. Medication use and activity will be monitored using sensors so there is a risk that the patient's behavior may be altered.

6 STUDY CONDUCT, MANAGEMENT & ETHICS

6.1 Ethics Committee/IRB Approval

The study will be submitted for Institutional Review Board (IRB) review.

6.2 Informed Consent

All participants will provide signed and dated informed consent prior to initiation of any study activities via the study consent form.

6.3 Data Protection

All data collected in this study will be strictly confidential in accordance with all appropriate legislation. Data from study devices and ePROs will be encrypted and automatically transmitted to Vendor A. EHR data, including PHI such as names, dates, and MRNS, will also be encrypted and sent to Vendor A via a PPD approved, secure portal. Vendor A's Insight Platform maintains a HITRUST certification to protect patient data. Vendor A will integrate the data from study devices, ePROs, and PPD on their secure network. Vendor A will de-identify the integrated study data set and transfer the de-identified data set to Vendor B.

Study staff will be instructed to maintain complete confidentiality of all collected data. Patient files will be kept on secure servers. The final study report will not contain any patient identifying information. Participants will be assigned a unique participant number in the final data set to ensure confidentiality and anonymity. Interview transcripts will be identified by this unique participant number and will not have any identifiers associated with the individual.

6.4 Personally Identifiable Information (PII)

The final data set will be de-identified and will not contain PHI. However, Vendor A will have access to participant names, dates, and MRNs to integrate data from multiple data sources including study device data, ePRO, EHR data, and Exit Interview transcripts. Vendor A will remove PHI elements from the dataset. PHI accessed for recruitment will only be seen by PPD staff. The final data set, housed by Vendor B, will be de-identified.

The data in the table below, including relevant dates, will be collected. The table also outlines who will have access to each type of data.

	PPD	GSK	Vendor A	Vendor B
Names	X		X	
Medical record number	X		X	
Telephone number	X			
Date of birth/date of death	X		X	
Information relevant to all encounters, admissions/discharges, clinical procedures, medications administered, problem list entries, and lab values	X	X	X	X
Baseline demographic variables of patients (age, sex, ethnicity, tobacco use, comorbidities)	X	X	X	X
Clinical outcomes and procedural related complications	X	X	X	X
Information from study devices, sensors, and electronic platforms	X	X	X	X
Information gather from patient interviews at study visits	X	X	X	X

Records of data generated in the course of the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

6.5 Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

While this study does not involve the direct solicitation of adverse experience information, it is possible that participants could spontaneously describe potential adverse events that occurred during the course of their normal clinical care.

As part of the site orientation process, study team members will be trained in the recognition of potentially-reportable adverse events.

If an AE (serious or non-serious) or product complaint is reported spontaneously by a subject during the course of the study and the subject associates the AE with any specifically named GSK product, the following AE reporting process will be completed:

- The site staff will complete the AE reporting form (including the patient study ID number, their age and sex, the patient's description of the adverse event, and the product the patient named).

The site staff will transmit the report to the GSK study team within 24 hours of being made aware of the AE.

Patients will be asked about adverse events related to the use of the devices provided during the study (mobile spirometer, device sensor, activity monitor and tablet) at regular intervals via the study provided tablet. These data will not be monitored in real time and patients will be educated on the need to contact their physician directly should they have any medical concern.

7 EXTERNAL INVOLVEMENT

7.1 Third Party Suppliers

- Vendor A: Accenture (device integration, EHR integration)

  Accenture, LLP
  1160 West Swedesford Road
  Berwyn, PA, 19312
  USA

- Vendor B: Medidata (ePRO, data and visualization platform)

  Medidata Solutions, Inc.
  350 Hudson Street, 9th Floor
  New York, NY 10014
  USA

- ActiGraph (activity monitors)

49 East Chase Street.
Pensacola, FL 32502
USA

- Propeller Health (sensors for MDI and DPI)

  634 West Main Street, Suite 102
  Madison, WI 53703
  USA

- MIR (mobile spirometry)

  5462 S. Westridge Drive
  New Berlin, WI 53151
  USA

7.2 External Expert/Health Care Professionals (Consultants & Research PIs)

PPD MD, PhD.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent and HIPAA Authorization

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

We are requesting a partial waiver of HIPAA authorization for pre-screening and contacting patients about the study will be requested by the IRB to allow the identification of potentially eligible participants from the medical record.

8.2 Protection of Human Subjects Against Risks

There is a risk of loss of confidentiality as PHI will be collected as part of the study. To minimize this risk, hard copy data will be stored in a locked environment that is only accessible only to the study team members and electronic data will be stored on a secure network (either PPD or Vendor A's HITRUST certified network). EHR data, including PHI, will be sent to

Vendor A through a secure portal approved by PPD governance. Vendor A will de-identify the dataset before sending the data set to Vendor B. All data transmissions will be encrypted. Only aggregate data without personal identifiers will be included when presenting results or submitting manuscripts for publication.

All subjects will be trained on the use of each device - it is important that all instructions be followed to minimize potential risks due to misuse.

Appendix 1. Schematic of a Prospective Study:

Clinic Visit 1
Day 1

- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Demonstrate devices
- Baseline data collection

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During the 6-month study period

- Perform mobile spirometry weekly
- Wear the activity monitor daily
- Complete the diary card daily (for COPD subjects)
- Complete the CAT/ACT monthly
- Attach sensors to rescue and maintenance inhalers (where appropriate)

⇩

Clinic Visit 2
Month 6

- Exit Interview
- Retrieval of devices