



MOP 11

**EXACERBATION SUBSTUDY
PROCEDURES**

**Version 1
July 30, 2014**

1.0 Objectives and Background for the Exacerbation substudy

1.1 Introduction

The SPIROMICS Exacerbation Substudy is a component of the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), an observational cohort study of COPD. The Exacerbation Substudy contributes to the two primary aims of SPIROMICS the identification of 1) homogeneous subgroups of COPD and 2) intermediate biological and clinical outcome measures for use as clinical trial endpoints. Exacerbations are considered sentinel events in the natural history of COPD. Their frequency and severity have been associated with multiple negative implications including worsening health status, worsening pulmonary function, increasing cost of care, and increased mortality.

1.2 Background

Although the topic remains controversial, a generally accepted definition of acute exacerbations of COPD is “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.” Several approaches to defining an acute exacerbation have been advocated, including symptom-based and health care utilization (HCU)-based definitions. Symptom-based definitions are the most frequently used for patient care. Importantly, several investigative groups have suggested that a significant proportion of patients underreport these events to health care professionals. HCU definitions have been utilized to circumvent difficulties with quantifying symptom changes, although this approach captures fewer events and does not standardize or quantify the symptomatic changes associated with diagnosis or treatment.

The limitations of the current definitions are, in part, responsible for the wide variety of reported rates of acute exacerbations in clinical trials and cohort studies. This variability may reflect the nature of data collection (prospective versus retrospective), disease severity, medications administered, vaccinations, and smoking status. In addition, it has been difficult to accurately define the natural course of individual acute exacerbation episodes to accurately quantify the total burden of acute exacerbations in individual patients.

The EXACT-PRO (**EX**acerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcome) is a multi-sponsor initiative that brought together clinical, research, methodology, and regulatory experts to develop a new PRO instrument to measure the frequency, severity, and duration of exacerbations in clinical trials of COPD. The PRO uses 14 items assess respiratory (breathlessness, cough and sputum, and chest symptoms) and systemic (tired/weak, sleep disturbance, psychological state, and difficulty with sputum) symptoms associated with COPD exacerbations, as described by patients and confirmed by clinical experts in COPD. The EXACT total score is used to define and characterize symptom-defined exacerbations. Three domain scores embedded in the instrument may be used in exploratory analyses to further understand the nature of symptom-defined or HCU events. EXACT total and domain scores were internally consistent and reproducible, correlated with physiologic measures of disease severity, health status, and symptoms. The scores changed over time and differentiated acute and stable patients.

Exacerbations are felt to be intensely inflammatory events with varying etiologies, including changes in ambient air quality and viral and bacterial infections. The varied definitions and etiologies and the clinical implications have led to aggressive efforts to identify biological signatures for individual episodes. A better understanding of the nature of these events and their symptomatic manifestations has the potential of leading to an improved understanding of the biological genesis of exacerbations and provide novel therapeutic approaches. In this regard, numerous groups have examined potential lung or systemic biomarkers of exacerbations. These concepts particularly apply to an understanding of HCU and symptom-defined events.

1.3 Goals of the Exacerbation Substudy

SPIROMICS offers a unique opportunity to address the biological processes underlying an acute exacerbation using subject driven, HCU and symptom-based definitions. As such, the overall objectives of the exacerbation substudy are to:

- a. Obtain clinical data and specimens on SPIROMICS participants before and during an acute COPD exacerbation defined by
 - i. Health care utilization triggered by the subject, or
 - ii. Symptomatic change (triggered by an EXACT defined threshold)
- b. Describe symptomatic changes occurring around HCU and symptom-defined (EXACT) events and their relationship to clinical and specimen data,
- c. Characterize the non-exacerbation “stable” state in COPD using the EXACT, including:
 - i. Symptom variability (EXACT),
 - ii. Clinical data and specimen parameters during a stable state (baseline),
 - iii. The relationship between clinical and specimen data and symptom severity and variability.
- d. Explore the characteristics of stable patients, defined as those who do not experience HCU or symptom-defined (EXACT) events during the sub-study period, using baseline clinical data and specimens and compare these characteristics with patients who experience HCU and/or symptom-defined events.
- e. Examine the relationship between HCU and symptom-defined exacerbation frequency during the first one-year period of follow-up for exacerbations and health outcomes, including 12-month change in lung function and COPD health status, and longer term morbidity and mortality, with the latter derived from long-term data from the larger SPIROMICS study.

2.0 Study Design

This is a prospective, longitudinal, naturalistic, observational study, which will allow the assessment of subject driven HCU and symptom-defined (EXACT threshold triggered) exacerbation events over time. This is an event driven study that will enroll up to 400 patients in order to capture 198 total events. The study duration will vary depending on the number of events observed but will be at least 12 months and a maximum of 24 months for each subject.

To maximize the number of each type of event assessed and minimize bias that could negatively influence interpretation, the study is divided into two waves: Wave 1 and Wave 2.

2.1 Wave 1

In Wave 1 of the substudy, 300 participants will be asked to complete an electronic diary with the EXACT each night before bed for up to 24 months and for a minimum of 12 months. The EXACT scores are not available to the participant. Participants will be instructed to contact the clinical center for a HCU event. The coordinator will query the study subject using a simple case report (CEA) to help determine whether the participant should come into the clinic for a visit. If a visit is needed, the coordinator should schedule the visits as soon as possible but no later than 72 hours after the participant contacted their primary care physician or changed their medications. Management of the acute event will be at the discretion of the subject's primary physician; this may or may not be a SPIROMICS investigator.

If during the SPIROMICS visit the event is felt by the investigator to be an acute exacerbation, a complete study assessment will be performed and the electronic diary will be re-programmed to alert the subject of an acute, sustained worsening in symptoms scores, using pre-defined change thresholds in EXACT scores (12 point increase for 2 days or 9 point increase for 3 days). The subject will be instructed to notify the SPIROMICS center to arrange a visit and assessment if such an EXACT triggered event occurs. Given our experience with the EXACT it is anticipated that the distribution of events will be as follows:

Table 1a. Expected Number of Exacerbations and Study Visits over 12 Months - Wave 1

| Overall | N | HCU Events | HCU Visits | EXACT Events | EXACT Visits | TOTAL VISITS |
|-------------------------|----------|-------------------|-------------------|---------------------|---------------------|---------------------|
| Frequent exacerbators* | 200 | 120 | 79 | 32 | 21 | 100 |
| Infrequent exacerbators | 100 | 22 | 15 | 6 | 4 | 19 |
| Total | 300 | 142 | 94 | 38 | 25 | 119 |

* - at least one treated exacerbation in the prior year.

2.2. Wave 2

Wave 2 will only be initiated at a site if the number of HCU events is fewer than anticipated. The number of subject-initiated HCU and symptom-defined events at each site will be monitored by the GIC during Wave 1. If the number of events at any given site is fewer than anticipated, Wave 2 will be initiated at that site. It will be smaller in scope (N=100 new patients enrolled) but with the EXACT trigger active on the PDA. The subject will be instructed to come to the clinical center for either a symptom-defined (EXACT) or subject-initiated HCU event. As with Wave 1, subjects will be followed for up to 24 months and for a minimum of 12 months.

Table 1b. Expected Number of Exacerbations and Study Visits over 12 Months - Wave 2

| | N | Event 1 | Visits 1 | Events 2 | Visits 2 | TOTAL VISITS |
|-------------------------|----------|----------------|-----------------|-----------------|-----------------|---------------------|
| Frequent exacerbators* | 75 | 45 | 30 | 9 | 6 | 36 |
| Infrequent exacerbators | 25 | 8 | 5 | 1 | 1 | 6 |
| Total | 100 | 53 | 35 | 10 | 7 | 42 |

* - at least one treated exacerbation in the prior year.

3.0 Sampling and Recruitment

3.1 Recruitment and Examination Goals by Center

For Wave 1, each CORE study site will enroll a total of 66-67 participants, 50 frequent exacerbations and 16-17 infrequent exacerbators. The number of events in Wave 1 will be monitored by the GIC. If the number of expected events is less than projected, Wave 2 will be activated at that site. For Wave 2, each site will recruit 12-13 frequent exacerbators and 4 infrequent exacerbators.

4.0 Recruitment, Eligibility, and Enrollment

4.1. Recruitment

Strata 3 and 4 participants who consent to being contacted about participating in additional substudies will be approached at any time after Baseline clinic visit to determine interest in the Exacerbation Substudy. Interested participants will then be screened and consented for the substudy. Clinic sites can either enroll participants in the Exacerbation Substudy on the same day as the clinic visit or schedule the participant for an enrollment visit at any time after the main study clinic visit.

If co-enrolled in the bronchoscopy substudy there should be a delay of at least four weeks between bronchoscopic procedure and enrollment in the exacerbation substudy.

4.2. Informed Consent

The informed consent is the first data collection item administered for the Exacerbation Substudy. A signed informed consent means the patient fully understands the requirements of the procedures and assessments included in the study as well as the risks of those procedures/assessments. It is important that the patient fully comprehends the time commitment required for participation, as well as the potential implications of specimen storage and dissemination of study findings. Exacerbation informed consent is recorded on the ECT form.

4.3 Participant Eligibility

Participants in the Exacerbation Substudy should meet all the inclusion/exclusion criteria of the main SPIROMICS study. In addition, only participants from Strata 3 or 4 may be enrolled in this substudy. Subjects can only be enrolled once in the exacerbation study, and in only one Wave of the substudy. Study coordinators should complete the Exacerbation Inclusion/Exclusion Criteria Form (EIE) to determine if a participant is eligible.

As shown in Table 2, participants in the Exacerbation Substudy will fall into one of two substrata:

- 1) Sub-stratum one (COPD patients at risk for acute exacerbation) – History of at least one exacerbation in the last 12 months. Subjects with two or more events in the previous year will be of particular interest and **should be prioritized** for enrollment.
- 2) Sub-stratum two (COPD patients not at risk for acute exacerbation) – History of no exacerbations in the last 12 months.

Table 2. Exacerbation Substudy Substrata

| Overall | Wave 1 | Wave 2 |
|--|---------------|---------------|
| Frequent exacerbators (history of one or more exacerbations) | 200 | 75 |
| Infrequent exacerbators (no exacerbation in previous year) | 100 | 25 |
| Total | 300 | 100 |

Additional inclusion criteria:

- Must be enrolled in the main SPIROMICS study
- History of ≥ 1 exacerbations which required antibiotics, steroids, ER visit or hospitalization within the past 12 months, but > 30 days without a HCU-defined exacerbation prior to substudy enrollment (Sub-stratum 1 only);
- History of no exacerbations within the past 12 months (Sub-stratum 2 only)
- Enrolled in strata 3 or 4 of the main SPIROMICS study

Additional exclusion criteria:

- HCU-defined exacerbation within the past 30 days;
- SPIROMICS investigator confirmed primary diagnosis of asthma;
- Visual or cognitive impairment that would interfere with participation.

4.4. Enrollment

After confirming eligibility via the EIE and entering the consent tracking form (ECT). To familiarize participants with the PDA, study coordinators will have participants complete the PDA and EXACT-PRO training screens.

Coordinators should provide participants with a copy of the Participant Information Card (available on the study website). Participants will be instructed to contact the study site if participants contact their physician because of worsening of COPD symptoms or if the participant makes a change in medical treatment as directed by his or her physician.

5.0 Exacerbation Clinic Visits

5.1. Determining Clinic Visit Eligibility

When a participant contacts the site, the coordinator will first assess whether the contact was prompted by HCU or symptoms/EXACT. In either case, the coordinator will screen the subject by phone using the Coordinator Exacerbation Assessment Form (CEA).

For Wave 1 and Wave 2, one participant may have up to three confirmed exacerbation study visits. Possible exacerbation events after that point will not be scheduled for a study visit.

5.1.1. Wave 1 – First Visit (HCU Visit)

For Wave 1, participants will be instructed to contact the clinical center to schedule a visit if they 1) satisfy criteria on an information card provided to the subject at the time of enrollment or 2) feel they are having an exacerbation. The coordinator will screen the subject by phone using a simple case report form (CEA). Participants should be encouraged to follow-up with their primary care provider.

In Wave 1 for the first visit as participant is eligible to come in for additional screening if:

- 1) He or she contacted the primary caregiver OR went or considered going to the emergency department or urgent care
- 2) He or she changed his/her medical treatment as directed by his/her physician because of the change in symptoms (i.e., filled a prescription of antibiotics)

If one of the above criteria are met and the participant has not previously had a confirmed HCU exacerbation as part of the Exacerbation Substudy, then he or she should be scheduled for a clinic visit within 72 hours of contacting the primary care provider or changing medical treatment as a result of the change in symptoms (whichever action occurred first starts the 72 hour clock).

If the coordinator is unable to schedule a visit, the participant is encouraged to follow-up with the primary care physician (specific language is provided on the CEA). The participant should continue to record symptoms on the daily diary.

5.1.1.1 Wave 1 – Subsequent Visits

For Wave 1, after the first clinically confirmed HCU exacerbation (confirmation via a clinic visit), participants should be instructed to contact the clinical center to schedule a visit if they meet the criteria for a HCU visit described in Section 5.1.1 OR they receive a message on their PDA to contact the clinic (the message will be triggered by EXACT scores meeting the threshold for a symptom-defined event). As with the first visit, the participant must be seen at the clinic within 72 hours of contacting the primary care physician, going to the ER/urgent care, considering going to the ER/urgent care, changing their medical treatment, or the EXACT triggering. **The 72 hour clock begins with whichever of the above events occurred first.**

As with the first visit, the coordinator will complete the CEA, first determining whether the visit is HCU, symptom/EXACT triggered, or both.

If the site is unable to schedule a visit, the participant continues recording the daily diary and is instructed to contact the site at the next possible exacerbation.

5.1.2. Wave 2 Visits

For Wave 2, participants will be instructed to contact the clinical center to schedule a visit if 1) they satisfy criteria on the information card worksheet, 2) feel they are having an exacerbation, or 3) receive a message on their PDA to contact the clinic (the message will be triggered by EXACT scores meeting the threshold for a symptom-defined event). Unlike Wave 1, the EXACT trigger will be active from the beginning of Wave 2, meaning there is no initial HCU visit required.

As with Wave 1, when participants contact the site, the coordinator will assess the event using the CEA. As with Wave 1, an HCU event is defined as one where the participant has had a change in medical treatment, either as the result of contacting the primary care physician or self-treatment by filing previously prescribed medications. An EXACT-event is one where the EXACT alerts the participant to contact the site AND the participant reports no HCU. As with the Wave 1, the participant must be seen at the clinic within 72 hours of contacting the primary care physician, going to the ER/urgent care, considering going to the ER/urgent care, changing their medical treatment, or the EXACT triggering. **The 72 hour clock begins with whichever of the above events occurred first.**

If the site is unable to schedule a visit or the event is not clinically confirmed by a study investigator, the participant continues recording the daily diary and is instructed to contact the site at the next possible exacerbation.

5.2 Preparing the Participant for the Clinic Visit

In order to obtain accurate results on the Pulmonary Function Tests (PFTs) and to reduce variability in the Biospecimen Collection, subjects should be asked during the scheduling phone call to withhold/refrain from the following activities for the duration indicated prior to the study visit:

Vigorous exercise (0.5 hours)
Smoking (1 hour)

Participants do not need to be fasting for the Exacerbation Clinic Visit.

The study participant should be told to fast starting at midnight the night before the exam. A snack is provided about two hours after the start of the examination. Fasting means no consumption of food or drinks (including alcohol), with the exception of water. The study coordinator should confirm that there are no medical reasons why the subject should not fast for this length of time, and alternate arrangements should be made, if necessary, after consulting with the clinical center PI. The study coordinator should also ask whether the patient has any dietary needs or restrictions, in order to ensure that an appropriate snack is available.

During the scheduling phone call, it is important that study staff remember to:

- explain where the clinic is located
- relay the appointment time
- ask about any special medical conditions (including temporary exclusion criteria and dietary restrictions for the study-provided snack)
- provide brief but complete instructions
- answer questions

5.3 Exacerbation Visit

For all clinic visits initiated by this study, participants will undergo an initial assessment to determine whether the event is a COPD exacerbation. The site will complete the Exacerbation Assessment Form (EAF), which includes a review of symptoms and medications as well as a clinician-completed section that provides a medical conclusion, including diagnosis of exacerbation or other diagnosis and treatment plan.

If the physician determines the event is an exacerbation, the coordinator should proceed with the rest of the visit, collecting Biospecimens, PFTs, spontaneous sputum, and questionnaires.

If the physician determines the event is not a COPD exacerbation, the participant is thanked for their time and instructed to continue to complete the daily diary.

5.3.1. Physical exam

The clinic visit for the confirmed events will follow the same procedures as described in Section 6.4 of the main SPIROMICS protocol and the study MOPs.

Participants will not have a CT scan specifically as part of this substudy.

5.3.2. Weight measurement

Study coordinators will collect the participant's current weight as described in Section 6.4.2 of the protocol and MOP 1. No other anthropometric measurements will be collected as part of the Exacerbation Substudy. Weight measurement will be collected on the Exacerbation Assessment Form (EAF).

5.3.3. Blood pressure

Study coordinators should follow the procedure for collecting blood pressure measurements outlined in MOP 1. Blood pressure should be collected on the Blood Pressure Form (BPF).

5.3.4. Biospecimen Collection

Biospecimens are only collected if the physician determines the participant is having a COPD exacerbation.

Biospecimens should be collected prior to initiating PFTs.

Blood and urine collection and processing in the Exacerbation Substudy will be the same as the baseline specimen collection in the main study. Coordinators should refer to MOP 4 and Section 6.4.5.3 in the study protocol for procedure details. Coordinators will use the BIO form as in the main study. Exacerbation sample Lab IDs will be recorded on the EID form.

The following blood samples should be collected:

- 2 tubes of blood allowed to clot for serum, which will be processed within 2 hours of collection as described in the Biospecimen Collection and Processing Manual of Procedures, MOP 4, for future batch shipment on dry ice to the GIC.
- 1 tube of plasma collected in a P100 tube for preservation of plasma proteins in anticipation of proteomics analyses. Plasma should be processed within 2 hours of collection as described in MOP 4 for future batch shipments on dry ice to the GIC.
- 1 tube of plasma collected in EDTA for submission directly to the local clinical laboratories for complete blood count with white blood cell differential and platelet count.

- Two tubes of blood collected in EDTA for plasma and DNA which will be processed within 2 hours of collection as described in MOP 4 for future batch shipment to the GIC.
- 1 tube of blood in PAX-Gene™ RNA tube. This tube will be shipped to the GIC laboratories for RNA extraction (including preservation of micro RNA species).
- 1 tube of plasma collected in citrate to be processed for plasma and buffy coat cells within two hours for future batch shipments on dry ice to the GIC.

Sites will also collect a urine sample, following the same procedures as the main study (See MOP 4).

Data on collection and processing of blood and urine will be recorded on the Biospecimen Information Form (BIO).

5.3.1. Pulmonary Function Testing

Pulmonary Function Testing will be conducted in the same manner as the main SPIROMICS study (see MOP 2 and Section 6.4.1 of the study protocol). In summary, prior to PFTs, participants will be asked to withhold/refrain from vigorous exercise (0.5 hours), smoking (1 hour), eating a large meal (2 hours), alcohol (4 hours), and caffeine (6 hours). Unlike the main study protocol, participants should not withhold breathing medications, namely inhaled albuterol, ipratropium, or any other bronchodilators. As in the main study coordinators should complete the Pulmonary Function Testing (PFT) form prior to starting spirometry.

Data will be collected in the following order:

- 1) Slow vital capacity (expiratory vital capacity method), including measurement of inspiratory capacity after a stable (at least 3 breaths) end-expired volume
- 2) Forced vital capacity
- 3) Bronchodilation with albuterol sulfate HFA and ipratropium bromide HFA four puffs each (30 minute waiting period before post-bronchodilator SVC or FVC)
- 4) Slow vital capacity, 30-120 minutes post bronchodilator (expiratory vital capacity method)
- 5) Forced vital capacity, 30-120 minute post bronchodilator

Exhaled CO will also be collected in the Exacerbation Substudy but a six minute walk will not.

Spirometry and eCO data will be collected using the Spirometry Data Form (SDF) form and the study spirometer.

5.3.5. Spontaneous sputum collection

5.3.5.1 Participant preparation

Participants should be seated in a non-rolling chair for sample collection. A baseline spirometry should be obtained. These values should be reviewed by a qualified healthcare provider prior to beginning the spontaneous collection.

Sites are encouraged to complete the spontaneous sputum collection immediately after the PFTs are completed. This allows the coordinator to use to recently collected spirometry data for a baseline value and ensures the participant is adequately dosed with bronchodilators prior to beginning the procedure.

If sputum is not collected immediately following the PFTs, participants should be re-dosed with albuterol as described in the SPIROMICS PFT Procedures (MOP 2).

5.3.5.2 Sample Collection

Step 1: Bring the subject to the sink, and have him/her gently rinse the mouth and gargle then spit contents into the sink.

Step 2: Have the subject clear the back of his/her throat, i.e. scrape the back of the throat and roof of mouth (demonstrate), and again expectorate this into the sink.

Step 3: Have the subject blow his/her nose and discard.

Step 4: Have the subject give a good cough effort from the chest (and not the throat) – and this must be done **without scraping the throat** – ie. passively bring the sample past the throat then expectorate the sputum into the specimen cup. Once the subject can no longer bring up sputum, repeat spirometry.

Date and time of spontaneous sputum collection is recorded on the SSC form.

Process samples using the same procedures described in MOP 5.

5.3.6. Questionnaires

A subset of the patient reported outcomes collected in the main study will be collected for the Exacerbation Substudy. In addition, two new global assessments of COPD health will be collected.

5.3.6.1 COPD Assessment Test

The COPD Assessment Test (CAT) is an eight-item questionnaire. These eight questions cover cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. Each question is rated on a likert scale ranging from zero to five, with high scores indicating poorer COPD-related health status. The questionnaire takes two to five minutes to complete.

5.3.6.2. Modified Medical Research Council Dyspnea Scale

The Modified Medical Research Council Dyspnea Scale (mMRC) is a five-item instrument to assess a patient's degree of breathlessness in relation to physical activity. Participants are asked to read each brief description of an activity and then select the statement that best describes their experience with dyspnea. This scale is used in calculating the BODE index, and takes approximately one minute to complete (Mahler et al, 1988).

5.3.6.3. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire. It has two subscales with seven questions each. One measures anxiety and the other measures depression (Funk et al, 2009). Each item is rated 0-3 resulting in scores between 0-21 for each subscale (Snaith, 2003). Scores ≥ 8 in either subscale indicate possible depression or anxiety (Funk et al, 2009). The questionnaire takes approximately 2 to 5 minutes to complete (Snaith, 2003).

5.4. Exacerbation Resolution

In order to distinguish between one exacerbation and another, it is important to assess whether an exacerbation has resolved. Exacerbation resolution is only assessed after a confirmed HCU exacerbation clinic visit. How this is assessed is dependent on the type of exacerbation visit.

5.4.1. HCU Exacerbation Resolution

In order to assess whether a HCU exacerbation has resolved, the study coordinator will contact the participant 28 days after the clinic visit to complete the Exacerbation Resolution Form (EEF). If the participant reports the exacerbation has resolved, the coordinator indicates this on the form. If the participant indicates the exacerbation has not resolved, the coordinator should contact the participant again in seven days to assess whether the exacerbation has resolved. The coordinator will contact the participant up to four more times (i.e., 28 additional days). If the participant continues to report the exacerbation as unresolved, the coordinator will note it on the form but will not continue to follow-up.

5.4.1. Wave 1 – First HCU Clinic Visit

In Wave 1, after the first HCU clinic visit, the EXACT trigger is not activated until the confirmed HCU exacerbation is resolved.

Twenty-eight days after the HCU exacerbation visit in Wave 1, the study coordinator will contact the participant to determine whether exacerbation symptoms have resolved. If the symptoms have not resolved, the coordinator will contact the participant again in seven days. Coordinators should repeat contacts every seven days until symptoms resolve OR more than 56 days have elapsed since the HCU exacerbation visit. When the participant reports his/her symptoms have resolved or more than 56 days have elapsed since the visit, the PDA must be updated to allow symptom-driven event triggering. To update the PDA, the coordinator will

instruct the participant to enter a site-specific pin that will activate the EXACT-PRO symptom visit trigger/pop-up message.

Participants are not eligible for another clinic visit, HCU or symptom/EXACT-triggered, until the previous HCU exacerbation is resolved or it has been 56 days since the clinic visit.

5.4.2. Wave 1 – Subsequent HCU Clinic Visit

In Wave 1 for subsequent HCU exacerbation clinic visits, the coordinator will follow-up to assess resolution but no change in the PDA is indicated regardless of the resolution status. Participants are not eligible for another clinic visit, HCU or symptom/EXACT-triggered, until the previous HCU exacerbation is resolved or it has been 56 days since the clinic visit.

5.4.3. Wave 2 –HCU Clinic Visits

In Wave 2 HCU exacerbation clinic visits are followed-up by the coordinator but no change in the PDA is indicated regardless of the resolution status. Participants are not eligible for another clinic visit, HCU or symptom/EXACT-triggered, until the previous HCU exacerbation is resolved or it has been 56 days since the clinic visit.

5.4.2. Symptom/EXACT Event Resolution

In either Wave 1 or 2, after a symptom/EXACT clinic visit, the event is considered resolved using an algorithm internal to the EXACT that assesses the participant's return (or not) to his or her baseline scores. This is handled by the PDA and the coordinator is not required to contact the participant to establish event resolution. The EXACT will not trigger the participant to come in for a visit until the EXACT has re-established baseline.

6.0 Tracking and Follow-up Information

6.1 Monthly Contacts

Participants in the Exacerbation Substudy will be contacted once a month for the duration of the substudy.

Calls should occur within 7 day window before and after the 'target' date for the contact. Coordinators should make every possible attempt to reach participants by phone for the monthly calls within the window. If unable to administer the Monthly Contact Form within the window, the coordinator should continue to attempt contact with the participant. If the next monthly call window opens before a previous call has been completed; the previous Monthly Contact Form should be set to permanently missing in the DMS. In addition to the MCF, the coordinator will administer the COPD Assessment Test (CAT).

Every three months the monthly contact will overlap with the Quarterly Contact for the main study. When this happens the Quarterly Follow-up Call form (FUQ) takes the place of the monthly contact form (NOTE: The FUQ will be collected in the main study DMS, not the

Exacerbation Substudy DMS). When this overlap occurs, the coordinator should also administer the CAT in addition to the FUQ.

6.2 Daily Symptom Diary (EXACT)

Participants will be given a PDA to enter symptom daily every night before bed. Study sites will be alerted when participants fail to complete the diary for 3 consecutive days. Study sites will need to contact the participant to encourage compliance (NOTE: Study sites should consider whether to complete the monthly contact during a compliance reminder call).

In Wave 1 after the first HCU event and in Wave 2 at all times, participants may receive an alert telling them to contact the site regarding a possible event. These symptom-driven events indicate the participant met a threshold of increased (from baseline) symptoms. Participants cannot see the EXACT score used to calculate these results.

6.3 Participant Withdrawal

A study subject can be withdrawn from the Exacerbation Substudy at the subjects request or at the PIs discretion, including a situation where the clinical center PI determines that it is unsafe or unethical for the subject to continue in the study.

Subjects may withdraw at any time for any reason. At the time of withdrawal, subjects can either 1) decline to provide any more data or specimens to the substudy but allow use of previously collected data and/or specimens, 2) withdraw all their data from substudy databases and request that any stored samples be destroyed, or 3) withdraw some portion of the data collected (i.e., subjects may withdraw specimens but not exam data or vice versa).

If a subject chooses to withdraw from the Exacerbation Substudy, the study coordinator will conduct an exit interview to determine the disposition of the subjects' study data. This information should be recorded on the EWF – Exacerbation Substudy Withdrawal Form. The subject may decline to participate in the exit interview, in which case the consent in place at the time of study withdrawal will be used to determine the status of the subject's data.

Participants may withdraw from the Exacerbation Substudy without withdrawing from the main study. If the participant wishes to withdraw from SPIROMICS altogether, the coordinator should complete the RSW form.