Protocol

STUDY TITLE: Prospective study of peripherally inserted venous catheters in CF patients
HOSPITAL OR INSTITUTION: Maine Medical Center
INVESTIGATOR: Jonathan Zuckerman, M. D.

INTRODUCTION/BACKGROUND: According to the U.S. CF Foundation Patient Registry, more than 25% of children and 40% of adults were treated with IV antibiotics for flares of lung disease in 2016. Medication for these flares is often delivered through a peripherally inserted central catheter (PICC). Case series have identified important complications of PICCs in CF patients such as blood clots and infection. The frequency of PICC-associated blood clots in CF patients ranges from 2 to 8%. Catheter-related complications may interfere with completion of therapy and lead to repeated procedures and other complex medical treatments. In some cases PICC complications may discourage patients from accepting future courses of IV antibiotics. Therefore, it is very important to identify patient- and device-related factors that are linked with more frequent complications and to figure out ways to reduce these risks. Proposed risk factors fall into several broad categories. First are catheter-related factors; second are patient factors; and third are catheter-management factors. To date, no multicenter trial has carefully studied PICC complications in a large group of adult and pediatric CF patients from the time each catheter is placed to when it is removed. The main purpose of this study is to see whether we can identify important factors in each of the three categories (patient, catheter, and catheter management) that are linked to blood clotting complications.

HYPOTHESIS: We hypothesize that the rate of PICC and midline vascular complications among CF patients is associated with specific patient level and line level factors as well as with line insertion and management practices.

SPECIFIC AIMS:
Specific Aim #1: To confirm associations between patient level factors and risk of subsequent PICC and midline complications and evaluate the strength of any associations.
Specific Aim #2: To confirm associations between catheter level factors and risk of subsequent PICC and midline complications and evaluate the strength of any associations
Specific Aim #3: To confirm associations between catheter management factors and risk of subsequent PICC and midline complications and evaluate the strength of any associations

SIGNIFICANCE: The proposed study would address an important unmet need, which is to rigorously establish the baseline rate of catheter-related complications and risk factors for complications among CF patients in order to: a) minimize risk of complications in CF patients through appropriate catheter selection and management strategies b) reduce the costs of care by suggesting systems approaches to modifiable risk factors and c) provide a framework for future interventional trials of anticoagulation upon which to base recommendations for treatment or prevention of catheter-related thrombosis

METHODS:
Study Design**:** This is a multicenter, prospective surveillance study to evaluate risk factors associated with vascular complications of PICCs and midline catheters. Both adult and pediatric patients with CF who receive care at participating centers will be eligible for participation. Each participant will be assessed for a number of study variables (Table) while being treated with IV antibiotics via a PICC or

midline for pulmonary exacerbation (PEx). Assessments will be performed according to a prescribed schedule of events (see below). Antibiotic selection and treatment duration, however, will be determined and overseen by the local CF team. Patients will potentially be seen for multiple episodes of care during the study period if additional treatment(s) with IV therapy is/are prescribed following treatment of the initial PEx.

Patient Level Factors	Catheter Level Factors	Catheter Management Factors
• Age/Height/BMI • Genotype • Microbiology • FEV1 % predicted • Akron Pulmonary Exacerbation Score • Antibiotic regimen • Number of previous PICCs • History of DVT • History or family history of thrombophilia • CBC, INR, CRP, D-dimer • Diabetes status	• Catheter insertion site • Catheter French size • Catheter lumen number • Intravascular length of catheter • Catheter brand/model	• Venue of catheter insertion • Training of line inserter • Number of passes for line placement • Use of the catheter for blood draws • Line flushing practices • Days of inpatient versus outpatient IV therapy

Table. Variables to be assessed during each course of IV antibiotics.

Study Population and Recruitment**.** Participants will be recruited from the population of CF patients who receive longitudinal care at 10 CF Centers (Maine Medical Center, University of Vermont, Dartmouth-Hitchcock Medical Center, Columbia University Medical Center, Johns Hopkins Hospital, Medical University of South Carolina, Michigan Medicine, Cleveland Clinic, Children's Hospital Colorado and The University of Kansas Medical Center). These sites represent CF programs of different size and geographic location around the continental United States and care for more than 2400 CF patients (1102 pediatric patients; 1361 adults). A survey of the study sites using the query tool in PortCF (www.portcf.org) indicates that during 2016, 1120 courses of IV antibiotics were delivered via PICCs or midlines to these patients. *Patients will be screened and enrolled at the time of hospitalization for PICC or midline placement. Patients who have a PICC or midline placed at the hospital but who then have the remainder of therapy in the home setting will be eligible to participate.* To reach our enrollment goal, we plan to study approximately 335 patients per year over a 30 month period In order to maintain appropriate representation of all centers, maximum enrollment per center will be 50 patients per year. This cap may be exceeded in the event that a previously enrolled patient has a subsequent PICC or midline placed in the same calendar year. One of the study goals is to look at the association of repeated PICC placement with the occurrence of complications, so we do not want gaps in follow up.

Screening and Enrollment: Inclusion and exclusion criteria are listed below. The rationale for some of the exclusion criteria is self-evident. However, one deserves additional explanation. We have elected not to study TIVADs, since the period of observation of this project is relatively short compared to the average "lifespan" of these devices. It would therefore be difficult to achieve adequate power to study complication risk factors in a 3 year study, even in a multicenter trial. Based on the finding that anticoagulation at prophylactic or treatment doses may increase the risk of complications and since there is no standardized regimen for anticoagulation in this patient population with indwelling lines, patients who are chronically anticoagulated will be excluded at screening. However, patients who have a

vascular complication after enrollment in the study and receive treatment as determined by their primary care team will be permitted to continue in the study, and all participants may receive deep venous thrombosis prophylaxis according to local institutional policies. It should be emphasized that this study is not designed as an interventional trial to test the safety and efficacy of anticoagulation but could lay the groundwork for such an investigation.

Inclusion criteria include the following:
● All ethnic groups
● Females and males
● 6 years of age and above (in order to perform spirometry on all study participants)
● Undergoing treatment for PEx with IV antibiotics via hospital-placed PICC or midline catheter
● Ability to communicate with pertinent staff.
● Ability to understand and willingness to comply with the requirements of the trial (allow repeated assessment of the catheter insertion site, photographs of the site, extremity measurement and face-to-face assessment on the day of line removal).
● Ability and willingness to give verbal consent (with the assistance of a parent or guardian, if appropriate) or assent (for pediatric patients)
● Diagnosis of cystic fibrosis consisting of both:
  - sweat sodium or chloride > 60 mEq/L by the pilocarpine iontophoresis method or cystic fibrosis genotype (homozygous for CFTR mutation or compound heterozygous for CFTR mutations)
  - clinical manifestations of cystic fibrosis

Exclusion criteria:
● Under age 6
● Planned use of a TIVAD or peripheral catheter for IV therapy for the full course of therapy
●
● IV treatment anticipated to extend beyond 21 days at the time of line insertion
● Patient taking anticoagulant medication (other than non-steroidal anti-inflammatory drugs) at the time of screening
● Inability/unwillingness to provide consent or assent or to return for a study visit at the time of catheter removal

Coordination of Study Sites: The principal investigator and co-principal investigator will be responsible for coordinating implementation of the study at the 10 listed centers. Shortly after initiation of the project, an investigators' webinar will be held in order to carefully review the study protocol, standards for data recording and use of the secure, online database. The study administrator will be responsible for assembly and distribution of an operator's manual to each participating CF Center. The manual will contain standard operating procedures for enrolling patients, entering historical information and laboratory findings into the study database and photographing the catheter insertion site. Monthly reports will be generated to review the progress of patient enrollment at each site and troubleshoot any issues regarding patient recruitment. The project website will have a "thermometer" to track enrollment by site against established targets. Subject enrollment will proceed at MMC and DHMC prior to the other study sites.

Each study site will have a physician sub-investigator and a research coordinator who will be responsible for obtaining local IRB approval, recruitment of patients, collection of samples and running blood tests in the local clinical lab facility and entering data into the study database (see below). All samples and forms for study purposes will be stripped of patient identifiers and linked to a study subject code to ensure the

privacy of all participants. Subject codes will be stored in a secure computer database managed by the study administrator. The REDCap database for this study will be managed by the analytic team at the Center for Outcomes Research and Evaluation (CORE) at Maine Medical Center. Biostatistics support will be provided by Dr. Lee Lucas at the MMC CORE.

Study Event Workflow: Potential study participants will undergo informed consent/assent on the day of catheter insertion. Additional tasks and procedures in the protocol are summarized in Figure 1.

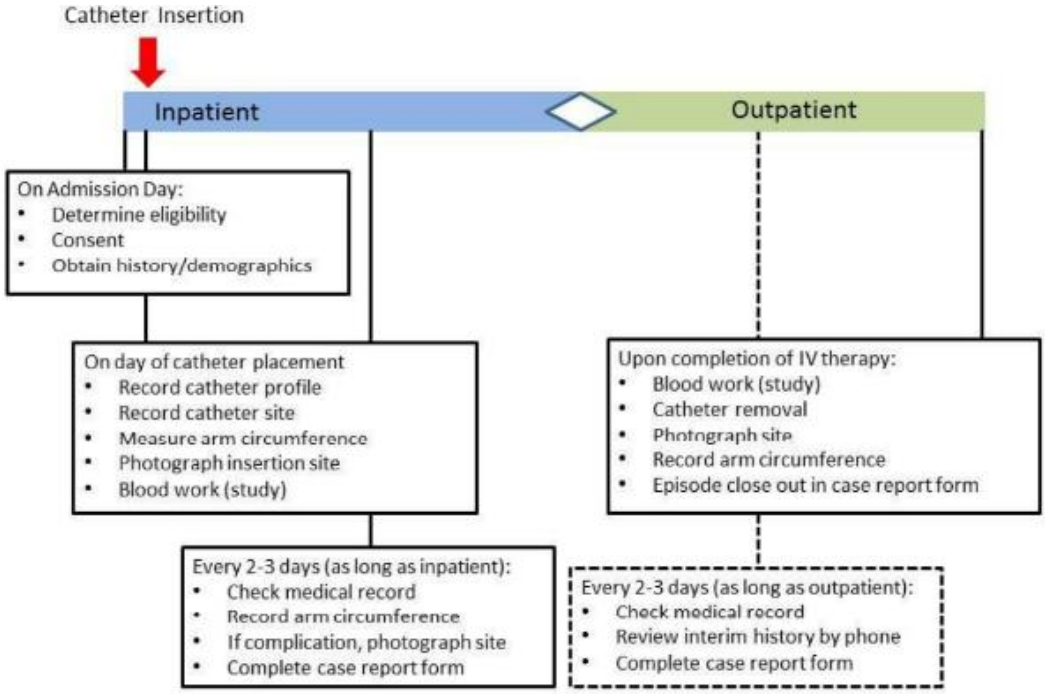

Figure 1: Workflow diagram of PICC assessments during PEx. Inpatient assessments will be done every 48-72 hours. Likewise outpatient assessments (dashed lines) will be done every 48-72 hours via phone interview. The white diamond denotes variable duration of inpatient (blue segment) and home IV (green segment) phases of therapy.

Study Endpoint Definitions:

Venous thrombosis: Catheter related venous thrombosis will be initially determined through use of the Constans Clinical Decision Score. One point is given for each of the following findings/symptoms: indwelling venous material (in this study—PICC or midline catheter), localized pain, unilateral pitting edema and a point subtracted for another diagnosis being at least as plausible. For the purposes of this study, probable DVT is defined as a Constans score of > 2. The sensitivity and specificity of this dichotomized score has been shown to be 86% and 65%, respectively. We believe this is a clinically useful endpoint, as it is based on symptoms, not simply a radiographic finding. Additional testing, such as compression ultrasonography or venography, will be performed at the discretion of the clinical team. If ultrasound is performed, then the results of testing will be collected and later used to further characterize the complication: confirmed DVT, superficial venous thrombosis (depending on the location of the thrombus) or no thrombosis.

Phlebitis: Treatment related phlebitis may result from irritation of vascular endothelium from the indwelling catheter or from chemicals in the infused fluids. Phlebitis may also result from extravasation of fluid due to catheter misplacement or fracture. For the purposes of the study, phlebitis is defined as a

Visual Infusion Phlebitis (VIP) score of > 2. The VIP score is a simple-to-use, standardized tool that has been used in other clinical studies. We will incorporate a photograph of the catheter insertion site along with the symptom score so that the appearance of the skin can also be confirmed by a blinded reviewer.

Central line associated bloodstream infection (CLABSI) The study definition for CLABSI follows the Centers for Disease Control guidelines and may be met by one of two criteria:

Criterion 1. Patient of any age has a recognized pathogen, which is an organism not included on the National Healthcare Safety Network (NHSN) common commensal list, identified from one or more blood specimens obtained by a culture or non-culture based microbiologic testing method AND organism(s) identified in blood is not related to an infection at another site.

Criterion 2. Patient of any age has at least one of the following signs or symptoms: fever (>38.0^{o}C), chills, or hypotension AND organism(s) identified in blood is not related to an infection at another site AND the same common commensal is identified by a culture or non-culture based microbiologic testing method from two or more blood specimens collected on separate occasions.

Study Measures

Spirometry testing Spirometry is not required as part of the study protocol, as historical data will be obtained from PortCF. The best value for FEV1 % predicted within the 12 months prior to enrollment will be utilized to categorize patients into functional severity categories. FEV1 percent predicted will be calculated based on the 2012 European Respiratory Society Global Lung Function Initiative reference equations. Severity of lung disease will be categorized as follows: FEV1 % predicted <40 = severe, 40-69 = moderate, > 70 = mild.

Akron Pulmonary Exacerbation Score (PES) In order to characterize the severity of acute illness of the patient at the beginning of treatment, a questionnaire combining subjective and objective elements will be administered at the time of study enrollment . These questions are part of routine care and terminology contained within this instrument is familiar to patients (and parents of pediatric patients) in the study population. It should be emphasized that study participants will not be completing the questions by themselves but will be asked the questions by the investigative team in a manner that ensures understanding of each item. This tool is found in the Appendix.

D-Dimer Assay D-dimer is the degradation product of cross-linked fibrin. It reflects ongoing activation of the hemostatic system and is typically elevated in the context of thrombus formation. It is also known to increase in a variety of injury states and following venipuncture, so its primary utility in the evaluation of venous thrombosis is to rule out the condition in scenarios where the pretest probability of clinically significant clot is low. Blood samples will be obtained within 24 hours of intravenous catheter insertion and time of removal. Obtaining samples at the time of catheter insertion (if possible) and removal will obviate the need for separate venipuncture. This standardized blood test will be performed in the clinical laboratory at each study center with the accepted unit of measure being ng/mL fibrinogen equivalent units (FEU).

C-Reactive Protein (CRP) C-reactive protein, a highly stable molecule, is synthesized in the liver, and levels in the blood increase in a number of inflammatory states. Recent studies have shown it to be a biomarker responsive to disease activity in CF and a predictor of time to next exacerbation. This well-standardized test will be performed in the clinical laboratory at each study center. CRP will be used in

conjunction with the Akron PES to assess severity of acute illness upon study entry. Blood samples will be obtained within 24 hours of intravenous catheter insertion and time of removal, per protocol.

Complete Blood Count (CBC) Polycythemia and thrombocytosis have been identified as risk factors for venous thrombosis in non-CF populations. Since a CBC is typically ordered as part of admission laboratory testing for treatment of PEx, we will capture the results of this test in the REDCap database, if available.

International Normalized Ratio (INR) There is controversy about whether CF is associated with significant thrombophilia. In some cases thrombophilic disorders, such as circulating lupus anticoagulant, may be associated with an elevated INR or activated partial thromboplastin time. More commonly in CF the INR may be elevated due to liver disease and/or vitamin K deficiency, increasing the risk of bleeding. Since INR is typically checked at least yearly as part of annual evaluation for fat soluble vitamin deficiency, most recent results from the prior 12 months will be captured in the REDCap database, if available.

Documentation of Skin Reactions The insertion site will be photographed after line insertion. A bar code label with the patient's study ID will be affixed temporarily to the arm for the photograph. The flat white label will assist with white balance and patient identification. Should any skin reaction be noted by the patient, care team or research team, a repeat photograph will be taken. A tape measure documenting arm circumference (in millimeters) 5 cm distal to the point of catheter insertion in the arm will be included in the field of view. Photographs can be taken with a Smartphone or iPad using software (Epitomyze™, https://epitomize.com) that enables capture and archiving of images on a platform that complies with Health Insurance Portability and Accountability Act (HIPAA) regulations. The data recorded in the case report forms will be used to determine the VIP score. Photographs will also be examined by blinded reviewers in an exploratory manner to assess inter-observer variability. We are particularly interested in this secondary endpoint. No prior study of PICCs has integrated imaging of the insertion site into outcome assessments.

Basic Demographic and Clinical Information The sex, age, body mass index, CFTR genotype profile, diabetes status, and sputum infection pattern of each patient will be tabulated in case report forms (CRFs) imbedded in the REDCap database. These data will be obtained from the local medical record and from the CF Patient Registry (a registry for which patients have previously signed consent for data storage and retrieval).

Medication Use We will collect data on type and infusion rate (i.e., rapid or extended) of IV antibiotics. We will also record information about use of prophylactic anticoagulation use.

Catheter attributes and insertion and maintenance techniques Details about the size, composition and design of each catheter placed, along with insertion technique and catheter/site maintenance will be archived using CRFs linked to a REDCap database. These elements are critically important for Aims 2 and 3 of the study and are a major focus of the project design. We will survey sites at the beginning of the study and at intervals thereafter about their use of specific brands of catheters and dressings. We will include these in "Picker Lists" on the CRFs to eliminate data entry ambiguity. Updating information on catheter and dressing brands used at study sites is essential for data fidelity because hospitals often change vendors. Similarly, PICC insertion and maintenance practices could change during the study period, and we want to capture these alterations at the site level.

Participant Reimbursement

Study subjects, including children, will receive a nominal stipend for participation as follows

- A $30 payment will be given upon completion of the study visit associated with each IV placement
- A $30 payment will be given upon completion of the final study visit associated with each IV removal
- Study participants will be reimbursed for travel for the final study visit in the event that they are returning to the hospital following a course of outpatient IV therapy and need to drive ≥ 20 miles to the appointment (reimbursed at $0.58/mile)

Data Handling Data will be entered and maintained in REDCap (Research Electronic Data Capture) version 7.3.6. REDCap is a secure HIPAA-compliant web application, where data are encrypted (i.e., SSL) and stored on secure REDCap servers behind firewalls, virus software, and user authentication protocols. On demand data quality checks will be available to all participating centers, including missing data and logic error checks. Additional spot checks will be done on an annual basis on 10% of subjects entered for each participating center. An analyst will also transfer data from REDCap to EventFlow (http://hcil.umd.edu/eventflow/), which will be used to assess treatment patterns and outcomes in a visual format that facilitates quick evaluation of aggregate data. The software allows one to quickly filter data types and thereby simplify pattern recognition. For instance, potential risk factors can be combined into clusters (e.g., combining all beta lactam antibiotics into one category or days of outpatient IV therapy into "short", "intermediate" and "long" categories). We will have an investigator portal to the REDCap database on a study website that will also house informational content for patients and families and running tallies of enrollment figures. Images of the catheter site captured through Epitomyze™ software will be stored in a secure cloud (Epitomyze™ Cloud). This platform complies with Health Insurance Portability and Accountability Act (HIPAA) regulations.

STATISTICAL PLAN

Statistical analysis. We will describe the study population using standard descriptive statistics, including means or medians as appropriate for continuous variables and proportions for categorical variables. We will assess for differences in management by center using chi-squared tests. These comparisons will allow us to decide whether there is enough variability in management within center to use center as a fixed effect in our models including management variables or whether we will define center by random effect.

In the subset of patients in whom we have ultrasound information, we will assess the performance of the Constans score in identifying vascular complications, comparing these results to ultrasound results as a gold standard test. Because we will have this information only in patients with suspected complications, we can identify false positives but will be unable to say anything about negatives. Using ultrasound as the gold standard, we will describe patients with a positive Constans score (> 2) as having no clot, superficial thrombosis, or DVT on ultrasound.

We will construct multilevel, mixed logistic regression models in order to account for both center effects and repeated measures. Patient will be entered in these models as a random effect to account for within person correlation. Center will be either a fixed or a random effect, depending on what we find in our preliminary analyses. The unit of observation will be PICC with a random effect for patient. As described above, we will use preliminary data analyses to decide whether to enter center into the model as a fixed or random effect. The dependent variable will be the occurrence of a vascular complication as defined by Constans score > 2. Predictors will be patient factors, catheter factors and catheter

management factors, as listed above. We will use a stepped approach, first estimating odds ratios associated with each factor, then grouping factors according to the preceding groups, then creating a final model with the best explanatory subset of variables, selecting variables to be included in each subset based on the size of the odds ratio and its statistical significance. We will use Likelihood Ratio Tests to compare nested models to assess the added explanatory power of the addition of new variable sets.

We will perform a sensitivity analysis, constructing similar models with a more rigorous definition of vascular complication. For this analysis, we will define vascular complication by ultrasound findings. Because we will not have ultrasound results for all patients, we will exclude those patients with a Constans score < 2 from these analyses and define patients with Constans score > 2 and a positive ultrasound (or venogram) finding as having a vascular complication, while patients with a Constans score < 2 OR a negative ultrasound will be categorized as not having a complication. We will assess whether results from this model are different descriptively (in both direction and magnitude of odds ratios) from those of the primary analysis.

Sample size calculation. Assuming a complication occurrence at mean of covariates of 6% and an average of two lines per patient over the 3 year period, our study has 80% power to detect a minimal odds ratio of 1.5 (two tailed α=0.05) for study variables with a sample size of 894 patients. We used pilot data from our recently published retrospective study about venous catheter complications to estimate the design effect for this study. In our data, the intraclass correlation coefficient (ICC) within patient was 0.13. The design effect is a function of both the ICC and cluster size. On average, our patients had two lines each; two thirds of patients had four or fewer. If we use 2 as the cluster size, given the ICC described above, the design effect is 1.13; if the cluster size is 4, the design effect if 1.39. These calculations account for the within patient correlation. If we enter center into our models as random effects, then we will also have within center correlation to account for. We have no pilot data to estimate this ICC, but have inflated the design effect to 2 to allow for this possibility. Our preference is to use center as a fixed effect if there is enough variability in treatment factors within center to allow us to do this; if the variability is too small (that is, if center A almost always uses 4 Fr catheters and center B almost never uses 4 Fr catheters), then this model will not be possible, and we will be forced to include center as a random effect. Note that the correlation involved in the design effect is not correlation in treatment, but rather correlation in outcomes. Assuming a dropout rate of approximately 10%, we have planned for enrollment of 1000 patients. We expect the dropout rate to be smaller than typical clinical trials because of the short period of observation and minimal risk, non-interventional nature of the study design. If the complication occurrence at the mean of covariates is higher, then the required sample size would be smaller.

POTENTIAL PROBLEMS: Information (or measurement) bias could be particularly harmful to a study like ours seeking to identify risk factors for certain events. To mitigate this type of bias, we have explicitly defined these events, and we intend to use standardized case report forms and a centralized data repository (REDCap). These safeguards are important because research personnel will not be blinded to the identities of cases and controls. We plan to have regularly scheduled investigator meetings (webinars) to elicit and answer questions from sites. We acknowledge that the test characteristics of our primary endpoint, the Constans score, are not perfect, but we are primarily interested in symptomatic PICC-associated DVT, which is what the score was designed to assess. Given the scale of our study, we anticipate that many patients with Constans scores ≥ 2 will ultimately undergo compression ultrasonography, the “gold standard” test for DVT. Thus, we can further characterize the utility of the Constans score in this subset of our study population. We will also collect arm circumference and D-

dimer data as secondary endpoints, which may also be used to better characterize the utility of the Constans score.

We will minimize confounding by employing multivariable statistical techniques. However, some caveats are pertinent to these methods. We will first create univariate logistic regression models for risk factors and then select those which meet a pre-specified level of significance (P <0.05) for inclusion in multivariable models. We will not include variables in these models that are highly correlated with each other (multicollinear), and we will assess the biological plausibility of each statistically significant risk factor. We will explore various imputation strategies for handling data assumed to be missing at random.

We have made several assumptions in our sample size calculations. If we have overestimated complication rates and/or the number of lines per patient, the minimum detectable difference in OR for our primary endpoint will change. We have attempted to minimize the risk of conducting an underpowered study by eliciting the help of multiple CF Care Centers and establishing an aggressive timetable for study initiation. We have included a design effect in our sample size calculation to account for within patient correlation.

TIMELINE:

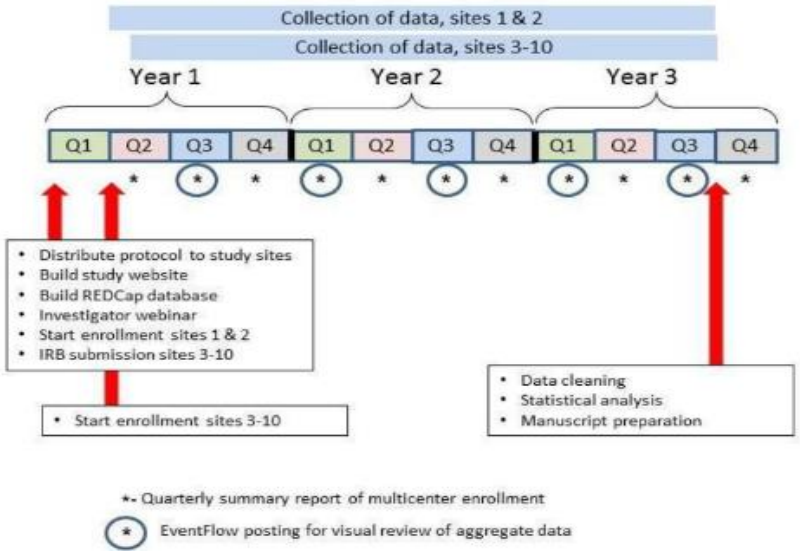

Figure 2. Study timeline showing plan for data collection, interim reporting, cleaning and analysis.

APPENDIX

Akron Pulmonary Exacerbation Score (PES) Sheet

Systemic Symptoms/Signs:

1. Fevers > 38C (100.4 F) in the prior 2 weeks?
   No = 0 Yes = 1

2. Malaise or fatigue in the prior 2 weeks?
   No = 0 Yes = 1

3. Any increased or new school or work absenteeism in the prior 2 weeks?
   No = 0 Yes = 2

4. Anorexia or poor appetite in the prior 2 weeks?
   No = 0 Yes = 1

5. Wt. Loss (≥ 5%) or poor wt. gain compared to last clinic visit (or in the last 3mo.)
   No = 0 Yes = 2

SUM OF SYSTEMIC SYMPTOM SCORES: _____

Pulmonary Symptoms/Signs:

1. Increased cough (frequency, duration or intensity) for ≥1 week?
   None = 0 Mild = 1 Significant = 2

2. Major change in sputum (new onset, increased, change in consistency) or change in chest congestion for ≥1 week?
   None = 0 Mild = 1 Significant = 2

3. Increased DOE or SOB at rest?
   No = 0 Yes = 2

4. Change in chest exam (wheezes, crackles, rhonchi, decreased air entry) or Increased WOB or Respiratory Rate?
   No = 0 Yes = 2

SUM OF PULMONARY SYMPTOM SCORES: _____

Objective Measurements:

1. Decrease in FEV1 (compared to highest value of the prior six months 6 months)?
   < 10% = 0 ≥ 10% = 3 ≥ 15% = 5

2. New Chest Radiographic Abnormality?
   None = 0 Increased air trapping, mucus plugging or bronchiectasis = 1 New atelectasis or infiltrate = 2 Pneumothorax = 5

3. Hemoptysis ?
   None = 0 Streaked = 3 Increased or new onset = 5

4. Decreased SaO_2 from baseline (compared to the highest value of the prior 6 months)?
   < 4% change = 0 ≥ 4% decrease = 2 ≥ 10% decrease = 5

SUM OF OBJECTIVE MEASUREMENT SCORES: _____

TOTAL PULMONARY EXACERBATION SCORE: _____

***All symptoms/signs/measurements will be compared to the patient's most recent baseline (within the previous 3 months) or as noted below.**

**If a patient has Systemic findings they must also have at least 1 finding from either the Pulmonary or Objective Measurement categories to have a PE. (i.e. a pulmonary exacerbation will not be present with Systemic symptoms alone).