The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Aim 3

Statistical Analysis Plan

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CAPTURE Statistical Analysis Plan

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3 Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAO	Chronic Airflow Obstruction
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FEV1	Forced Expiratory Volume in 1 second
FFR	Federal Financial Report
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
PRISm	Preserved Ratio, Impaired Spirometry
SNO	Symptomatic Non-Obstructed

4 Introduction

4.1 Preface

This Statistical Analysis Plan (SAP) describes statistical methods and analyses for the CAPTURE (**C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk) study, with emphasis on methods and analyses for the clinical trial component (Aim 3) of the CAPTURE Study Protocol version 7.0, dated June 25, 2023. This document should be read in tandem with the CAPTURE Study Protocol. When mentioned, CAPTURE Study Protocol Aim 1 and Aim 2 goals and analyses are grayed out in this document because they are out of scope of this SAP.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the US and a major cause of morbidity, mortality and health care expenditures. In primary care settings, the primary contact point for individuals seeking health care, COPD is often under diagnosed and associated opportunities for correct disease management are missed. The CAPTURE tool was developed to identify individuals

with undiagnosed COPD, and preliminary data has shown high sensitivity and specificity towards this goal. However, its use in primary care settings, where its potential impact on improved health care utilization is high, has not yet been studied.

The clinical trial component (Aim 3) of the CAPTURE study is a cluster-randomized trial of 100 primary care practices affiliated with seven practice-based research networks (PBRNs). Randomization to one of two interventions takes place at the practice level. Both interventions provide clinicians in participating practices with basic COPD education (enhanced usual care). Clinicians from practices randomized to the CAPTURE intervention additionally receive an educational module (CAPTURE education) on the CAPTURE tool. Each of the 100 practices is expected to enroll 50 patients (5000 total patients). In a single visit, each enrolled patient participant completes CAPTURE screening, pre- and post-bronchodilator spirometry and completes demographic, and general and respiratory related health questionnaires. Practices randomized to the CAPTURE intervention are provided with patient-level CAPTURE tool results for the patients it has enrolled in the study. One-year follow-up chart reviews and participant surveys are used for a pre-identified subset of participants to assess whether CAPTURE screening and sharing of results with clinicians results in higher rates of guideline-concordant COPD care in those with a positive CAPTURE tool result (CAPTURE+). Study investigators hypothesize that providing CAPTURE screening results to primary care clinicians will increase rates of COPD diagnosis and increase guideline concordant COPD care.

4.2 Scope of the Analyses

The primary analysis of the cluster-randomized trial is to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint of guideline-concordant COPD care in the two intervention arms. From medical record review and follow-up patient survey responses, the composite endpoint is met if one of the following is recorded: 1) referral for or completion of clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long-acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/treatment, or 5) referral for or completion of pulmonary rehabilitation. In addition to providing more details on the primary analysis, this document will describe secondary and exploratory analyses of interest that make use of data collected as part of the cluster-randomized trial (CAPTURE Aim 3). Analyses relating to the ancillary study objectives outlined in Aims 1 and 2 of the CAPTURE protocol are not the focus of this SAP; when mentioned, details of those analyses are grayed out.

5 Study Objectives and End Points

5.1 Primary Objectives

The Aim 1 objective from the CAPTURE protocol is to define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. The Aim 2 objective of the CAPTURE protocol is to explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. The objective of the cluster-randomized trial described in Aim 3 of the CAPTURE protocol is to define the impact of CAPTURE information provided to clinicians in identifying and managing CAPTURE+ patients across a broad range of primary care settings. Table 1 below outlines primary and secondary objectives and endpoints for the cluster-randomized trial described in Aim 3 of the CAPTURE protocol.

Table 1. CAPTURE Study Objectives, Endpoints for Aim 3.

OBJECTIVES	ENDPOINTS
Primary	
Define the impact of CAPTURE information provided to clinicians in identifying and managing CAPTURE+ patients across a broad range of primary care settings.	Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/treatment, or 5) referral for or completion of pulmonary rehabilitation.
Secondary	
Define the impact of providing CAPTURE education and patient-level CAPTURE information to clinicians on selected clinician interventions for the management of CAPTURE+ patients.	Proportion of CAPTURE+ participants who have each of the following occur within 12 months of study baseline (separate endpoints to be evaluated individually): 1-5) each component of the Aim 3 primary endpoint, and 6) recommendation or administration of influenza vaccination.
Assess the impact of CAPTURE education and patient-level CAPTURE information on clinician interventions specific to smokers who are CAPTURE+.	Proportion of CAPTURE+ participants currently smoking at the baseline study visit who have any of the components of the Aim 3 primary endpoint or any of the following occur within 12 months of baseline (evaluated as a composite endpoint and as individual endpoints): 1) clinician counseling or recommendation for smoking cessation, 2) referral to a smoking cessation program, 3) referral to a smoking quit line, and 4) newly prescribed medication for smoking cessation.
Determine the impact of CAPTURE education and patient-level CAPTURE information on patient symptoms, exacerbations, hospitalizations, and mortality among CAPTURE+ patients.	In CAPTURE+ participants, change in CAT score between baseline and follow-up at 12 months after baseline, and proportion of patients who experience exacerbations, hospitalizations, or mortality within 12 months of baseline.
Determine the impact of CAPTURE education and patient-level CAPTURE information on identification and management of patients with respiratory burden.	All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) preserved ratio, impaired spirometry (PRISm), and 4) symptomatic non-obstructed (SNO).
Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening.	All of the above endpoints for Aim 3, in all of the analysis populations named above, separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic.

6 Study Methods for Cluster Randomized Trial (CAPTURE Protocol Aim 3)

6.1 General Study Design and Plan

Overview: This is a prospective multi-PBRN, cluster randomized clinical trial to assess the operating characteristics of the CAPTURE COPD screening approach and compare respiratory related clinical actions and patient health status during the year following clinician receipt vs non-receipt of the CAPTURE results. Figure 1 provides a summary of the details of the study flow and data collection.

PBRNS: Seven PBRNs were selected from a pool of PBRNs with prior experience in large scale clinical trials. The selection process included surveying each candidate PBRN, reviewing survey responses and conducting telephone interviews with the director of each of those PBRNs. The final seven were selected based on interest, availability, prior experience in respiratory related clinical trials, geographic spread, socioeconomic, and racial/ethnic diversity of patients within the PBRN practices as well as willingness to participate in a five-year trial. These PBRNs were to enroll (collectively) 100 practices with 50 enrolled patients per practice completing spirometry and other study entry materials.

Practices and Clinicians: Each PBRN identified and enrolled practices based on interest and availability of space to complete the research visit within the practice building and willingness of the practice's clinicians to view the required educational modules. Enrolled practices were randomized in a 1:1 ratio to receive either basic COPD education or basic COPD education augmented with education on the CAPTURE Tool.

Patient Participants: Within each enrolled practice, potentially eligible patients of clinicians completing the required education are identified and invited to participate using one of two methods: (1) eligible patients identified by research and clinical staff are approached as they visit the clinic or (2) research staff are provided a list of patients with future appointments, and those aged 45-80 years are sent invitation letters by the PBRN to allow further contact and evaluation of eligibility and interest. The chosen method is based on prior PBRN experience and requirements of the local health systems and Institutional Review Boards (IRBs).

Patients who are eligible and agree to participate in the study sign informed consent, complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, provide past medical history, and demographic information. Local/PBRN study coordinators perform the study procedures and record baseline information into the electronic data capture (EDC) system. The study coordinators calculate a CAPTURE score for each participant. For patients in a practice randomized to CAPTURE+COPD education, their practitioner is provided with CAPTURE results for their patient. Practitioners at sites randomized to the COPD education only intervention are blinded to CAPTURE scores. Practitioners in both intervention arms are blinded to research spirometry results.

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

Cohort	**Definition**
CAPTURE+	Participants with • CAPTURE score ≥ 5, or • CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
CAPTURE-	Participants with • CAPTURE score < 2 or scores 2-4 with normal PEF (defined as ≥ 350 L/min for males and ≥250 L/min for females)
Spirometrically Defined COPD	Participants with abnormal spirometry, defined as post-bronchodilator FEV_1/FVC <0.7. If a participant is unable to complete a post-bronchodilator spirometry

	(refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.
Clinically Significant COPD	Participants with abnormal spirometry, defined as spirometrically defined COPD plus at least one of the following: • FEV_1 < 60% predicted or • ≥1 exacerbation like event within the past 12 months.
Mild COPD	Participants with spirometrically defined COPD plus both of the following: • FEV_1 ≥ 60% and • No prior history of ECOPD
Preserved ratio, impaired spirometry (PRISm)	Participants without spirometrically defined COPD who have post-bronchodilator FEV_1 < 80% predicted. Among participants who do not complete post-bronchodilator spirometry and have pre-bronchodilator FEV_1/FVC ≥ 0.7, those with FEV_1 ≥ 80% predicted will be considered not to have PRISm and those with FEV_1 < 80% predicted will be considered to have undetermined PRISm status in primary analyses.
Symptomatic non-obstructed (SNO)	Participants without spirometrically defined COPD and without PRISm who have a COPD Assessment Test score ≥ 10.

Longitudinal Follow-up

A pre-defined subgroup of enrolled participants, who meet any of the below criteria, will undergo longitudinal follow-up at 12 months:

1. CAPTURE+ participants, as defined above.
2. Participants who have spirometrically defined COPD, as defined above, or post-bronchodilator FEV_1 <80% predicted at baseline. If post-bronchodilator spirometry is not completed, then pre-bronchodilator FEV_1 <70% predicted will be considered to satisfy this criterion for follow-up.
3. A random sample of approximately 5% who do not meet criteria 1 – 2.

Participants who meet the criteria for follow-up will be sent notification/reminder letters within the first three weeks of enrollment and at three, six, and nine months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

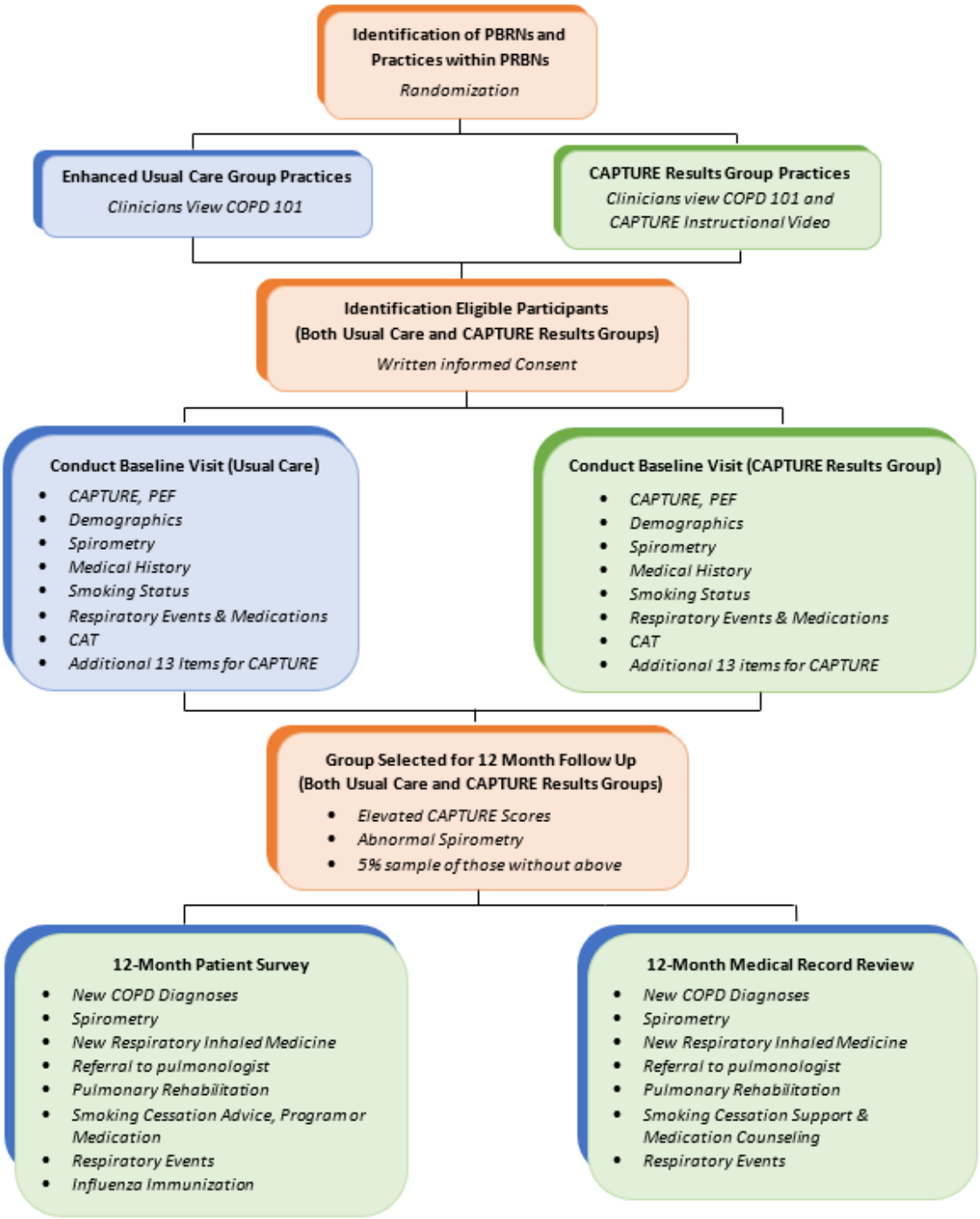

Figure 1

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

7 Inclusion-Exclusion Criteria and General Study Population for Aim 3

7.1 Inclusion Criteria

- Men or women between the ages of 45 and 80 years of age
- Ability to read and complete visit in English or Spanish
- Stated willingness to comply with all study procedures and availability for the one-year duration of the study
- Provision of signed and dated informed consent form

7.2 Exclusion Criteria

- Previous clinician diagnosis of COPD
- Treated respiratory illness (with antibiotics and/or systemic steroids) in the past 30 days prior to study visit
- Unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
    - Chest surgery
    - Abdominal surgery
    - Eye surgery
    - Heart attack
    - Stroke
- Unwilling or unable to complete all components of the single study visit

7.3 Randomization and Blinding

Randomization: Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding: This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV_1 is less than 30% predicted. For all other

participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post- bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

7.4 Study Assessments

The following table provides the Schedule of Evaluations used in the study:

7.5 Schedule of Activities (Aims 1 and 3)

Table 2:

	Pre-Visit Contact[1]	**Baseline**	**12 Months**[3]
Contact (C)/ Visit (V)/Medical Record Review (MRR)	**C1**	**V1**	**C2/MRR**[5]
Time point, days (Visit window)	**Prior to outpatient visit (≤-1)**	**Within 30 days of pre-visit contact**	**365 ±30 (C2)**
Contact patient re: interest in study visit[1]	X		
Informed consent		X	
Demographics		X	
Medical history (Co-morbidities)[2]		X	
Vaccination status		X	X
CAPTURE 5-item questionnaire		X	X
CAPTURE item additional questionnaire		X	
Peak Expiratory Flow (PEF)		X	
Height and weight		X	
Respiratory medications review		X	X
Spirometry[4]		X*	
Respiratory symptoms, exacerbation assessment		X	X
Smoking exposure history		X	
Smoking cessation review[6]			X
COPD Assessment Test (CAT)		X	X
Adverse Events		X	
Medical record review			X

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score $\geq$ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as post-bronchodilator $FEV_1/FVC < 0.70$ or $FEV_1 <$ 80% predicted at baseline, or pre-bronchodilator $FEV_1/FVC < 0.65$ or $FEV_1 < 70\%$ predicted for patients who do not complete post-bronchodilator spirometry; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol-specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.
4. Pre-bronchodilator spirometry will be done for all participants. Post-bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC <$ 0.70 or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.
5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.
6. This will be completed in those that are smoking at V1.

7.6 Baseline Assessments and Data Collection

CAPTURE Questionnaire: Participants will complete the five-item self-administered questionnaire. The questionnaire will be scored on a scale of 0-6, with higher scores indicating a higher likelihood of COPD diagnosis. The score calculated and recorded by study site personnel will be used in all primary analyses, regardless of whether the score agrees with the individual CAPTURE questionnaire responses, since the study site personnel's CAPTURE scoring represents the information conveyed to clinical providers.

Peak Expiratory Flow (PEF): PEF will be measured for all participants in L/min, with a quality assurance range of 100-1000 L/min. The participant will perform three PEF tests. All three measurements will be recorded, and the largest of the measurements will be used in the CAPTURE Tool. The study site personnel's indication on the scored CAPTURE form about whether the maximum PEF falls below the predetermined threshold of <350L/min (males) or <250L/min (females) will be used to define CAPTURE+ participants in all primary analyses, regardless of whether that indication agrees with the individually recorded PEF values.

Spirometry: Spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV_1), and calculation of FEV_1/FVC. FEV_1 and FVC are measured in liters and have expected ranges of 0.4-8.0 liters. FEV_1 values less than 30% of the predicted values will be adjudicated by the study chair.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to calculate the predicted lung function levels. These require the input of age, height, race, and sex. For people of mixed or unknown race the White prediction equations will be used.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry: The presence of obstruction is determined by the presence of an FEV_1/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV_1/FVC is less than 0.70 or whose FEV_1 is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and Weight: Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded in inches, and weight will be measured in pounds.

Demographic Data Collection: Demographic data including date of birth, gender, ethnicity, race, educational level, current employment status, living arrangement and health insurance will be entered into the EDC system.

Medical History: Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory, and malignant disorders. Influenza vaccination history will also be recorded.

Concomitant Medication Review: Respiratory medications will be recorded at baseline for all participants.

CAPTURE Additional Items Questionnaire: Participants will complete the 13 item self-administered questionnaire.

COPD Assessment Test (CAT): Participants will complete the eight item self-administered questionnaire. Each item is on a scale of 0-5 with higher scores indicating worse health status.

Respiratory Symptoms, Smoke Exposure and Exacerbation-Like Events: History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded.

Adverse Events: Adverse events related to study procedures will be recorded by the coordinator.

Practice Characteristics: The locations of participating clinical practices will be categorized based on designation as rural by the Federal Office of Rural Health Policy (FORHP) / Health Resources & Services Administration (HRSA). A practice location will be classified as rural if the ZIP code appears in the Eligible ZIP Codes file downloadable from the FORHP website: https://www.hrsa.gov/rural-health/about-us/definition/datafiles.html. Other data describing the characteristics of participating practices will be collected from study site personnel.

6.6.2: Longitudinal follow-up

Follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 6.1).

Table 3: Data collected from medical records include:

All participants undergoing 12-month follow-up as described in section 6.1	**Current Smokers Only**
Clinical spirometry ordered or administered	Smoking cessation counseling
New recorded clinical diagnosis of COPD	New prescription for smoking cessation medication
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	Formal smoking cessation program referral/completion
Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration)	Referral to a smoking quit line
Vaccination status	
Formal pulmonary rehabilitation program referral/completion	

Data related to COVID-19 confirmed and suspected cases	

Table 4: Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail- based methodologies directly from participants and administered by COPD Foundation study personnel includes:

All participants undergoing 12-month follow-up as described in section 6.1	**Current Smokers Only**
Spirometry referral/completion	Referral to a smoking cessation program
New diagnosis of COPD	Referral to a smoking quit line
Referral to pulmonologist or other respiratory specialist	New prescription for smoking cessation medication
Exacerbation like event assessment	Over-the-counter patches/gum for smoking cessation
New prescription for respiratory medication (long acting bronchodilator, inhaled steroids, oral anti-inflammatory)	
CAT score	
Attendance of pulmonary rehabilitation	
COVID-19 related questions	

7.7 Imputation of Dates

If partial dates occur, the convention for replacing missing dates for the purpose of calculating derived variables is as follows:

- Missing day is imputed as the 15th of the month.
- In 12-month follow-up forms and chart reviews, missing month is imputed as 12 months from the patient's enrollment into the study.

Missing year is imputed as the year the practice enrolled the participant for baseline forms and the following year for 12-month follow-up forms.

7.8 Laboratory Reporting

No safety laboratory values are collected in the CAPTURE study.

8 Sample Size

8.1 Primary Objectives

Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

8.2 Practice Behavior in Sites With Vs Without Capture Education and Patient Level Capture Data Provided

Primary Hypothesis 3: Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.

From medical record review and follow-up patient survey responses, the composite endpoint is met if one of the following is recorded: 1) referral for or completion of clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/ treatment, or 5) referral for or completion of pulmonary rehabilitation.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of 5,000 patients). We project that within each practice there will be at least five patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample size computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 5 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions

(https://www.abdn.ac.uk/hsru/research/research-tools/study-design/). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients, and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 5). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

9 General Analysis Considerations

Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/cluster) vs usual care (50 practices/cluster), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice.					
Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.72	0.89	0.99	>0.99	>0.99
ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.59	0.79	0.97	>0.99	>0.99

9.1 Timing of Analyses

The final analyses will be performed after
(1) All 100 practices and 5000 participants have been enrolled
(2) Participants selected for follow-up have completed their 12-month data assessments or been lost-to-follow-up
(3) Chart review has been completed for those selected for follow-up
(4) All corresponding data have been entered, cleaned, locked and unblinded as per SABER SOPs.

This SAP document was finalized and approved prior to the double-blind database lock and unblinding.

9.2 Blinded Data Review

Prior to database lock and the start of any formal analyses, blinded data reviews will be completed, including summary statistics of key variables. This will allow the data for key variables to be examined to identify unusual values that need to be queried and patterns of missing values. In addition, the data reviews will allow the Executive and Publication Committees to assess the format of the data presentations. Note that blinded data reviews incorporate real data but random intervention assignment (i.e., investigators do not receive data summarized by actual intervention group, rather they review data on two randomly formed groups). All decisions will be made and documented in this SAP document prior to unblinding and database lock.

9.3 Analysis Populations for the Cluster-Randomized Clinical Trial (Aim 3)

All enrolled practices will be used in descriptions of practice characteristics. Because the CAPTURE study involves a cluster randomized design, with the intervention given at the cluster level, we have natural intent-to-treat populations for analysis at the practice level. That is, patient and practice outcomes will be ascribed to the assigned intervention group for that practice. We will not define a per-protocol analysis population as part of this study. Protocol deviations will be described, but not used to adjust analysis populations inappropriately. The safety population is all patient participants selected for follow-up as part of the cluster-randomized trial described in Aim 3 of the CAPTURE protocol.

There are eight analysis populations:

1) CAPTURE + (Primary Analysis Population)
2) CAPTURE –
3) Spirometrically defined COPD
4) Clinically Significant COPD
5) Mild COPD
6) No COPD
7) Preserved ratio, impaired spirometry (PRISm)
8) Symptomatic non-obstructed (SNO)

9.4 Covariates and Subgroups

The effect of the CAPTURE intervention will be explored in predefined subgroups of interest with results tabulated (estimated difference in average proportion of CAPTURE+ patients per practice meeting composite endpoint between intervention arms by subgroup, corresponding 95% confidence interval and p-value) as well as displayed via forest plots. These analyses will proceed similarly to that described for the primary endpoint in section 11.1. Individual-level covariates used to define subgroups of interest are categorical age (45-59 years, 60-69 years, 70-80 years), gender (Male, Female), race (American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, Unknown or Not Reported), ethnicity (Hispanic/Latino, Non-Hispanic/Latino, Unknown or Not Reported), educational status (Less than High School Graduate, High School Graduate/GED, Vocational/Some College, College Degree, Professional/Graduate Degree, or Not Reported), insurance status (private, public, none), living arrangements (alone, not alone), employment status (working, not working, unknown), smoking status (Current, Former, Never), asthma history, baseline respiratory medications (short-acting bronchodilator, maintenance respiratory medication, or none), cardiac morbidity, COPD Assessment Test (CAT) score (10 or above versus less than 10), BMI (Below 25.0 [Normal/Underweight], 25.0-29.9 [Overweight], 30.0-39.9 [Obese], 40.0 and Above [Severely Obese]), as well as cohorts defined in section 6.1 (Spirometrically Defined COPD, Clinically Significant COPD, Mild COPD, No COPD by Spirometry, PRISm, and SNO). Practice level covariates include practice type (Part of large health system/ACO/similar, Part of academic medical center/health system, Federally Qualified Health Care Center, Independent practice, Other), location (Rural, Non-rural), being a residency site, having in-house spirometry, and number of MD/DO/NP/PA primary care clinicians (0-4, 5-9, 10 or More). Because of the possible impact of the SARS-CoV-2 pandemic on study outcomes, these analyses will be repeated in subgroups defined by whether the one-year follow-up period had entirely elapsed by March 19, 2020 (date when PBRNs paused study enrollment due to SARS-CoV-2); that is, the analyses will be repeated separately in the cohort with baseline visit completed on or before March 19, 2019, and separately in the cohort with baseline visit completed after March 19, 2019. Chart review and patient follow-up survey need not be completed by March 19, 2020 for a patient to be categorized as having pre-pandemic follow-up for this subgroup analysis.

9.5 Missing Data

Baseline data, except for spirometry measurements, are expected to have few or no missing values. Baseline spirometry measurements are expected to be missing for a small portion of patients due to patient refusal/inability, administration error, or spirometry measurements having insufficient quality. Data from the 12-month medical record review are expected to be missing for a small portion of patients (among those selected for follow-up) due to various problems accessing the medical record. Data from the 12-month patient survey are expected to be missing for a significant portion of patients due to patients not returning completed surveys.

Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. We will summarize the extent of missing data by intervention group. Patient demographics, other baseline characteristics, and available 12-month follow-up data will be compared between those with and without complete follow-up data, among those who were prospectively selected for follow-up, overall and by intervention group.

The primary analysis of the primary and secondary endpoints will be among those with complete follow-up (complete data for the relevant portions of both the chart review and follow-up survey).

For each Aim 3 endpoint that is collected via both medical record review and patient survey, sensitivity analyses will be conducted by imputing missing outcome data using different assumptions and applying the primary analysis method to the resulting data sets. Sensitivity analyses will include

1. Imputation of negative responses (i.e., responses indicating that the outcome has not occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review data
2. Imputation of positive responses (i.e., responses indicating that the outcome has occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review data; and
3. Multiple imputation of all missing outcome data using the observed outcomes and covariates, as described below, followed by analysis of all patients selected for follow-up.

Multiple imputation of missing values in the baseline and 12-month follow-up data will be used to create 20 complete data sets. The set of patients included in each data set will be all of those selected for 12-month follow-up. The imputation method will be multivariate imputation by chained equations (MICE)[6] as implemented in the R package 'mice'[7].

Missing values of baseline spirometry FVC % predicted and FEV_1 % predicted will be imputed using linear regression models with the following predictors: age, gender, height, race, education, BMI, CAT score, asthma history, short-acting bronchodilator use, maintenance respiratory medication, and any follow-up outcomes for which baseline spirometry measurements will serve as predictors (selection of those predictors is described below). Predicted FVC and FEV_1 volumes will be calculated from the NHANES reference equations, allowing for calculation of the FVC, FEV_1, and FEV_1/FVC corresponding to the imputed % predicted values as needed.

For the purpose of organizing the imputation procedures, the 12-month follow-up outcomes will be grouped as follows:

- Pulmonary care outcomes:
    - Spirometry referral/completion
    - New diagnosis of COPD
    - New prescription for respiratory medication
    - Referral to pulmonologist or other respiratory specialist
    - Pulmonary rehab referral/completion
- Flu vaccination:
    - Flu shot recommended/ordered/administered
- Smoker-specific outcomes:
    - Counseling/recommendation for smoking cessation
    - Smoking cessation program referral/completion
    - New prescription for smoking cessation medication
    - Referral to a smoking quit line

Missing values of follow-up outcome variables, all of which will be binary (yes or no), will be imputed

using logistic regression models. For each outcome variable, the predictors will include, minimally, the following:

- All other variables from the medical record review and follow-up survey within the same group of outcomes. That is, medical record review data will be used to impute missing follow-up survey data, and follow-up survey data will be used to impute missing medical record data.
- Intervention group interacting with CAPTURE status. Intervention group must be included to avoid bias when using the imputed data to estimate the intervention effect. Interaction with CAPTURE status is included because the intervention effect is hypothesized to depend on the different recommendations associated with being classified as CAPTURE+ vs CAPTURE–.

Additional baseline predictors for imputing outcome variables will be included in the imputation procedure based on examination of study data that are blinded with respect to intervention group (pooled across intervention groups), assessing the association of each baseline variable with 1) whether the outcome data is missing, and 2) the outcome itself (among those with complete outcome data). To avoid including extraneous predictors, which may cause problems in fitting the logistic regression models and generating accurate imputations, we will use only baseline predictors that are associated with *both* the outcome missingness *and* the outcome itself, for at least one outcome in the group, based on p-values <0.01 from t tests[1] and chi-square tests[2]. These additional baseline predictors will be selected separately for the medical record review variables and for the follow-up survey variables.

Based on the study data on March 21, 2023, from study sites for which all follow-up data have been collected (representing about 84% of the patients selected for follow-up), the additional baseline predictors for each outcome group would be the following:

Outcome variable(s)	**Predictors for medical record review**	**Predictors for follow-up survey**
Pulmonary care outcomes	PBRN Practice type Practice size (# clinicians) Patient enrollment date Education	Race Education Health insurance Smoking status FEV_1 % predicted
Flu vaccination	PBRN Practice type Practice is a residency site Race Ethnicity Education	PBRN Age Race Education Health insurance Ever had flu shot
Smoker-specific outcomes	PBRN Practice type Practice is a residency site Practice size (# clinicians) Education	PBRN

9.6 Interim Analyses and Data Monitoring

There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity every 6 months.

9.7 Multiple Testing

Two-sided p-values will be reported. When the primary analysis is repeated for each component of the primary endpoint (spirometry referral/completion, new COPD diagnosis, newly prescribed inhaled medication, referral to a respiratory specialist, and pulmonary rehabilitation referral/completion), a Bonferroni correction will be applied to that set of hypothesis tests. Otherwise, no adjustments for multiplicity will be made across analyses of primary and secondary endpoints and other exploratory analyses. Thus, corresponding p-values for these secondary and exploratory outcomes will be interpreted with caution. Confidence intervals will be provided to summarize treatment differences for efficacy end points.

10 Summary of Study Conduct Data

Descriptive summary statistics will be tabulated for baseline patient demographics and clinical characteristics as well as practice characteristics, separately by intervention group and overall. Intervention groups will be characterized as "Basic COPD Education" and "Basic COPD plus CAPTURE Education". For pooled summaries, "All" will be used as the column heading. All tables will be annotated with the total population size relevant to that table, including any missing observations.

For continuous variables, sample means and standard deviations will be reported. P-values corresponding to two-sample t-tests[1] comparing mean differences between intervention groups will be reported. For categorical variables, number and percentages will be reported (excluding missing values). P-values corresponding to Pearson's[2] chi squared statistic or Fisher's[3] Exact test for testing association between categorical predictors and intervention groups, as appropriate, will be given.

10.1 Practice and Subject Disposition

Practice Disposition: The number of practices approached for study participation, those that subsequently enrolled in the study and those that declined will be given in a CONSORT Diagram.

Subject Disposition: The number of participants approached for study participation either by phone or in person, the number that subsequently consented and enrolled versus not enrolled (including reasons: screen failures, refusals) will be summarized in a CONSORT diagram. The number of participants selected for 12-month follow-up, and who subsequently had complete versus incomplete follow-up will also be given.

10.2 Protocol Deviations

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level.

The most likely protocol deviation is missing 12-month follow-up data in those selected for follow-up, which will be summarized in a CONSORT diagram as described in section 10.1.

10.3 Demographic and Baseline Variables

Demographic and baseline variables for patient participants include:

- Age in years at consent
- Sex (Male, Female)
- BMI
- Race (American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, Unknown or Not Reported)

- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino, Unknown or Not Reported)
- Educational status (Less than High School Graduate, High School Graduate/GED, Vocational/Some College, College Degree, Professional/Graduate Degree, or Not Reported)
- Employment status (Working, Not working, or Not Reported)
- Smoking status (Current, Former, Never, or Not Reported)
- Living arrangement (Alone, Not alone, or Not Reported)
- Insurance provider (Private, Public, None, or Not Reported)
- Baseline FVC
- Baseline FEV_1
- Baseline FEV_1/FVC
- Use of rescue respiratory medication (Yes if participant uses at least one short-acting bronchodilator, No, or Not Reported)
- Use of maintenance respiratory medication (Yes if participant uses at least one of the following: LABA, LAMA or inhaled corticosteroid [ICS]; No; or Not Reported) and type/combination of medications (ICS alone, LABA or LABA alone, LABA combined with ICS, LAMA combined with ICS, LABA combined with LAMA, LABA and LAMA combined with ICS)
- Cardiac morbidity (Yes if participant lists angina, coronary artery disease, heart attack, coronary artery bypass surgery, angioplasty/cardiac stents or congestive heart failure, No, or Not Reported)
- Use of supplemental oxygen (Yes, No, or Not Reported)
- COPD Assessment Test (CAT) Score
- Cohort membership as defined in section 6.1 (Spirometrically Defined COPD, Clinically Significant COPD, Mild COPD, PRISm, SNO, No COPD by Spirometry).

Practice-level baseline covariates include:

- Location (Rural, Non-rural)
- Type of practice (Federally Qualified Health Care Center
  Part of large health system, ACO or similar (not affiliated with a medical school),
  Part of academic medical center/health system, Independent practice, Other)
- Presence of a residency program (Yes, No)
- Practice size as defined as the total number of primary care MD/DOs and NP/PAs
- Ability to perform in-house spirometry (Yes, No).

The primary study demographic and baseline variables table will have columns for CAPTURE positive, CAPTURE negative, and overall study populations. A separate demographics table will be constructed with columns depicting spirometrically defined COPD populations.

10.4 Intervention Fidelity

Completion of the clinician education is confirmed by either review of an attendance sheet for group education or online registration of the required educational videos. For patient participants who are enrolled in a CAPTURE intervention site, confirmation of giving the completed and scored CAPTURE screening tool to the patient participant's clinician is confirmed by written affirmation of the research associate completing the patient's study visit. For each practice, we will summarize the percentage of participating clinicians who completed educational training. For practices randomized to the CAPTURE intervention arm, we will summarize the percentage of enrolled participants whose CAPTURE information is provided to clinicians. Summary statistics for each of these variables across practices will be provided.

On-site monitoring visits are conducted to review all scoring of the CAPTURE tool. In the subset of participants where on-site monitoring is conducted, we record: 1) whether or not the CAPTURE Tool

is scored correctly on the source document and 2) whether or not the score is transcribed correctly into the clinical database. We will provide percentages for 1 and 2 overall and by practice.

Additionally, all spirometry tests are reviewed and graded for quality by one of the investigators (DMM). Quality results are reviewed with PBRN teams and any needed retraining completed to achieve the goals of 100% CAPTURE scoring accuracy and 90+% interpretable spirometry results. We will define a usable spirometry value for each participant as being of quality A-D. Using this information, we will summarize the percentage of participants with usable spirometry, overall and by practice.

11 Efficacy Analyses for the Cluster Randomized Trial (Aim 3)

11.1 Primary Efficacy Analysis

The primary efficacy analysis is restricted to CAPTURE+ participants, denoted in section 9.3 as population 1 (Primary Analysis Population). The primary analysis will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE+ subjects will not contribute to this analysis. A two-sample test comparing average cluster sample proportions will be used that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE)[4] regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) an identity link function so that the coefficient parameter corresponding to CAPTURE intervention group represents a difference in outcome probability. The primary analysis would then correspond to a test for whether the CAPTURE intervention group parameter is non-zero.

Technical Details of the Primary Analysis:
This analysis is restricted to CAPTURE+ participants (Primary Analysis Population)
Let $\pi_{ij} = P(\text{Participant } j \text{ from Practice } i \text{ Meets the Primary Endpoint})$.
Let $CAPTURE_i = I(\text{Practice } i \text{ Received Basic COPD plus CAPTURE education intervention})$
Let PRACTICE take on values $i = 1, \ldots, 100$ denoting the enrolled practices
For the primary analysis, the GEE model takes the form
$\pi_{ij} = \beta_0 + \beta_1 CAPTURE_i$, where binary outcomes from the same practice are assumed to follow a compound symmetry correlation structure.

R code for the Primary Analysis:

If the R dataset representing CAPTURE+ patients is called **final** and variables are
MetComp=1 if individual met primary (composite) outcome, 0 otherwise
CAPTURE=1 if individual was from a practice randomized to the Basic COPD plus CAPTURE education intervention, 0 otherwise
Practice is a variable with values $1, \ldots, 100$ denoting the enrolled practices
Then using the **geeglm** function from the **geepack** package, the R code to run the primary analysis is

```
geeglm(MetComp ~ CAPTURE,
    family = binomial(link = "identity"),
    data = final,
    id = Practice,
    corstr = "exchangeable")
```

11.2 Secondary Efficacy Analyses

Secondary Analyses of Primary Outcome: The primary analysis as described in section 11.1 will be repeated in analysis populations 2-8 as given in section 9.3 overall and by subgroups described in section 9.4. For analysis population 1, the primary analysis as described in section 11.1 will be repeated in subgroups described in section 9.4.

In addition, multivariable GEE regression analyses will be conducted separately in populations 1-8 from section 9.3, where the primary composite outcome is modelled using individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed.

Efficacy Analyses of Secondary Outcomes: All analyses in this section will be conducted (separately) for each study population 1 through 8 described in section 9.3 overall and by subgroups described in section 9.4.

We will use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to the CAPTURE intervention group.

In the subset of patients who report being current smokers at baseline, we will study additional binary outcomes, such as incidence of physician counselling/recommendation to stop smoking, physician referral to a formal smoking cessation program, newly prescribed smoking cessation medication, and referral to a smoking quit line, individually and in a composite outcome that also incorporates the primary outcome components.

Multivariable GEE models will incorporate individual and practice level covariates into the analysis of individual components of the composite outcome. Model selection in multivariable secondary analyses will be based on statistical significance at the 0.05 level using GEE robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest as given in section 9.4.

Change in CAT score and change in number of episodes of respiratory illness requiring antibiotic/steroid treatment will be analyzed using mixed[5] models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Subject to having sufficient mortality events, survival analysis[6] allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE.

Secondary Analyses Using Single Imputation: Primary and secondary efficacy analyses of outcomes collected via both medical record review and patient survey will be repeated among patients with complete medical record review data, imputing a single value for missing outcome components from the patient survey. One analysis will impute a negative outcome (i.e., the event did not occur) for each missing survey response; another analysis will impute a positive outcome (i.e., the event did occur) for each missing survey response. Complete-data analyses described in sections 11.1 and 11.2 will be performed on each complete data set produced by imputation.

Secondary Analyses Using Multiple Imputation: Primary and secondary efficacy analyses will be repeated using data sets generated by the multiple imputation procedure described in section 9.5. Complete-data analyses described in sections 11.1 and 11.2 will be performed on each complete data set produced by multiple imputation. Parameter estimates and standard errors will be

combined across the multiply imputed data sets using the method of Rubin[8], which is implemented by the pool() function in the R package 'mice'. Specifically, for each parameter of interest, let Q_i be the parameter estimate from data set i , with associated complete-data variance U_i. Let *m* be the number of imputed data sets. Then

$\overline{Q} = \frac{1}{m}\sum_{i=1}^{m} Q_i$ (the average of the *m* estimates)

is the overall parameter estimate. Let

$\overline{U} = \frac{1}{m}\sum_{i=1}^{m} U_i$ (the average of the *m* variances)

and

$B = \frac{1}{m-1}\sum_{i=1}^{m}\left(Q_i - \overline{Q}\right)^2$ (the variance in estimates between data sets).

Then the overall parameter estimate $\overline{Q}$ has variance estimated by

$$T = \overline{U} + \left(1 + \frac{1}{m}\right)B$$

A confidence interval and p-value for the test of whether the parameter is non-null will be computed from $\overline{Q}$ and T based on a *t* distribution.

12 Safety Analyses

Safety data, including AEs and SAEs will be summarized descriptively overall and by treatment group for the safety population. Coding into organ system will be performed by the study chairs for AEs and SAEs. The following organ systems will be summarized: cardiovascular disorders, dermatological disorders, gastrointestinal disorders, hematological disorders, metabolic disorders, musculoskeletal and connective tissue disorders, neurological disorders, psychological disorders, pulmonary disorders, renal and urinary disorders, hepatobiliary disorders, and other disorders.

12.1 Extent of Exposure

The summary statistics will be produced using intervention fidelity measures given in section 10.4.

12.2 Adverse Events

Descriptive summary statistics for adverse events (AEs) during the baseline visit will be reported. The number of AEs during baseline and the frequencies (number and percentage) of participants with one or more AEs will be summarized by treatment group and overall.

In accordance with clinicaltrials.gov reporting requirements, the following table summarizing adverse events is required and will be provided:

- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed 5% within either treatment group, grouped by organ system, with number and frequency of such events in each treatment group.

The summary statistics will be produced in accordance with section 10.

12.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Descriptive summary statistics for serious adverse events (SAEs) during baseline will be reported. The number of SAEs during baseline and the frequencies (number and percentage) of participants with one or more SAEs during baseline will be summarized overall, by treatment group, and by body system.

A subject listing of all SAEs during baseline, SAEs during baseline causing study discontinuation, and deaths will be presented.

In accordance with clinicaltrials.gov reporting requirements, the tables below summarizing deaths and SAEs are required:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each treatment group.
- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each treatment group.

The summary statistics will be produced in accordance with section 10.

12.4 Pregnancies

No relevant measures are collected as part of the CAPTURE study.

12.5 Clinical Laboratory Evaluations

No relevant measures are collected as part of the CAPTURE study.

12.6 Prior and Concurrent Medications

Prior relevant medications are summarized as baseline variables in section 10.3:

- Use of rescue respiratory medication (Yes if participant uses at least one short-acting bronchodilator, No, or Not Reported)
- Use of maintenance respiratory medication (Yes if participant uses at least one of the following: LABA, LAMA or anti-inflammatories, No, or Not Reported)
- Use of supplemental oxygen (Yes, No, or Not Reported)

12-month follow-up assessments record new prescriptions for respiratory medication after the baseline visit (long acting bronchodilator, inhaled steroids, oral anti-inflammatory), vaccination status, and in smokers, a new prescription for smoking cessation medication

12.7 Other Safety Measures

No additional safety measures are collected as part of the CAPTURE study.

13 Other Analyses

13.1 SARS-COV-2 Impact on Study Enrollment, Follow-up and Power

We have performed additional analyses for the CAPTURE DSMB regarding the impact of SARS-COV-2 on study power for the cluster randomized clinical trial described in Aim 3 of the CAPTURE protocol, summarized in a Memo dated March 30, 2020. Sections of the memo relevant to the SAP are repeated below.

At the time of placing enrollment on hold, the CAPTURE study was ahead of enrollment projections with a goal of completion of all patient enrollment by January 31, 2021. Table 1 displays enrollment data for each of the CAPTURE study's six enrolling PBRNs as of March 19, 2020, the date the last of

the six PBRNs temporarily stopped enrollment.

Table 6.

PBRN site	Date enrollment put on hold	Number of practices enrolled as of 19MAR2020 (goal)	Number of patients enrolled as of 19MAR2020 (goal)	Estimated date of resumption of enrollment
A	13MAR2020	15 (20)	663 (1000)	Indeterminate
B	16MAR2020	15 (20)	750 (1000)	Indeterminate
C	16MAR2020	9 (20)	431 (1000)	Indeterminate
D	19MAR2020	6 (8)	280 (400)	Indeterminate
E	13MAR2020	11 (20)	468 (1000)	Indeterminate
F	16MAR2020	12 (13)	446 (650)	Indeterminate

As of April 1, 2020, none of the sites has an estimate of when enrollment will be able to resume. This information will be added as soon as such information becomes available.

Projected Enrollment Impact

To facilitate planning, projections on patient and practice enrollment impacts for Aim 3 have been developed. These projections are based on several assumptions.

1. Monthly enrollment rates of 100 or 125 patients as continuation and 5 new practices enrolled per month, consistent with prior data.
2. Two, four and six-month delays in enrollment.

Table 7.

Enrollment suspension length assumption	Enrollment re-start date	Enrollment rate/month	Total number of participants (practices) enrolled by 31JAN2021	Total number of participants enrolled by 31MAR2021
2 months	1-Jun-20	100	3850 (100)	4050
4 months	1-Aug-20	100	3650 (100)	3850
6 months	1-Oct-20	100	3450 (90)	3650
2 months	1-Jun-20	125	4050 (100)	4300
4 months	1-Aug-20	125	3800 (100)	4050
6 months	1-Oct-20	125	3550 (90)	3750

We evaluated other scenarios including being able to increase enrollment to 150 patients per month with delays of two, four and six months and ending enrollment in January 2021 and March 2021.

Impact on Follow-up

The tables below present information on the initiation dates of the 12-month medical record abstraction by PBRN and the information on 12-month patient survey follow up as of March 25, 2020.

Table 8. 12-month Medical Record Abstraction (As of March 19, 2020)	
PBRN Site	**Original ideal date of starting for 12- month medical records abstraction**
A	23MAR2020
B	30MAR2020
C	Unknown
D	Unknown
E	06APR2020
F	No eligible patients until September 2020

Table 9. 12-month Patient Survey – COPD Foundation As of 3/25/2020	
Number Eligible	380
Phone Only	118
Email	256
Mail Only	6
Completed 12 Month Survey	248 (65%)
Web	84
Phone	134
Mail	30
Mailed Surveys	120
Lost to Follow-Up	20

Since all surveys are done by email, telephone call or mailings, there are no planned disruptions of the 12-month follow up patient surveys. All staff triggering email surveys, making telephone calls or preparing mailings are working from home.

Impact on Power

The goal of Aim 3 is to define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. This Aim depends on the overall number of patients identified who are CAPTURE+, the number of practices enrolled as well as the ability to complete longitudinal follow-up.

Calculations were performed assuming 10 CAPTURE+/practice based on 67 total practices with > 1 CAPTURE+ patients (actual current state) taking into account loss of power due to variable cluster sizes. These data suggest that we are on track for having a well powered study for the primary analysis, even if additional data is difficult to obtain post-COVID crisis.

Table 10. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group vs usual care, assuming 5% performance rate in usual care; 67 total practices; 10 CAPTURE+/practice					
Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	0.76	0.92	>0.99	>0.99	>0.99

ICC=0.10	0.65	0.84	0.98	>0.99	>0.99
ICC=0.15	0.55	0.76	0.95	>0.99	>0.99

However, we have important secondary analyses that include determining whether care is improved for patients who have spirometrically defined COPD. Based on data accumulated to date, we have a prevalence of roughly 2 spirometrically defined COPD patients per practice. These subsequent calculations demonstrate that based on 2 COPD patients/practice but with otherwise similar assumptions to Table 6, we would not be well powered for small effect sizes. Hence, while we would have important usable data should the study be unable to continue, the returns on investment made to date are far from fully realized. We strongly believe that all attempts should be made to complete the study as planned if we want to have the impact originally intended for this study, namely understanding whether screening benefits undiagnosed patients with COPD.

Table 11. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group vs usual care, assuming 5% performance rate in usual care; 67 total practices; 2 COPD/practice

Improvement over usual care	+7.5%	+10%	+15%	+25%	+50%
ICC=0.05	<0.50	<0.50	0.69	0.95	>0.99
ICC=0.10	<0.50	<0.50	0.67	0.95	>0.99
ICC=0.15	<0.50	<0.50	0.65	0.94	>0.99

14 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

14.1 Changes from Protocol-Planned Analyses

The following describes additional analyses that were not described in the protocol (Version 3.0, 26 September 2019) or modifications of protocol-specified analyses. These changes reflect advances in our knowledge since the design of the study in 2018 that were not incorporated as protocol amendments, but were discussed during the formation of the Statistical Analysis Plan. These changes were made prior to the database lock.

14.2 New SARS-COV-2 Inspired Analyses

The SARS-COV-2 pandemic has affected patient and practice enrollment and will potentially affect practice patterns moving forward. As part of the next protocol revision, the CAPTURE study plans to collect additional SARS-COV-2 inspired patient and practice information. This is a placeholder to update analyses once the next version of the protocol is complete. Of particular note will be analyses of additional data collected in response to SARS-COV-2 and analyses studying trends of 12-month outcomes that account for calendar time of collection

Protocol: N/A

SAP: 10.2.1 Secondary analyses of primary outcome

Additional sensitivity analyses will be conducted to assess the influence of the SARS-COV-2 pandemic on primary and secondary analyses. For the purpose of these analyses, we assume that participants who have completed their 12-month visit by March 19, 2020 provided baseline and 12-month follow-up measures that were unaffected by SARS-COV-2. We define an indicator variable SARS-COV-2=0 if a participant's baseline and 12-month follow-up measures were unaffected by SARS-COV-2 or SARS-COV-2=1 if participant's baseline or 12-month follow-up measures were affected by SARS-COV-2. All primary and secondary analyses will be repeated in the two cohorts defined by SARS-COV-2=1 or SARS-COV-2=0.

Protocol: N/A

SAP:10.2.2 Efficacy analyses of secondary outcomes

15 References

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16 Listing of Tables, Listings and Figures

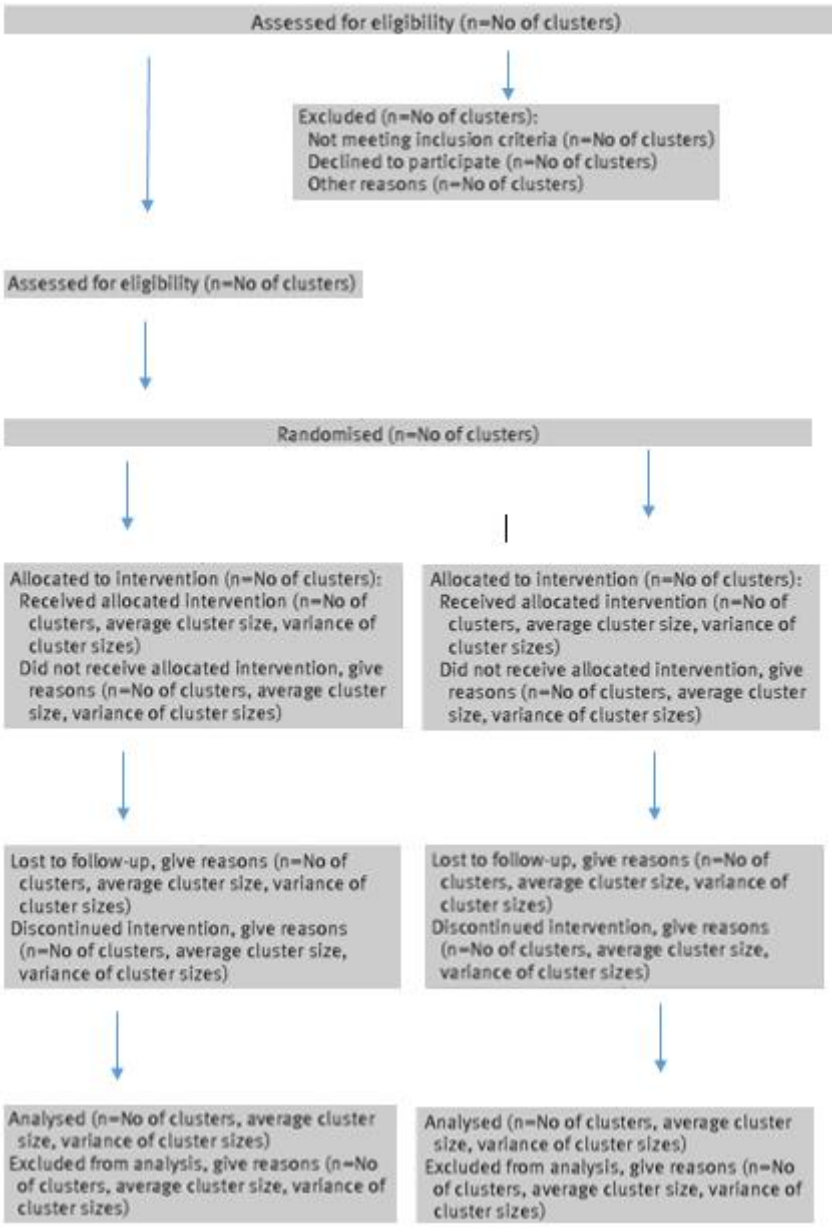
Assessed for eligibility (n=No of clusters)
Excluded (n=No of clusters):
Not meeting inclusion criteria (n=No of clusters)
Declined to participate (n=No of clusters)
Other reasons (n=No of clusters)
Assessed for eligibility (n=No of clusters)
Randomised (n=No of clusters)
Allocated to intervention (n=No of clusters):
Received allocated intervention (n=No of clusters, average cluster size, variance of cluster sizes)
Did not receive allocated intervention, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Allocated to intervention (n=No of clusters):
Received allocated intervention (n=No of clusters, average cluster size, variance of cluster sizes)
Did not receive allocated intervention, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Lost to follow-up, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Discontinued intervention, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Lost to follow-up, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Discontinued intervention, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Analysed (n=No of clusters, average cluster size, variance of cluster sizes)
Excluded from analysis, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)
Analysed (n=No of clusters, average cluster size, variance of cluster sizes)
Excluded from analysis, give reasons (n=No of clusters, average cluster size, variance of cluster sizes)

Figure. 12