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CARE FOR ALL

Change Asthma Clinical Practice through Guideline Education and Implementation For All Patients with Asthma: an Evaluation of an Asthma Quality Improvement Program

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number:

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Study Intervention: GINA guideline education and implementation
Study Phase: Not applicable

Short Title: CARE FOR ALL: an Evaluation of an asthma QIP

Acronym: **CARE FOR ALL**

Study Physician Name and Contact Information will be provided separately

National principal investigator

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Change Asthma Clinical Practice through Guideline Education and Implementation For All Patients with Asthma: An Evaluation of an Asthma Quality Improvement Program

Short Title:

CARE FOR ALL: an Evaluation of an asthma QIP

Rationale:

Asthma is a chronic inflammatory disease that affects more than 300 million people worldwide, and is associated with impaired asthma control, risk of acute exacerbation, and compromised health-related quality of life, leading to increasing use of health care resources. Despite existing updated guidelines and the availability of recommended and effective therapies, the awareness and implementation of evidence-based management among physicians and patient outcomes in the real world setting remain sub-optimal in China. There is a significant gap between guideline recommendations and clinical practice in China. Physicians play a critical role in implementing guidelines and adopting recommended treatment pathways. The objective of CARE FOR ALL study is to bridge the gap that exists between GINA guideline recommendations and current clinical practice by demonstrating the benefits of an asthma quality improvement program (QIP), i.e. a standardized pulmonologist-targeted GINA guideline education and practice implementation.

Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• To evaluate the change in GINA guideline-recommended treatments after guideline education and implementation.	• Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 48
Secondary	
• To describe the asthma control after guideline education and implementation.	• Change from baseline in the proportion of participant with well-controlled asthma (ACQ-5 ≤ 0.75) at week 48 • Distribution of ACQ-5 average scores [proportion of subjects well-controlled (ACQ-5 ≤ 0.75), partially controlled (0.75 to 1.5) and not

	well-controlled (ACQ-5 ≥ 1.5)] at week 12, 24, 36 and 48
• To describe the change in GINA guideline-preferred treatments during guideline education and implementation.	• Change from baseline in the proportion of participants on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48
• To describe the change in asthma control during guideline education and implementation.	• Change from baseline in ACQ-5 average score at week 12, 24, 36 and 48 • Change from baseline in the proportion of participants achieving an improvement in ACQ-5 MCID of 0.5 units or more at week 12, 24, 36 and 48
• To describe the change in GINA guideline-recommended treatments during guideline education and implementation.	• Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36
• To describe asthma related treatment patterns during the study duration.	• Asthma related treatment patterns – Asthma treatment distribution at baseline and weeks 12, 24, 36, and 48, e.g., ICS-containing medications, ICS-LABA, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, Traditional Chinese Medicine
Exploratory	
•	•
	•
•	•

Overall Design

This is an evaluation on an asthma Quality Improvement Program (QIP, including GINA guideline education/training and implementation) to understand the change of physician behaviours, which leads to the change of patient outcomes.

Number of Participants:

A total of around 30 eligible Tier 3 and Tier 2 hospitals will be selected across China. Approximately 1500 eligible asthmatic patients fulfilling the following inclusion and exclusion criteria will be enrolled consecutively from participating hospitals,.

Inclusion criteria:

1. Participant must be 14 years of age or older, at the time of signing the informed consent.
2. Physician-confirmed asthma diagnosis with documented evidence of variable expiratory airflow limitation (e.g. from bronchodilator reversibility testing or other tests)
3. Participating patients and/or their legally authorised representative must provide signed and dated written informed consent form prior to any mandatory study specific procedures.

Exclusion criteria:

1. Previous diagnosis of chronic obstructive pulmonary disease (COPD) or other clinically relevant chronic respiratory disease other than asthma
2. Any significant disease or disorder (e.g. cardiovascular, pulmonary other than asthma, gastrointestinal, hepatic, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study
3. Disease or condition other than asthma that requires treatment with systemic or oral steroids
4. Participation in another clinical study with an Investigational Product administered in the last 3 months prior to Visit 1.

Intervention Groups and Duration:

The QIP (including GINA guideline education/training and implementation) will be delivered at the hospital level, targeting pulmonologists and specialist nurses at participating hospitals, including initial comprehensive education, reinforcement learning, and performance assessment and feedback of pulmonologists' guideline implementation, along with multiple online and offline approaches serving as reminders and supportive tools to ensure consistent education and to facilitate the asthma management in routine clinical practice in accordance with GINA 2021 recommendation. The online approach will also facilitate pulmonologist and specialist nurses to manage their patients.

The GINA guideline education content is based on GINA 2021 recommendations, e.g., asthma diagnosis and assessment, GINA 2021 recommended evidence-based asthma treatment, patient education, and asthma action plan.

Immediately after the completion of patient recruitment at each participating hospital, pulmonologists and specialist nurses will be requested to attend an initial comprehensive training. pulmonologists are encouraged to implement the asthma management in their routine clinical practice, in accordance with GINA 2021 recommendation. During the study period,

pulmonologists and specialist nurses are required to attend the reinforcement learning organized by the director of the respiratory department at each participating hospital, focusing on guideline reinforcement, target learning based on feedback from the assessment of guideline implementation performance, and case discussion from clinical practice.

Guideline implementation performance will be assessed against pre-defined key performance indicator (KPI) and feedback will be provided to the PI of respiratory departments and national principal investigator.

The patient management online approach includes but not limited to be a repository for patient education material, patient self-management tools [e.g. asthma control questionnaire (ACQ)].

Data Monitoring Committee: Not applicable

Data Collection and Management

The Electronic Data Capture (EDC) system will be used for data collection and query handling. Except for the questionnaires to be completed by participants, all data will be based on what have been generated during routine clinical practice, if available.

At baseline visit (V0), after signed informed consent, patients' demographic and clinical characteristics information will be collected, along with current asthma treatment information and two patient-reported outcomes (PRO) questionnaires (i.e., Asthma Control Questionnaire-5 [ACQ-5] and Asthma Quality of Life Questionnaire (+12) AQLQ(S)+12.

After the initiation of the intervention program, participating patients will return to the study hospital every 12 weeks for on-site follow-up visits (V1 to V5), in accordance with guideline recommendations. During on-site visits, the usual care activities can be performed as needed. Participants are encouraged to come back to the study hospital if they have asthma-related conditions or symptoms worsening. If in emergency case, they can choose to visit a hospital other than the study hospital, and they should report it to study pulmonologists or study staffs once it is possible. In case there are data generated from other hospitals that need to be collected as per protocol, i.e. hospitalization due to exacerbation, the data and supportive documents (e.g., medical record of hospitalization summary) will be required at next on-site visit.

At follow-up visits (V1 to V5), data on asthma-related hospitalizations and outpatient visits will be collected. In addition, PROs, including ACQ-5 and AQLQ(S)+12, will be administered to participants at site and entered by study personnel into the EDC system. MARS-A questionnaire, Questionnaire of asthma knowledge for patient, Inhale skill score for patient, Patient's expectation for asthma treatment will also be administered.

Statistical Methods

The change in GINA guideline-recommended treatment after guideline education and implementation, will be compared between the proportion of patients on with an ICS-based maintenance and/or reliever treatment at Week 48 and the proportion at baseline.

Sample Size Estimations:
Approximately 1500 participants will provide 80% power at a significant level of 0.05 to detect a change from baseline in the proportion of patient on the treatment in accordance with GINA recommendations at Week 48 of 5%. The baseline proportion is assumed to be 40% and a within-participants correlation is assumed to be 0.25. The proportion of missing postbaseline assessment at week 48 is assumed to be 30%.

Statistical Analysis:

General Rules

Unless otherwise stated, all the descriptive summary in this study will be based on the following general methods.

All categorical data will be presented in contingency tables, using absolute and relative frequencies. Percentages will be rounded to the first decimal place and, therefore, may not always add up to 100%. When applicable, 95% confidence intervals (CIs) will be presented with estimates of proportions.

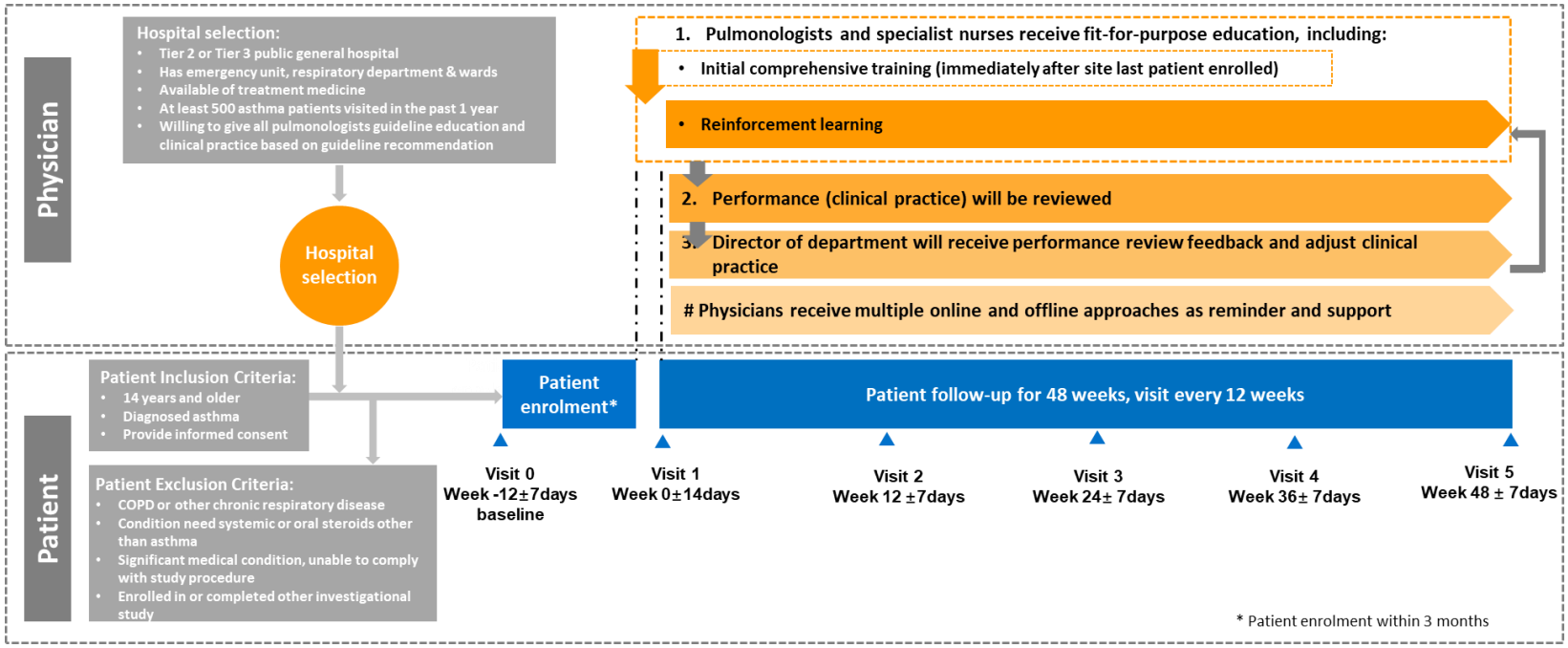
All continuous data will be summarized via relevant descriptive statistics, such as number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1 and Q3) when applicable, minimum and maximum.

Primary Analysis

The primary analysis will use mixed effect logistic regression model, taking the measurement timepoint (baseline/post- baseline) as the fixed effect, hospital, pulmonologist and patient as the random effects. In case of lack of convergency, hospital and prescriber factors will be removed from the model. Within the framework of this model, the 95% confidence interval of the primary endpoint will be estimated and presented. The analysis will be based on FAS population.

1.2 Schema

Figure 1 Study Design



1.3 Schedule of Activities

Table 1 Schedule of Activities (participating patients related)

	Baseline Period	Intervention Period					Details in CSP Section or Appendix
Study Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5 (Study completion/ withdrawal)**	
Weeks	-12 ±7	0 ± 14	12 ±7	24 ±7	36 ±7	48 ±7	
Informed consent [a]	X						
Inclusion and exclusion criteria	X						Sections 5.2.1 and 5.2.2. 2
Demographics [b]	X						
Vital Sign [c]	X						
Subject status [d]	X						
Smoking status [e]	X						
Medical history (comorbidities) and medications [f]	X						
Asthma history & related treatment [g]	X						
Severe asthma exacerbation		X	X	X	X	X	
Hospitalization due to asthma exacerbation since last visit		X	X	X	X	X	Section 8.1.4
ACQ-5	X	X	X	X	X	X	Section 8.1.5.1
AQLQ(S)+12	X	X	X	X	X	X	Section 8.1.5.2
PFT	X					X	
MARS-A questionnaire	X		X	X		X	
Questionnaire of asthma knowledge for patient	X		X	X		X	
Inhale skill score for patient		X	X	X		X	

	Baseline Period	Intervention Period					Details in CSP Section or Appendix
Study Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5 (Study completion/ withdrawal)**	
Patient's expectation for asthma treatment	X		X	X		X	
Laboratory assessments within prior 3 months (if available in medical records) [h]	X	X	X	X	X	X	
PFT/BPT/PEF/FeNO within prior 3 months (if available in medical records)	X	X	X	X	X	X	
Medical records on asthma related assessment and treatment	X	X	X	X	X	X	
Questionnaire for Asthma Patients during COVID-19[i]	X						Section 8.1.9
Patient evaluation on whose pulmonologists 1. assess symptom control, 2. watch the patient using their inhaler, educate their technique, 3. have a discussion about adherence, 4. develop or review the written asthma action plan, provide patient education, 5. had a PFT before dosage reduction	X	X	X	X	X	X	Section 6.1.2.3

PFT = Pulmonary Function Testing; BPT = Bronchial provocation test; PEF = Peak expiratory flow; FeNO = Fractional exhaled nitric oxide

a. Informed consent must be conducted prior to performing any study procedures including data collection.
b. Demographic includes patient age, gender, race, ethnicity and
c. Vital signs include body mass index (BMI, calculation by height and weight)
d. Subject Status education level, family monthly income, job, residence (urban communities or rural villages), etc
e. Smoking status include current smoker or stopping smoking or restarting smoking, smoking pack-years
f.Asthma related comorbidities, including allergic history, rhinitis, chronic rhinosinusitis, nasosinusitis, gastroesophageal reflux disease, obesity, obstructive sleep apnea, depression, anxiety, eczema, and atopic dermatitis according to ICD-10-CM. Medication includes drugs administered for these asthma related comorbidities within 4 weeks before enrolment
g. Historical data, e.g., the first diagnosed date of asthma and ~~total asthma exacerbation,~~ total number of prescription of systemic glucocorticoid treatment for at least 3 days or emergence visit or hospitalization due to asthma exacerbations during previous 12 months (an emergency room visit due to asthma that required use of systemic corticosteroids or hospitalization due to asthma), home PEF availability, asthma symptoms, severity class evaluated by self-assessment, asthma control level, first asthma-diagnose hospital and Tiers level, hospital numbers for asthma clinic visit in past 12month, medical insurance category, Patient's expectation for asthma treatment , etc
h. Clinical laboratory testing data include CBC with differentiation~~,~~ blood gas analysis (pH, SaO_2, PaO_2, $PaCO_2$, and HCO^{3-}); C-reactive protein; skin allegen prick, total IgE or specific IgE

i: If the patient got COVID-19 infection, then answer the questionnaire, the uninfected patients are not necessary to response. Every subject if has a new infected with COVID-19 should answer one time .

2 INTRODUCTION

2.1 Background and Study Rationale

Asthma is a chronic inflammatory disease that affects more than 300 million people worldwide (Global Asthma Network 2018). Around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected (Global Asthma Network 2018). Globally, asthma is ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease, as measured by disability-adjusted life years. Asthma also imposes significant economic burden on patients, healthcare systems, and the society in all parts of the world. Within China, the overall prevalence of asthma is 4.2% among adults aged 20 years or older, representing 45.7 million adults, as reported by the China Pulmonary Health (CPH) study, a nation-wide survey in China (Huang et al 2019). Meanwhile, asthma in China is likely to increase rapidly due to fast changes in environment and lifestyle, as well as the aging population (Huang et al 2019).

Asthma is associated with impaired asthma control, risk of acute exacerbation, and compromised health-related quality of life (HRQoL), leading to increasing use of health care resources. In the CPH national survey, 15.5% asthma patients reported at least one emergency visit and 7.2% reported at least one hospital admission in the past 12 months due to an exacerbation of respiratory symptoms (Huang et al 2019). Asthma exacerbations range from mild attacks, which interrupt daily life and work productivity, to severe and life-threatening attacks.

The Global Initiative for Asthma (GINA) Strategy Report provides updated evidence-based strategy for asthma management and prevention. For safety, GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone. All adults and adolescents with asthma should receive ICS-containing controller treatment to reduce their risk of serious exacerbations and to control symptoms. Track 1, in which the reliever is low dose ICS-formoterol, is the preferred treatment approach recommended by GINA. Track 2, in which the reliever is a SABA, is an alternative approach if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current therapy. A detailed description of GINA guideline-preferred treatment (Track 1) and guideline-alternative treatment (Track 2) can be found in GINA 2021 (www.ginasthma.org).

Quality of care is often measured in terms of how care is provided in practice in comparison with care recommended in clinical practice guidelines. Clinical practice guidelines synthesize the best available evidence and serve as usual tools to guide clinical decision-making, aiming to minimize the substantial variation in for healthcare delivery in practice. The ultimate goal of clinical guidelines is to improve patient outcomes through a change to evidence-based physician practices. Despite existing updated guidelines and the availability of recommended and effective therapies, the awareness and adherence to evidence-based management among

physicians and patient outcomes in the real world setting remain sub-optimal in China. In short, clinical practice guidelines themselves do not consistently change physician behavior in practice.

Substantial gaps exist between the development and dissemination of clinical guidelines and their implementation in practice. Hospitals where patients sought help for asthmatic symptoms, 96% were tertiary and second level hospitals (internal report).A recent survey of physicians regarding Chinese clinical practice guidelines showed that 86% of Chinese doctors are aware of clinical practice guidelines but self-reported adherence rate was only 50% (Liu et al, 2017). As reported in the CPH study, among people with physician-diagnosed asthma, only 10.2% had received ICS therapy (Huang et al 2019). The current asthma control rate among Chinese asthma patients is around 28.5% (Lin et al, 2017). The sub-optimal management might contribute to the poor control and high exacerbation burden of asthma in China.

The reasons leading to poor patient adherence were self-defined symptom improvement, poor inhaler technique, forgetting to take medication, reluctance to use ICS due to consideration of side-effects, drug dependence or drug tolerance (Du et al, 2021). A face-to-face interview with asthma patients reported certain patient-physician interaction, such as insufficient explanation of asthma and its management, and lack of a patient-centricity approach by the physician, as barriers to long-term ICS use (Suvina Amin et al, 2020).

Physicians play a critical role in implementing guidelines and adopting recommended treatment pathways, and improving patients' self-management and adherence through patient-centricity approaches, such as education. If effective approaches are in place to implement guidelines, recommended management in clinical practice and physicians' adherence to guidelines are expected to increase.

Xie et al conducted a single-hospital retrospective study, where the 2,207 times hospitalization data due to asthma from 2008 to 2017 were retrospectively collected and analyzed. The results showed the implementation of a hospital-level standardized protocol could gradually and persistently reduce the risk of hospitalization as well as exacerbations (Xie et al, 2019). In another study, 3 months after an education program in 83 hospitals in Shanghai (Fang et al 2012), 38.6% of the physicians in the intervention group (vs. 22.9% in control group) reported that they were familiar with GINA. This study suggested that improvement can be achieved in most relevant indices of quality of care through educating the physicians. This evidence suggest a future program of GINA guideline education and implementation in hospital level will increase the adherence to the guideline.

Evidence indicated that various approaches of education can improve patient outcomes. The Colorado Asthma Toolkit Program (CATP) which combined education with decision support tools, electronic patient records and other online support materials, showed positive outcomes. During the study, clinicians received 3 sessions which included training in guideline-based

methods for evaluation and treatment of asthma, coaching to implement these methods in real world practices, and training in communication skills to promote asthma self-management. It was reported that the increase of inhaled corticosteroids in asthma management was 40.4%, with the median percentage of patients taking inhaled corticosteroids rising from 25% to 50% (Bruce G Bender et al 2011).

Meanwhile, the use of electronic health (E-health) has shown the benefits on managing asthma patients especially during COVID-19 pandemic. E-health such as Mobile health applications, might provide disease knowledge, remind medication administration, support asthma self-management, as well as timely communication between physicians and patients, potentially leading to improved patient outcome, and reduce the overall cost for asthma care (Perea et al, 2020).

Several studies have indicated that remote management systems could positively impact patient perceptions about quality of care, which was positively associated with clinical outcome comparing with baseline. A 6-month, prospective multicenter single-arm study, using a novel, remotely connected diabetes management system was associated with increased treatment satisfaction, reduced diabetes distress, and improved glycemic controls in patients (Pablo et al 2017). Another 12-week, single-arm clinical trial of the mobile app intervention described improvement of self-care adherence, diabetes outcome and quality of life (Bree et al 2021).

The objective of the CARE FOR ALL study is to bridge the gap that exists between the recommendations from GINA 2021 and current clinical practice by demonstrating the benefits of an asthma quality improvement program (QIP), i.e. a standardized pulmonologist-targeted GINA guideline education and practice implementation.

We expect that through the QIP, pulmonologists' awareness and adherence to GINA guideline will improve, providing evidence-based treatment and management to patients diagnosed with asthma, leading to reduction in asthma disease burden and improvement in patient outcomes.

2.2 Benefit/Risk Assessment

The CARE FOR ALL study will contribute to our understanding on the impact of improving pulmonologists' adherence to asthma management guidelines, supporting the development of an effective future model for guideline training and implementation.

Pulmonologist education will improve their capability for providing standard management of asthma in terms of correctly diagnosing suspected asthma patients, giving patients recommended asthma medication, and improving the management of asthma patients. It is anticipated that patients participating in CARE FOR ALL are more likely to receive guideline-recommended treatment where they are under the care of pulmonologists who have been successfully educated on the GINA 2021 Treatment Strategy.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the change in GINA guideline-recommended treatment after guideline education and implementation.	• Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 48
Secondary	
• To describe the asthma control after guideline education and implementation.	• Change from baseline in the proportion of participant with well-controlled asthma (ACQ-5 ≤ 0.75) at week 48 • Distribution of ACQ-5 average scores [proportion of subjects well-controlled (ACQ-5 ≤ 0.75), partially controlled (0.75 to 1.5) and not well-controlled (ACQ-5 ≥ 1.5)] at week 12, 24, 36 and 48
• To describe the change in GINA guideline-preferred treatments during guideline education and implementation.	• Change from baseline in the proportion of participants on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48
• To describe the change in asthma control during and after guideline education and implementation.	• Change from baseline in ACQ-5 average score at week 12, 24, 36 and 48 • Change from baseline in the proportion of participants achieving an improvement in ACQ-5 MCID of 0.5 units or more at week 12, 24, 36 and 48
• To describe the change in GINA guideline-recommended treatments during guideline education and implementation.	• Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36
• To describe asthma related treatment pattern during the study duration.	• Asthma related treatment pattern – Asthma treatment distribution at baseline and weeks 12, 24, 36, and 48, e.g., ICS-containing medications, ICS-LABA, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, Traditional Chinese Medicine

Table 2 Objectives and Endpoints

Exploratory	

Table 2 Objectives and Endpoints

4 STUDY DESIGN

4.1 Overall Design

The study will select a total of around 30 Tier 2 and Tier 3 hospitals across China and enrol approximately 1500 asthma patients ≥14 years old with all severities from the 30 participating hospitals. To represent the real-world situation of patients, pulmonologists and treatment practice, hospital selection will include as many as provinces or municipalities in mainland China, where the altitude is below 1,500 meters, while balancing hospital grade (e.g. 10 Tier 2 and 20 Tier 3). Patients will be recruited in hospital outpatient setting, where all potentially eligible asthma patients will be consecutively approached and invited to join the study, e.g., regardless of new patients or treated, exacerbation or regular follow-up.

The QIP (i.e., GINA 2021 guideline education/training and implementation) will be delivered to pulmonologists and specialist nurses in participating hospitals at hospital level, including pulmonologist-targeted initial comprehensive education based on GINA 2021, guideline implementation performance assessment and feedback, reinforcement learning, along with multiple online and offline approaches serving as reminders and supportive tools to ensure consistent education and to facilitate the asthma management in daily clinical practice in accordance with GINA 2021 recommendation.

Immediately after last patient has been enrolled at each site, the study intervention will be initiated, i.e., the initial comprehensive training on GINA 2021 will be offered to pulmonologists and specialist nurses in this hospital. All successfully enrolled participating patients will be followed up for up to 48 weeks and return to recruiting hospital for study visits every 12 weeks. The total participating duration in this study for each participating patient will be approximately 60 weeks.

The study aims to bridge the gap between the recommendations from GINA 2021 and current clinical practice via an asthma QIP (including GINA guideline education/training and implementation).

4.2 Scientific Rationale for Study Design

CARE FOR ALL is designed to evaluate the possibility to change the clinical practice by a QIP, focusing on pulmonologist-targeted GINA2021 guideline training and multiple approaches to ensuing its implementation.

GINA 2021 recommends asthma patients to be assessed every 1 to 3 months during treatment initiation and every 3 months thereafter. Therefore, participating patients will be followed up every 12 weeks, with a total of 6 visits during the study period.

The primary endpoint is to evaluate an ICS-based maintenance and/or reliever treatment,

which is a direct measure of pulmonologist's behaviour on asthma treatment. The key secondary endpoint is to evaluate well-control asthma rate indicated by ACQ-5 ≤ 0.75, which reflect the extent of patients' asthma symptom control. ACQ-5 is a numerical tool assessing asthma control recommended by GINA and widely used in clinical practice and research worldwide.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

Not applicable.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participating patient in the study shown in the Schedule of Activities.

5 STUDY POPULATION

Hospitals will be recruited according to the following selection criteria. The QIP will be delivered at hospital level to all pulmonologists and specialist nurses in the respiratory department.

5.1 Hospital Selection

Tier 2 and Tier 3 hospitals that meet all of the following criteria will be considered for inclusion in this study:

1. Public general hospitals (exclude Traditional Chinese Medicine hospitals)
2. The hospital has emergency unit, respiratory department, with corresponding wards and fundamental respiratory facilities, e.g., spirometry
3. Availability of guideline recommended treatment medicines in the hospital
4. At least 500 asthma patients visited the hospital in the past 1 year
5. Willing to give all the pulmonologists regular guideline education, diagnose and treat asthma patients according to the preferred approach according to the recommendation given by GINA 2021.

To represent the real world situation of patients, pulmonologists and treatment practice, hospital selection will include as many as provinces or municipalities in mainland China, where the altitude is below 1,500 meters, while balancing hospital grade (e.g. 10 Tier 2 and 20 Tier 3).

5.2 Patient Selection

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Patient will be recruited in hospital outpatient setting and all potential eligible patients will be consecutively approached and invited to join the study, e.g., regardless of new patients or treated, exacerbation or regular follow-up, to avoid selection bias.

5.2.1 Patient Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be 14 years of age or older at the time of signing the informed consent.

2. Physician-confirmed asthma diagnosis with documented evidence of variable expiratory airflow limitation (e.g. from bronchodilator reversibility testing or other test)

3. Participating patients and/or their legally authorised representative must provide signed and dated written informed consent form prior to any study specific procedures.

5.2.2 Patient Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Previous diagnosis of chronic obstructive pulmonary disease (COPD) or other clinically relevant chronic respiratory disease other than asthma
2. Any significant disease or disorder (e.g. cardiovascular, pulmonary other than asthma, gastrointestinal, hepatic, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study

3. Disease or condition other than asthma that requires treatment with systemic or oral steroids

4. Participation in another clinical study with an Investigational Product administered in the last 3 months prior to Visit 1.

5.3 Lifestyle Considerations

No lifestyle restrictions will be required in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. These patients should have the reason as "Eligibility Criteria not Fulfilled", i.e., patients do not meet the required inclusion/exclusion criteria.

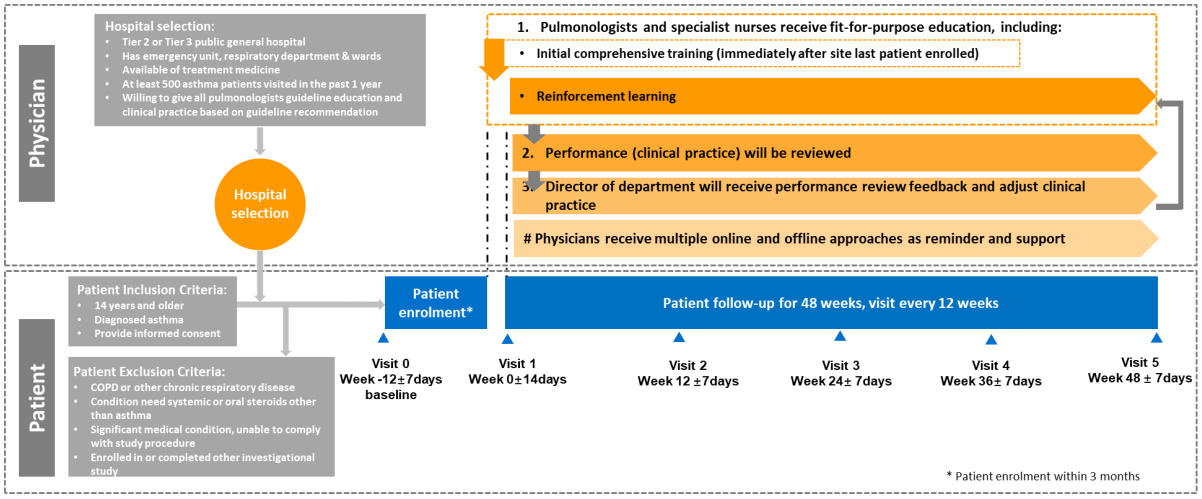
A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information that will be collected on the eCRF includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6 STUDY INTERVENTION

6.1 Study Intervention – Quality Improvement Program

The intervention of Quality Improvement Program (i.e., GINA guideline education/training and implementation) will be delivered at the hospital level, targeting all pulmonologists and specialist nurses at participating hospitals, as illustrated in Figure 1. A scientific steering committee will be established and responsible for the overall quality and successful implementation of the QIP.

Figure 1 Study Design



The guideline education/training part includes pulmonologist-targeted GINA 2021 based initial comprehensive education and regular reinforcement learning (including but not limited to guideline training reinforcement, targeted education based on guideline implementation assessment and feedback, and case discussion). If GINA is updated, the updated content will also be delivered in educational interventions. The investigator information will be collected and analysed, including job category (doctor or nurse), age, years of work experience,

professional title, education background, assessment of inhaler skill score, etc.

The guideline implementation part focuses on regular assessment and feedback on guideline adherence performance in practice. The feedback will be used to guide QIP adjustment, e.g., reinforcement learning.

Multiple online and offline approaches serving as reminders and supportive tools to the QIP. The online approach will also facilitate pulmonologists and specialist nurses to manage their patients.

6.1.1 The Scientific Content of Guideline Education

The education content is based on GINA 2021 recommendations, including the following major components:

- Asthma disease knowledge
- Asthma diagnosis and assessment
- GINA 2021 recommended evidence-based asthma treatment, e.g., low-dose ICS-formoterol as preferred reliver and the scientific rationale. A GINA 2021 based treatment pathway will be suggested to be followed by participating pulmonologists.
- How to educate and manage patients, e.g., written action plan, shared goals development, rationale for medication adherence, difference between reliever and controller, prevention of symptoms and flare-ups, how to recognize worsening asthma and what actions to take, etc.

The scientific steering committee (see section 6.1.2.4) will ensure the education and training materials are scientifically and clinically appropriate and fit-for-purpose.

6.1.2 The Process of Intervention

The QIP includes pulmonologist-targeted guideline education and guideline implementation.

- Guideline education includes the initial comprehensive training and reinforcement learning. The initial comprehensive education will be delivered at each participating hospital by a dedicated qualified team, immediately after last patient enrolled at each site. The PI of respiratory departments from participating hospitals are responsible for arranging the delivery of hospital-level reinforcement learnings, multi-centres reinforcement training and so on. and ensuring the quality and success of hospital-level guideline implementation.
- The pulmonologists' guideline adherence and performance at participating hospitals will

be regularly assessed during the study period.

6.1.2.1 Fit-for-Purpose Pulmonologist-Targeted Education

Guideline education includes the initial comprehensive training and reinforcement learning. Pulmonologists and specialist nurses are required to attend these educations during the study period; and to apply the treatment pathway and patient management into daily clinical practice, in accordance with GINA recommendation, including educating their asthma patients, developing the written asthma action plan and timely interacting with patients.

1) **Initial Comprehensive Training**

Immediately after the completion of patient recruitment at each participating hospital, pulmonologists and specialist nurses will be requested to attend an initial interactive comprehensive training provided by a dedicated and qualified training team (section 6.1.2.5). A questionnaire about the awareness of asthma-related diagnosis and treatment will be conducted to all pulmonologists before the training. A training quiz will be conducted to ensure the successful delivery of the training. It is required that pulmonologists pass the Quiz (score 80 and above). Re-training and re-test will be performed to those pulmonologists who have not passed the Quiz.

After the initial comprehensive training, pulmonologists are encouraged to implement the asthma management in accordance with GINA recommendation in their routine clinical practice, including asthma patient assessment, treatment pathway, patient management, developing and reviewing written asthma action plan.

2) **Reinforcement Learning**

The hospital-level reinforcement learnings will be integrated into the regular department lectures. The PI of respiratory departments from participating hospitals are responsible for the delivery of hospital-level reinforcement learnings, and ensuring the quality and success of hospital-level guideline implementation.

During the study period, pulmonologists, especially those who will work at out-patient department in the upcoming 2 months, are required to attend the reinforcement learning, focusing on guideline training reinforcement, target learning based on feedback from the assessment of guideline implementation performance, and case discussion from clinical practice. The PI of the respiratory departments are responsible for arranging a platform to deliver the reinforcement learnings in case of worsening COVID-19 pandemic.

The frequency of the learning will be monthly in the first 3 months, and it can be decreased to bi-monthly or quarterly in the following study period, if the average proportion of each KPI checkpoint achievement (see section 6.1.2.3) of the respiratory department reaches 80% or

above and obtain the approval from scientific steering committee (see section 6.1.2.4).

For the common clinical issues in the GINA implementation by participating centers, training for all participating centers can be conducted every 3 months.

6.1.2.2 Multiple Online and Offline Approaches as Reminder and Support

Multiple approaches will be used to ensure consistent education and to facilitate the effective implementation of GINA 2021 in routine clinical practice.

1) **Offline Approaches**

- Clinic posters will be provided to illustrate the standard asthma diagnosis, assessment and recommended treatment algorithm included in the training materials, serving as a reminder to pulmonologists and specialist nurses during their clinical practice.

- Patient pamphlets will be provided to pulmonologists and/or specialist nurses to aid patient instruction, e.g. basic information on asthma disease and treatment, treatment compliance, inhaler technique, exacerbation identification in daily life. The content will be in plain language appropriate for laymen.

2) **Online Approaches**

An online platform through WeChat, a unit set-up independently during study period, will support the online approach for pulmonologist-targeted GINA guideline education and for facilitating the patients management by pulmonologists and/or specialist nurses.

- Pulmonologist-targeted GINA guideline education

    - The platform will be a repository for guideline training course and material.

    - The summary of reinforcement learning will be available as a reminder for those who attended and as a supplementary learning material for those who did not.

    - Frequent Asked Questions (FAQ) from Patients will be developed and kept up-to-dated during the study conduct, facilitating patient management by pulmonologists and/or specialist nurses.

- Facilitating the patient management by pulmonologists and/or specialist nurses. The patient management online approach will be a mini-program through WeChat, including but not limited to

    - A repository for patient education material, e.g. how to avoid environmental exposure, how to recognize worsening asthma and what actions to take, inhaler

technique video

- Patient self-management tool to facilitate physician timely evaluate the symptom control and risk factors

- A platform for the communication between pulmonologist and patients (e.g. questions and answers)

6.1.2.3 Guideline Implementation Performance Assessment with Feedback and Adjustment

Guideline implementation performance will be monthly assessed based on pre-defined key performance indicator (KPI).

The guideline implementation performance will be evaluated based on the following 6 checkpoints for each participating participant's visit.

1. Whether or not the pulmonologist or the specialist nurse has assessed the patient's symptom control over the past 4 weeks

2. Whether or not the pulmonologist or the specialist nurse has watched the patient using their inhaler and educate the technique

3. Whether or not the pulmonologist has a discussion about treatment adherence

4. Whether or not the pulmonologist has developed or reviewed the written asthma action plan

5. Whether or not the pulmonologist has reduced the dosage of asthma treatment? If yes, whether or not the patient had a PFT before dosage reduction?

6. Whether or not the pulmonologist has provided the treatment with ICS-containing medication

During the study, the first 5 questions will be evaluated by participating patients with a questionnaire after his/her visit to the pulmonologist(include nurses). The last question will be checked based on the treatment options.

The proportion of each checkpoint achievement will be calculated at department level. identifying where the improvement and the issue might be, to facilitate the future education/training more targeted. The criteria of KPIs will be reviewed by the scientific steering committee (see section 6.1.2.4).

The regular feedback on hospital-level guideline implementation performance will be

provided toThe PI of respiratory departments and national principal investigators. If the guideline implementation performance is not satisfying, the scientific steering committee will lead the discussion with the director of respiratory department on root cause analyses, and provide guidance/instruction for improvement plan.

6.1.2.4 Scientific Steering Committee

A scientific steering committee will be established and responsible for the quality and successful implementation of the overall program. It will consist of external asthma experts and investigators. The Scientific Steering Committee duty include:

- To deliver lecture as a speaker at initial comprehensive education
- To advise the sponsor on amendments to the study design and provide recommendations on issues related to the study conduct, if required.

6.1.2.5 Dedicated Qualified Team to Deliver Initial Comprehensive Education

Initial comprehensive education will be delivered at each participating hospital by a dedicated qualified team, immediately after last patient enrolled at each site. The major topics will be delivered by asthma expert in the same province or in the same region of the participating hospital.

6.2 Preparation/Handling/Storage/Accountability

Not applicable.

6.3 Study Intervention Compliance

Please refer to section 6.1.2.3 Guideline Implementation Performance Assessment with Feedback and Adjustment. Pulmonologists' guideline implementation performance will be assessed monthly based on pre-defined key performance indicator (KPI) and give feedback to the PI of the respiratory department of participating hospital.

6.4 Concomitant Therapy

Medication not related to asthma that the participant is receiving at the time of enrolment or receives during the study will not be recorded, except for systemic or oral steroids, with its medical rationale.

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5 Dose Modification

Not applicable.

6.6 Intervention After the End of the Study

Not applicable.

6.7 Study Bias and Mitigation Plan

A single-arm design is chosen for its potential benefit to recruit more patients into an interventional arm instead of being randomized into a control arm. Before-intervention and post-intervention change will be described within individuals, which will reduce the variability. However, since single-arm studies do not include a direct, concurrent comparison group, their role in informing comparative effectiveness questions is not straightforward. The observed change might be impacted by the factors other than the intervention. This study might be subject to Hawthorne effect, e.g., pulmonologists and patients might change their behavior solely as a result of knowing that they are participating a study and being observed rather than as a result of the intervention. This may present a challenge to result interpretation.

There may be a hospital and patient selection bias, e.g., potential hospitals and patients can refuse to participate in this study leading to impact on the representativeness of the target hospitals and patient population. A total of around 30 hospitals will be selected in this study. To represent the diversity of patients, pulmonologists, and treatment practice in real world, hospital selection will include as many as provinces or municipalities in mainland China, where the altitude is below 1,500 meters, while balancing hospital grade (e.g. 10 Tier 2 and 20 Tier 3). Patients will be recruited in hospital outpatient setting. To minimize patient selection bias, all potentially eligible asthma patients will be consecutively approached and invited to join the study, e.g., regardless of new patients or treated, exacerbation or regular follow-up. The hospital selection and patient enrolment process will be appropriately documented.

Prior to the study intervention, there is 3-month patient recruitment period. During the 3 months, patients' health status may change and they may seek medical care due to asthma. These changes will not be captured in this study.

The intervention will be targeting pulmonologists at site hospitals. To reflect the real world practice, all pulmonologists attending outpatient clinics will be expected to recruit patients. However, depending on the scale of the selected hospitals and actual study operation, the number of participating pulmonologists will vary, as well as the number of pulmonologists who recruit patients, and the number of patients recruited per pulmonologists. These variations may introduce biases into this study. During the study conduct, patient recruitment will be closely monitored for unusual pattern. In addition, the statistical analyses will take into account the within-hospital and within-pulmonologist correlation, by including the hospital and pulmonologist effect into the model as random effect.

Retrospective data based on electronic medical records (EMR) offers a potential source of data collection. However, the original purpose of collecting EMR is for clinical care

management rather than research purpose, so there are inherent limitations in using EMR data to conduct clinical research, e.g., information incompleteness and data inaccuracy. Some data required by the protocol, e.g., ACQ-5 and AQLQ(S)+12, are not routinely collected in clinical practice. As this is a pragmatic study, patients can potentially go to any hospitals or pulmonologists for care during the study and EMR data from site hospitals will not be able to capture all the information. Given these inherent limitations of EMR data, we choose to prospectively collect data from patients in this study.

For data collection in this study, there are a few sources. For example, baseline clinical characteristics information will be based on patients self-reporting. During the study, patients may seek care in a hospital other than the study hospital, which may lead to missing data or inconsistency in data collection. The multiple data sources may introduce inconsistencies in the data and affect the data quality. To minimize the impact, firstly, for baseline data collection, data on treatment pattern and PROs, baseline data will be collected during V0; data on hospitalization due to exacerbation history will also require participating patients to provide evidence, e.g., medical records. Participating patients will be encouraged to visit study participating hospitals if feasible. On the other hand, if participating patients seek care in hospitals other than the study hospital, then data will be collected based on patient-provided hospital medical records.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Not applicable.

7.2 Participant Withdrawal from the Study

- A participating patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

- A participating patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating pulmonologists, or information from medical records).

- At the time of withdrawal from the study, if possible, an Early Study Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

- If the participating patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow up

A participating patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participating patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the participating patient and reschedule the missed visit as soon as possible and counsel the participating patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the participating patient wishes to and/or should continue in the study.

- Before a participating patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participating patient (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

The Electronic Data Capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

Except for the questionnaires to be completed by participants (see SOA), all data will be based on what have been generated during routine clinical practice. Data collection for all enrolled patients will follow up version 2.0.

Baseline data collection

At baseline visit (V0, week -12), the following patient data will be collected from patients:

- Demographic information

- Vital signs include body mass index
- Subject Status
- Asthma history, comorbidities, and medications (historical data)
- Laboratory and clinical testing within 3 months (if available in medical records), including CBC with differentiation, blood gas analysis (pH, SaO_2, PaO_2, $PaCO_2$, and HCO^{3-}), C-reactive protein, skin allegen prick, total IgE or specific IgE, PFT (pulmonary function testing), BPT (bronchial provocation test), PEF (peak expiratory flow) and FeNO (fractional exhaled nitric oxide)
- Current visit asthma treatment information
- Two patient-reported outcomes (PRO) questionnaires (ACQ-5 and AQLQ(S)+12)
- MARS-A questionnaire
- Questionnaire of asthma knowledge for patient
- Inhale skill score for patient
- Patient's expectation for asthma treatment

Follow up data collection

After the initiation of the intervention program, participants will return to the study hospital every 12 weeks for on-site follow-up visits (V1 to V5), in accordance with guideline recommendation. During on-site visits, the usual care activities can be performed as needed.

Participants are encouraged to come back to the study hospital if they have asthma-related conditions or symptoms worsening. If in emergency case, they can choose to visit a hospital other than the study hospital, and they should report it to study pulmonologists or study staffs once it is possible. In case there are data generated from other hospitals that need to be collected as per protocol, i.e. hospitalization due to exacerbation, the data and supportive documents (e.g., medical record of hospitalization summary) will be required at next on-site visit.

At follow-up visits (V1 to V5), the data generated from usual care activities after the initiation of the intervention will be collected from patients, including severe asthma exacerbation, asthma-related hospitalizations, emergency attendances, and outpatient visits, and medications.

In addition, two PRO questionnaires (ACQ-5 and AQLQ(S)+12) will be administered to participants at site at each visit and be entered by study personnel into the EDC system. MARS-A questionnaire, Questionnaire of asthma knowledge for patient, Inhale skill score for patient,

Patient's expectation for asthma treatment will also be administered.

The schedule of assessments and procedures are summarized in Table 1.

8.1 Effectiveness Assessments

8.1.1 GINA Guideline-Recommended Treatment

The primary endpoint is the proportion of patients with an ICS-based maintenance and/or reliever treatment, which is indicated by whether or not the treatment option includes ICS-containing medication.

The pulmonologist will record the current treatment (reliever and controller) at this visit.

8.1.2 GINA Guideline-Preferred Treatments

One secondary endpoint is the proportion of patients on the treatment of ICS-formoterol as reliever, without concomitant SABA.

8.1.3 Asthma Related Treatment Pattern

Asthma related treatment patterns will be evaluated by treatment distribution at baseline and at weeks of 12, 24, 36, and 48, e.g., ICS-containing medications, ICS-LABA, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, Traditional Chinese Medicine and combination.

8.1.4 Hospitalization due to Exacerbations

Hospitalization due to asthma exacerbation is defined as deterioration of asthma that requires a medical intervention as described below:

- A hospital admission.

And

- Prescription with one or more of the following medications to treat asthma symptoms worsening:
  - Systemic corticosteroids
  - Nebulized SABA or SAMA or SABA/SAMA combination
  - Theophylline (injection)
  - New prescription of ICS or increased dose of ICS for at least 3 days (nebulized or inhaled)

8.1.5 Severe Exacerbations

A severe exacerbation defined as worsening asthma leading to the prescription of systemic glucocorticoid treatment for at least 3 days or hospitalization or an ED visit.

8.1.6 Patient Reported Outcomes (PROs)

During the study, two PRO questionnaires (ACQ-5 and AQLQ(S)+12) will be administered to participants at site at weeks of -12 (baseline), 0, 12, 24, 36, and 48. The participants should be given adequate time to complete all items in a quiet environment, ideally prior to their meeting with the pulmonologists. PROs will be completed by participants themselves independently prior to other study procedures. Site personnel should check whether participants completed the questionnaires at the appropriate visit. See Appendix C.

8.1.6.1 Asthma Control Questionnaire-5 (ACQ-5)

Change from baseline in the proportion of patients with well-controlled asthma rate evaluated by ACQ-5, change from baseline in ACQ-5 score and distribution of asthma control status evaluated by ACQ-5 will be evaluated.

The ACQ-5 is a shortened version of the full 7-item ACQ (Juniper et al 1999) that assesses asthma symptoms (night-time awakening, symptoms on awakening, activity limitation, shortness of breath, and wheezing) but omits the FEV1 measurement and SABA use from the original ACQ assessment. Patients are asked to recall how their asthma has been during the previous week by responding to 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-5 score is the mean of the responses. Mean scores of ≤0.75 indicate well controlled asthma, scores between >0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of ≥0.5 are considered to be clinically meaningful (Juniper et al 2005).

The ACQ-5 will be administered to participants at baseline (week -12), week 0, week 12, week 24, week 36, and week 48 and entered into the EDC. ACQ-5 must be completed by the participant at each visit (weeks of 0, 12, 24, 36, and 48) prior to any other study procedure.

8.1.6.2 Asthma Quality of Life Questionnaire (+12) AQLQ(S)+12

The AQLQ(S)+12 (Juniper et al 1992, Juniper et al 2005) is a PRO that measures the health-related quality of life experienced by asthma patients 12 years old and above. The questionnaire comprises 32 items in 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Patients are asked to recall their experiences during the previous 2 weeks before each visit and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥0.5 are considered clinically meaningful (Juniper et al 1994).

A validated Chinese version of AQLQ(S) +12 will be used. AQLQ(S)+12 must be completed by the subject at weeks of 0, 24 and 48, after the ACQ-5 evaluation, prior to other study procedures.

Participants are asked to recall their experiences during the previous 2 weeks before each visit and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The total score is calculated as the mean response to all questions. The 4 individual domain scores are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥ 0.5 are considered clinically meaningful (Juniper et al 1994).

8.1.6.3 Patient Evaluation on Guideline Implementation KPIs

Guideline implementation performance will be assessed based on pre-defined key performance indicator (KPI). After seeing their pulmonologists, participating patients will be asked the following 5 KPI questions:

- Whether or not your pulmonologist or specialist nurse has assessed your symptom control over the past 4 weeks?
- Whether or not your pulmonologist or specialist nurse has watched you using your inhaler and educate the technique?
- Whether or not your pulmonologist has a discussion about why you need a long-term medication adherence?
- Whether or not your pulmonologist has developed or reviewed the written asthma action plan?
- Whether or not the pulmonologist has reduced the dosage of asthma treatment? If yes, whether or not you had a PFT before dosage reduction?

8.1.6.4 Patient's expectation for asthma treatment Questionnaire

Measures of patient's expectation were obtained from the following items that were part of the enrolment interview. Part patients were asked the open-ended question: ''What do you expect from your asthma treatment?" these answers were collected, and high frequency sentences are adopted as options. (Appendix C3)

An established multicomponent model to examine possible variables related to the expectation of being cured, which is also integrated in this questionnaire (Mancuso CA, 2003)

8.1.6.5 Disease Knowledge Questionnaire for Asthma Patients

The questionnaire was designed from ‘The Validity and Reliability of an Asthma Knowledge Questionnaire Used in the Evaluation of a Group Asthma Education Self-Management Program for Adults with asthma’ covers etiology, pathophysiology, drug and disease severity assessment, symptom management (including reducing triggers and exercise). Each question is answered "correctly", "wrongly" or "unsure", the scoring method is positive questions, and the score is correct, and the score is wrong. 1 point for correct judgment and full is 25 points, no points for wrong judgment and unsure choice. (Allen, 1998) According to a local study, based on this questionnaire, it was optimized to 25 items to evaluate the effect of asthma education (Tian, 2014). (Appendix C4)

8.1.6.6 Patient Self-Assessment of Asthma Severity

A question is asked respondents to self-report their asthma severity: “What is the level of severity of your asthma?”. The response choices for questions were “mild”, “moderate”, or “severe”. This question is used to define asthma severity based on self-reported severity. （Ding，2017）

8.1.6.7 Patient Adherence Assessment

Adherence assessment include PDC(proportion of days covered), MPR(medication possession ratio)(Carlyne M.2022)and based on Medication Adherence Report Scale for Asthma, the self-assessment of adherence is developed, more details in Appendix C6, C7.

MARS-A scale consists of 10 items, which are self-reported, and each question is scored on a scale of 1 to 5. The higher the score, the better the adherence. In the end, the average score of 10 questions was taken, and a score of 4.5 or above indicated good adherence. Items have both general and asthma-specific questions. The problem statement is in a negative way. (Jessica 19L Cohen 2009 , Yu 2014) and analysis of the reasons for non-compliance with doctor's orders, the influencing factors of compliance are based on a regional compliance study design in China (Shi, 2019)

8.1.7 Investigator asthma knowledge questionnaire

Asthma knowledge questionnaire for investigator is designed base on CPH survey and asthma guideline. More details in Appendix D.

8.1.8 Inhaler skill score assessment

Regarding the technical standards of inhalation, there are relevant regulations in national guidelines, and the overall process is consistent (Chinese expert consensus on standard application of inhalation device in stable chronic airway disease patients, 2019). Regarding the technical standards of inhalation, there are relevant regulations in national guidelines, and

the overall process is consistent (Chinese expert consensus on standard application of inhalation device in stable chronic airway disease patients, 2019). The study is designed for 7 steps, with 1 point for each step, and the full score is 7 points. The technical evaluation of inhaler is based on devices which commonly used by researchers participating in the study. Inhaler skill shall be assessed by the group from leading site before and after education, and the subjects shall be instructed only after investigators pass this assessment. Random inspections will be conducted during the follow-up period. V1 allows the subjects to demonstrate the inhalation process such as the dosing or the using method with the prepared device, and the researcher controls the operating standard as the baseline. It is recommended that each centre recommend 1-2 physicians or nurses, who are trained and qualified to be responsible for this work, and adopt uniform standards. (Appendix E)

8.1.9 Questionnaire for Asthma Patients during COVID-19

The design of the questionnaire for Asthma patients during COVID-19 refers to the Chinese Cough Alliance “COVID-19 Infection Cough Characteristics and Prognosis Survey Version 1.0” (released in January 2023). If the patient got COVID-19 infection, then answer the questionnaire, the uninfected patients are not necessary to response. Every subject if has a new infected with COVID-19 should answer one time .

8.2 Safety Assessments

Not applicable.

8.3 Collection and Reporting of Adverse Events/Adverse Drug Reactions

8.3.1 Collection of Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section. The definitions of an AE or SAE can be found in Appendix B.

Adverse Events related to AZ product will be collected from the time of starting the study throughout follow-up period specified in the protocol. Regardless the relationship with AZ products, all SAEs will be actively collected. Investigators and/or site staff should report the SAEs to study representatives within 24 hours from awareness, and study representatives need to report the SAEs to AstraZeneca Data Entry Site (AZ DES) within 5 days. For fatal or life-threatening SAEs, the reporting to AZ DES should be within 1 day.

Any AEs that are unresolved at the patient’s last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recorded in the CRF. AstraZeneca retains the right to request additional

information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary.

8.3.2 Reporting of Serious Adverse Event (SAE)

All SAEs have to be reported, whether or not considered causally related to the AstraZeneca product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

8.3.3 Reporting of non-serious Adverse Drug Reaction (ADR)

Any non-serious ADR related to AZ product occurs in the course of the study must be reported per the China regulation.

If any non-serious ADR related to AstraZeneca products occurs in the course of the study, then investigators or other site personnel should inform the AstraZeneca representatives within 5 calendar days when he or she becomes aware of it.

8.3.4 Reporting of Special Situations

Special situations are situations of relevance for monitoring the safety of AZ products and which may or may not be associated with an AE. The investigator must inform the Sponsor Study Representative immediately but no later than 24 hours after becoming aware of any special situation reports.

Individual case safety reports (ICSRs) with special situations will be entered into the AZ Global Safety Database, regardless of whether they are associated with an AE or not. The Sponsor Study Representative will ensure special situation reports without associated SAEs are reported to AZ DES within 30 days of awareness.

8.3.4.1 Overdose

Investigators are advised that any patient, who receives a higher dose than indication use should be monitored closely, managed with appropriate supportive care, and followed up expectantly.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

8.3.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

8.3.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the outcomes of any conception occurring from the date of the first dose of study medication until 1 month after the last dose of AstraZeneca medication must be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the efficacy of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

The same timelines apply when outcome information is available.

8.3.4.2.2 Paternal exposure

Pregnancy of the patient’s partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented. If allowed by

local regulations, information about a pregnancy from the partner of a male patient can be captured. If so, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing must be followed up and documented.

8.3.4.3 Medication errors

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for AstraZeneca products that either causes harm to the patient or has the potential to cause harm to the patient. A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an Error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, e.g., kept in the fridge when it should be at room temperature
- Wrong drug administered to patient

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately, and no later than 24 hours of when he or she becomes aware of it.

8.3.4.4 Other Special Situations

Besides situation above, other special situations related to AZ products should be collected, the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately, and no later than 24 hours of when he or she becomes aware of it:

- Exposure to product whilst breastfeeding
- Off label use/product use issue
- Drug Abuse
- Drug Misuse
- Occupational exposure
- Product Quality Complaints/issues (PQCs) incl. Counterfeit/Falsified product
- Lack of efficacy and disease progression
- Medical Device/Device Constituent Part malfunction or deficiency

8.3.5 Reporting Contact Information

Contact information of AstraZeneca Data Entry Site:

For studies that are using the EDC system Rave the below e-mail address should be used for the automatic safety reporting e-mail notifications;

AEMailboxWBDCTCS@astrazeneca.com

The following e-mail address should be used for all other clinical study case reports;

AEMailboxClinicalTrialTCS@astrazeneca.com

Fax: +1 302 886 4114 / +46 31 776 37 34

8.4 Human Biological Samples

In the study, there is no proactively intervention to collect biological samples for any assessment. Clinical laboratory data will be collected if available in medical record as specified in the SoA.

8.5 Human Biological Sample Biomarkers

Not applicable.

8.6 Optional Genomics Initiative Sample

Not applicable.

8.7 Healthcare Resource Utilization (HCRU)

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The change in GINA guideline-recommended treatment after guideline education and implementation, will be compared between the proportion of patients on with an ICS-based maintenance and/or reliever treatment at Week 48 and the proportion at baseline. For each treatment arm, the proportions along with the 95% confidence intervals the rates and the difference Δ will be computed. The hypothesis test is formed as follows:

The null hypothesis to be tested is:

H0: Proportion of patients with ICS-based maintenance and/or reliever treatment at baseline = Proportion of patients with ICS-based maintenance and/or reliever treatment at Week 48

Against the alternative hypothesis:

Ha: Proportion of patients with ICS-based maintenance and/or reliever treatment at baseline ≠ Proportion of patients with ICS-based maintenance and/or reliever treatment at Week 48

9.2 Sample Size Determination

Approximately 1500 participants will provide 80% power at a significant level of 0.05 to detect a change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 48 of 5% (Zhao et al 2014). The baseline proportion is assumed to be 40% and a within-participants correlation is assumed to be 0.25. The proportion of missing postbaseline assessment at week 48 is assumed to be 30%.

9.3 Populations for Analyses

Effectiveness analyses will be performed using an FAS population. Demographic and baseline

characteristics will be presented for both all participants analysis set and FAS.

The following populations are defined:

Table 3 Populations for Analysis

Population/Analysis set	Description
All Enrolled Participants	All participating patients enrolled for the study without screen failure will be included in the All Enrolled Participants population.
Full Analysis Set (FAS)	All enrolled participants with at least one non-missing post-intervention GINA guideline treatment assessment.

9.4 Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Unless otherwise stated, all statistical methods in the subsequent sections will be based on the following general methods.

All categorical data will be presented in contingency tables, using absolute and relative frequencies. Percentages will be rounded to the first decimal place and, therefore, may not always add up to 100%. When applicable, 95% confidence intervals (CIs) will be presented with estimates of proportions.

All continuous data will be summarized via relevant descriptive statistics, such as number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1 and Q3) when applicable, minimum and maximum.

Missing data will not be imputed unless otherwise specified.

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior or concomitant medications/procedures.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

9.4.2 Effectiveness

9.4.2.1 Primary Endpoint(s)

Change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 48

Prescription will be used to define this endpoint. The primary analysis will use mixed effect logistic regression model, taking the measurement timepoint (baseline/post-baseline) as the fixed effect, hospital, pulmonologist and patient as the random effects. In case of lack of convergency, hospital and pulmonologist factors will be removed from the model. Within the framework of this model, the 95% confidence interval and p value of the primary endpoint will be estimated and presented. The analysis will be performed in FAS.

Another sensitivity analysis will be conducted with generalized estimating equations (GEE) model using the same covariates as the primary analysis.

9.4.2.2 Secondary Endpoint(s)

Change from baseline in the proportion of participant with well-controlled asthma (ACQ-5 ≤ 0.75) at week 48

The change from baseline in proportion of well-controlled asthma evaluated by ACQ-5 score at week 48 will be derived using the percentage of patients with ACQ-5 score ≤0.75, its 95% confidence interval (95% CI) will be summarized. Normal approximation method will be used to calculate 95% CI.

Distribution of ACQ-5 total scores at week 12, 24, 36 and 48

Distribution of ACQ-5 average scores will be described using the frequency and percentage at each category listed below, a shift table will be generated wherever applicable:

Well controlled: ACQ-5 ≤ 0.75

Partially controlled: 0.75 <ACQ-5< 1.5

Not well-controlled: ACQ-5 ≥ 1.5

Change from baseline in the proportion of participants on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48

Change from baseline in the proportion of patients on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48 and its 95% confidence interval (95% CI) will be summarized. Normal approximation method will be used to calculate 95% CI.

Change from baseline in ACQ-5 average score at week 12, 24, 36 and 48

The ACQ-5 overall score will be calculated as the average of the non-missing 5 symptom

questions. At least 4 out of the 5 symptom items are needed to provide an ACQ-5 overall score. Number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1 and Q3), minimum and maximum will be presented.

Change from baseline in the proportion of participants achieving an improvement in ACQ-5 MCID of 0.5 units or more at week 12, 24, 36 and 48

Responder status will be descriptively summarized by visit as the number (%) of responders and non-responders. A responder status at post-baseline will be calculated as

- Responder: (post-baseline – baseline) ≤ -0.5
- Non-responder: (post-baseline – baseline) > -0.5

Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36

Change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36 and its 95% confidence interval (95% CI) will be summarized. Normal approximation method will be used to calculate 95% CI.

Asthma related treatment pattern

Asthma related treatment patterns will be evaluated by treatment distribution at baseline and at weeks of 12, 24, 36, and 48.

9.4.2.3 Exploratory Endpoint(s)

9.4.3 Subgroup Analyses

Subgroup analyses will be performed as appropriate. Any subjects with a missing value for the defined subgroup will be excluded from the analysis of that subgroup.

The subgroups to be explored may include:

- Age be category: >65, ≥18 to ≤65, <18
- Age of onset: <20 years old, <40 years old, ≥40 years old
- Phenotype of asthma: allergic or non-allergic
- Hospital Tier: Tier 2, Tier 3
- Job: related to asthma, no-related to asthma
- Baseline characteristic
- Questionnaire with response and non-response subjects
- Adherence
- Patient expectation of asthma treatment
- Asthma history information
- Asthma severity class
- Hospital Type: PCCM, non-PCCM
- Geographic region

- ICS containing change: with-to-with, with-to-without, without-to-with, without-to-without ICS containing
- ICS-formoterol as reliever: with-to-with, with-to-without, without-to-with, without-to-without ICS-formoterol as reliever

Missing data characteristics will be described in baseline characteristics, primary endpoint and secondary endpoints if applicable. The subgroups to be explored will include:

- Participants complete status: Missing at Week 48, not Missing at Week 48
- Participants complete status: Missing at Week 24, not Missing at Week 24

These analyses are exploratory and the result from these analyses will not affect the choice of terms used in the model for the primary analysis.
Other baseline variables may also be assessed if there is clinical justification.

9.5 Interim Analyses

There will be two interim analyses, first interim analyses will be operated for all subjects enrolled at baseline, another will happen when all subjects complete week 12 visit.

9.6 Data Monitoring Committee

No data monitoring committee is planned for this study.

10 DATA MANAGEMENT

Data management will be performed by AstraZeneca or other party.

The EDC system will be used for data collection. Trained site personnel will be responsible for entering these data into the EDC system according to data collection requirements. The eCRF Instructions will guide the study centre in performing the data entry. All entries and any changes performed will be tracked to provide an audit trail. The data will be reviewed, queried, and updated as needed.

Medical Coding will be performed using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug^{TM} Dictionary.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. When all data have been coded, validated, signed, and locked, data cleaning will be completed. The final database will be locked.

11 STUDY CONDUCT AND OPERATIONAL CONSIDERATIONS

The conduct of the study and the analysis and reporting of the data shall be in accordance with all applicable laws, regulations and accepted standards.

11.1 Monitoring of the Study

AstraZeneca representatives will visit the research centre before the first subjects enter the study to:

- Discuss with the investigator (and other related researchers) their responsibilities regarding compliance with the research protocol and the duties of AstraZeneca or its representatives. These discussions will be documented in the clinical study agreement between AstraZeneca and the investigator.

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that the investigational team is adhering to the protocol, that data is being accurately and timely recorded in the eCRFs
- Perform source data verification, including verification of informed consent of participating patients. This will require direct access to all original records for each subject (e.g., clinic charts)

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

11.2 Audits and Inspections

Authorized AstraZeneca representative, a regulatory authority, an independent ethics committee (IEC), institutional review board or review board (IRB) may perform audit or inspection at the centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11.3 Training of Study Site Personnel

The Principal Investigator will maintain a record of all individuals involved in the study

(medical, nursing and other staff). The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

11.4 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, the amendment or new version of the study protocol must be notified or approved by each IRB or IEC before implementation and, if possible, submitted to the local regulatory authority for approval. The requirements of local laws and regulations must be observed.

If a protocol amendment requires a change to a centre's Informed Consent Form (if applicable), AstraZeneca and the centre's IRB or IEC must be notified. AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). It is the responsibility of the Principal Investigator(s) to present this document to the IRB/IEC and to other personnel in their research centres. The submission of these documents to regulatory authorities will be subject to local requirements.

11.5 Clinical Study Agreement

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement. In the event of any inconsistency between the Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail.

11.6 Ethical Considerations

The final version of the study protocol and the final written informed consent form (if applicable) must be approved or agreed in writing by the IEC/IRB. Written consent must be given to AstraZeneca prior to enrolling any subject.

It is the responsibility of the Investigator to notify the IEC/IRB of any modifications to the protocol in accordance with local requirements. Study protocols must be submitted annually to the IEC/IRB for re-approval in accordance with local requirements.

The study will be conducted in accordance with the Helsinki Declaration, the International Harmonized Conference on Technical Requirements for the Registration of Medicines for Human Use (ICH), the Good Clinical Practices (GCPS), and the ethical principles consistent

with the laws and regulations applicable.

11.7 Written Informed Consent

The principal investigator(s) his/her representative will ensure that the participant or his/her legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The authorised person obtaining the informed consent must also sign the ICF.

The principal investigator(s) must store the original, signed Written Informed Consent Form. A copy of the signed ICF(s) must be provided to the participant or the participant's legally authorised representative. If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

11.8 Confidentiality of Study and Subjects' Data

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.9 Contingency Plan for the COVID-19 (Novel Coronavirus)

Investigator and subject need to decide the best course of action regarding complying hospital visits and comply with the general principle of National Health Commission of The People's

Republic of China regarding to the control of the spread of the major infectious disease:COVID-19 (Novel Coronavirus).

- If a hospital visit is appropriate, patient may continue as per protocol with sufficient protection under the investigator 's evaluation.
- If a hospital visit is not appropriate, site staff should keep in close contact with the subjects, to use a telephone call and keep aware of subject’s status and specially to identify endpoints, give corresponding medical guidance and direct subject’s treatment and remind subjects to proactively report their personal health status and medication information to their investigators. Communications should be documented in the subject’s medical records.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

  – European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Committees Structure

A Scientific Steering Committee is established and responsible for the quality and implementation of the overall program, consisting of external experts (pulmonologists) of asthma. The Study Steering Committee has contributed or will contribute:

- To develop the overall design and diagram of GINA guideline education and implementation

- To ensure the education plan and related materials scientifically and clinically appropriate and fit-for-purpose

- To lead the discussion with the Director of respiratory department on root cause analyses, and provide guidance/instruction for improvement plan, if the implementation performance is not satisfying

- To advise the sponsor on amendments to the study design and provide recommendations on issues related to the study conduct, if required.

In addition, the committee will be involved in the review and interpretation of the study results. The Study Committee will be governed by a charter, detailing roles and responsibilities and processes.

A 4 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com <<and http://www.clinicaltrials.gov>> as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 5 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for [15] years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No

records may be transferred to another location or party without written notification to the sponsor.

A 6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in [Monitoring Plan].

A 7 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant

and should assure appropriate participant therapy and/or follow-up.

A 8 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious;

examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

Appendix C Patient Reported Questionnaires

C 1 Asthma Control Questionnaire (ACQ-5)

ASTHMA CONTROL QUESTIONNAIRE©
(LANGUAGE VERSION FOR COUNTRY)

PATIENT ID: _____

DATE: _____

Page 1 of 1

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

ACQ-5 - Canada/English - Mapi.
ACQ-5_AU1.0_eng-CAor1.doc

C 2 ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

Self-administrated (≥12 years)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Page 1 of 5

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

C 3 Patient's expectation for asthma treatment Questionnaire

Patient's expectation for asthma treatment Questionnaire

What do you hope to achieve with asthma treatment? (If you have other supplements, please fill in item 14. 0-10, 0 is not important, 10 is the most important)

1 Hope to be live as normal people

2. Control asthma as much as possible and no affect life and work

3 No need to take medication anymore, or do not take daily medication, or reduce medication

4. Symptoms such as cough and chest tightness are usually reduced, and do not get worse when catch a cold

5 No wheeze in normal time

6. Medication can control asthma and rare asthma exacerbation

7 Cure and eliminate asthma

8 No present symptoms at night and sleep well

9 No asthma attack, or no recurrence/aggravation when seasons in turn

10 Use medicines with faster-acting and fewer side effects

11 Stop worrying about asthma

12 Learning asthma knowledge, and deal with asthma condition change by myself in normal time

13 Can communicate with doctors via Call and WeChat to guide treatment, no need to go to hospital at every visit

14 Others:

C 4 Disease Knowledge Questionnaire for Asthma Patients

Disease Knowledge Questionnaire for Asthma Patients

Here are some questions about asthma in general. Circle T, if you think the statement is

true; F, if you think that the statement is false; NS, if you are not sure or do not know

whether the statement is true or false.

The nature of the disease

1. Asthma is a chronic inflammatory disease that requires long-term treatment（T）

2. Asthma is a neurological or psychological illness（F）

3. During asthma attacks, the muscles around the airways tighten and the tubes become narrow. (T)

4. During asthma attacks, more mucus is produced in the airways (T)

Attack trigger

5. Asthma often attacks without warning (F)

6. Strong emotions can trigger asthma attacks(T)

7. Diet and environment can trigger asthma attacks(T)

8. Smoking or passive smoking can make asthma attack or worsen (T)

9. If asthma triggers are identified and avoided, the number of exacerbations will be reduced (T)

10. When knowing that you will be exposed to an asthma trigger, you should wait until symptoms appear before taking medication F

11. If exercise causes occasional asthma attacks, you should not exercise (F)

12. Taking bronchodilators (such as albuterol, etc.) ten minutes before exercise can prevent asthma attacks during exercise (T)

therapeutic drug

13. Although asthma cannot be cured, it can be controlled with the right medication. (T)

14. Long-term inhaled corticosteroids are the most effective way to prevent asthma attacks (T)

15. Treat asthma attacks with antibiotics (F)

16. It is not necessary to use glucocorticoids regularly when there is no attack(F)

17. Asthma must be treated daily with a bronchodilator (eg Ventolin) (F)

18. If you have a cold or flu, you should increase your asthma medication dosage (T)

19. Oral medications work just as fast as inhaled medications (F)

20. Because inhaled drugs work locally in the respiratory tract, they have fewer side effects than oral drugs. (T)

21. Asthma-relieving drugs (such as Ventolin or Terbutaline) do not work well if they are always used (T)

Condition monitoring

22. If the asthma does not have an attack, it is not necessary to visit the outpatient clinic regularly (F)

23. Regular pulmonary function tests can monitor changes in the condition (T)

24. Monitoring with a peak flow meter can provide an early indication of asthma exacerbation (T)

25. Keeping an asthma diary every day will help you know well your own condition (T)

Total 16T 9F

C 5 Patient Self-Assessment of Asthma Severity

Patient Self-Assessment of Asthma Severity

How severity level do you think your asthma is? (according to personal understanding)

A mild

B Moderate

C severe

C 6 Patient Adherence Assessment at baseline

Patient Adherence Assessment at baseline

1. Has your doctor told you that your asthma medication is for long-term use?

Yes

no

(Answer "yes", skip to 2)

2. Are the drugs you are currently using is inhaler?

Yes

no

(Answer "yes", skip to 3)

3. Please try to recall your usual medication situation. If you always agree with the following descriptions, please check "Level 1" after the corresponding description. If you do not do this at all, please check "5" level", and so on.

(1-always, 2-often, 3-sometimes, 4-rarely, 5-never)

Answer the following 10 questions

1. I only use this medicine when I need it
2. I only use it when I feel breathless
3. I decided to miss out a dose
4. I try to avoid using it
5. I forget to take it
6. I alter the dose
7. I stop taking it for a while
8. I use it as a reserve if other treatment doesn’t work
9. I use it before doing something which might make me breathless
10. I take it less than instructed

4. When you were enrolled in the group, you did not take the medicine as prescribed by the doctor. What was the reason? (Multiple choice)

1. Forgetting medication, difficult to adhere to for a long time
2. The device is troublesome to use and inconvenient to carry
3. Unreasonable drug prices and unaffordable economy

4. It is troublesome to dispense the medicine, and the medicine cannot be dispensed continuously

5. Reluctance to use inhalation for a long time

6. Fear of drug dependence, fear of adverse drug reactions

7. Self-improvement without medication

8. Medication does not work well

9. The above situation has never happened and always follow the doctor's advice

C 7 Patient Adherence Assessment in follow-up

Patient Adherence Assessment in follow-up

1. Has your doctor told you that your asthma medication is for long-term use?

Yes

no

(Answer "yes", skip to 2)

2. Are the drugs you are currently using is inhaler?

Yes

no

(Answer "yes", skip to 3)

3. After you were enrolled in this study, did you take medication according to the doctor's advice?

Yes

No

(Answer "yes", skip to 4)

4. Please try to recall your usual medication situation. If you always agree with the following descriptions, please check "Level 1" after the corresponding description. If you do not do this at all, please check "5" level", and so on.

(1-always, 2-often, 3-sometimes, 4-rarely, 5-never)

Answer the following 10 questions

1. I only use this medicine when I need it
2. I only use it when I feel breathless
3. I decided to miss out a dose
4. I try to avoid using it
5. I forget to take it
6. I alter the dose
7. I stop taking it for a while
8. I use it as a reserve if other treatment doesn't work
9. I use it before doing something which might make me breathless
10. I take it less than instructed

5. When you are in study follow up, you did not take the medicine as prescribed by the doctor. What was the reason? (Multiple choice)

1. Forgetting medication, difficult to adhere to for a long time
2. The device is troublesome to use and inconvenient to carry
3. Unreasonable drug prices and unaffordable economy
4. It is troublesome to dispense the medicine, and the medicine cannot be dispensed continuously
5. Reluctance to use inhalation for a long time
6. Fear of drug dependence, fear of adverse drug reactions
7. Self-improvement without medication
8. Medication does not work well
9. The above situation has never happened and always follow the doctor's advice

C8 Questionnaire for Asthma Patients during COVID-19

1. Have you ever been infected with COVID-19?

1) Yes ((skip to question 2)

2) No (end of question)

3) Uncertain (end of question)

2. How you were diagnosed with COVID-19 (multiple choice)

1) COVID-19 Antigen Test

2) COVID-19 Nucleic Acid Detection

3) Chest CT or chest X-ray

4) Confirmed by physician

5) None of the above (end of the question)

3. The date of COVID-19 first symptoms appearance:

___ Year___ Month___Day

4. The date of COVID-19 antigen/nucleic acid positive test result been got (if not, do not fill in)

___ Year___ Month___ Day

5. Whether the antigen or nucleic acid test result turns negative

1) Yes (skip to question 6)

2) No (skip to question 7)

3) Not rechecked (skip to question 7)

6. The date of antigen or nucleic acid test result turning negative (if not, do not answer)

___ Year___ Month___ Dare

7. Have you got vaccinated with COVID-19 vaccine?

1) No (skip to question 9)

2) Yes, 1st dose completed

3) Yes, 2nd dose completed

4) Yes, 3rd or more doses have been completed

8. How long since the last COVID-19 vaccination?

1) Within half a year

2) Within Half a year to one year

3) Within 1 year or more

9. Did you go to the hospital for treatment due to COVID-19

1) Yes, receive treatment in outpatient or emergency department

2) Yes, hospitalized

3) No, just self-treat medication

4) No, no medication

10. During the infection of COVID-19, whether the chest CT/X-ray scan was carried out?

1) Yes (If the answer is "Yes", please continuing to question 11)

2) No (skip to question 12)

11. Do chest CT/X-ray scan indicate lung inflammation?

1) Yes

2) No

3) Uncertain

12. Have you ever had the following symptoms since you suffered from COVID-19 (multiple choice)

1) High heat (>39 ° C)

2) Cough

3) Dyspnea

4) Chest tightness

5) Expectoration

6) Muscle pain

7) Diarrhea

8) Fatigue

9) a loss to your sense of smell

10) Sore throat

11) Nasal congestion

12) Headache

13) No symptoms above

13. For all the symptoms you mentioned in the previous question, how many days did them last?

1) 1-3 days

2) 3-7 days

3) 7-14 days

4) More than 14 days

14. During the infection of COVID-19, how do you think the severity of your COVID-19 symptoms is?

1) Mild

2) Medium

3) Heavy

15. During the infection of COVID-19, do you have any exacerbation of asthma symptoms (such as "wheezing, shortness of breath, cough, chest tightness and other symptoms")?

1) Yes

2) No

16. What kind of asthma medicine do you use now? (multiple choice)

1) Salmeterol fluticasone (such as Seretide)

2) Budesonide Formoterol（such as Symbicort）

3) Beclomethasone Formoterol（such as Foster）

4) Other inhaled glucocorticoids (such as Flixotide)

5) Inhalation short-effect β 2-receptor agonists (such as Ventolin)

6) Biological agents (such as Xolair)

7) Oral drugs (such as Singular, aminophylline)

8) Other medication

9) not routinely used medication

17. During the infection of COVID-19, did you take additional inhalation of asthma medication？

1) Yes (skip to question 18)

2) No (skip to question 21)

18. What kind of medication do you take as additional inhalation?

1) SABA (short effect β 2-receptor agonists, such as salbutamol)

2) ICS (inhaled glucocorticoids, such as budesonide and formoterol, salmeterol and fluticasone)

3) Others

19. What is the average frequency of taking inhaltion in daily?

1) 1-2 inhalation/day

2) 3-6 inhalation/day

3) 7-10 inhalation/day

4) >10 inhalation /day

20. How many days have you taken additional inhalation?

1) 1-3 days

2) 4-6 days

3) >7 days

21. Did you add-on oral or intravenous glucocorticoids (such as prednisone, methylprednisolone, metoprolol, dexamethasone) during the infection of COVID-19?

1) Yes

2) No

Appendix D Investigator asthma knowledge questionnaire

CAREFORALL Asthma Knowledge Test

Your Name:

Where the hospital is located: province (autonomous region) _, city_

Hospital Tier level: Tier 3_ Tier 2_

Doctor Title: Chief Physician_ Deputy Chief Physician_ Attending Physician_ Resident Physician_

Part 1 Single Choice Questions

1. Asthma is an _ inflammatory disease of the airways ()

A. acute B. chronic

2. Cough variant asthma is _ as the sole or main symptom ()

A. cough

B. Breathing

C. Shortness of breath

3. Mild asthma: those who can achieve complete control after the first treatment ()

A. step1

B. step 2

C. step1,2

4. Risk factors for future exacerbations of asthma include: uncontrolled asthma, continuous exposure to allergens, comorbidities, irregular medication, poor compliance, and visits to the emergency room or hospitalization for acute asthma exacerbations in the past year. ()

A. Ture

B. False

5. Can FENO be used to predict and assess the response to ICS therapy? ()

A. Flase

B. Ture

6. During an acute asthma attack, the preferred reliever drug is ()

A. Salbutamol Aerosol

B. Low-dose ICS + formoterol

C. ICS

7. The most effective drug for controlling asthmatic airway inflammation is ()

A. Leukotriene Modulators

B. Glucocorticoids

C. Aminophylline

8. If asthma control is maintained for at least _ months, step down treatment can be considered to find the lowest effective treatment step for maintaining asthma control ()

A. 14 days B. 1 month C. 3 months D. 6 months

9. In step 1, if patients only presented occasional, transient daytime symptoms less than twice a month, each last several hours, without nocturnal symptoms and risk of acute exacerbation, meanwhile normal lung function. The recommended treatment is ()

A. As-needed low-dose ICS + formoterol inhalation

B. Inhaled low-dose ICS and as-needed inhaled SABA

C. Inhaled anticholinergic drugs (e.g, ipratropium bromide), oral SABA, or short-acting theophylline

10. In step 2, recommended treatment is ():

A. LTRA

B. Low-dose ICS plus as-needed reliever medication

11. Patients with persistent asthma symptoms or acute exacerbations who are treated at Step 4 need to be referred to an asthma specialist for treatment of severe asthma. Do inhalation technique and adherence need to be assessed before considering severe asthma? ()

A. required

B. not required

12. The frequency of follow-up for asthma treatment depends on the level of initial treatment, responsiveness to treatment, and the patient's ability to self-manage. Follow-up visits are usually required every _ weeks after initiation of treatment. ()

A.2-4

B.8

C.12

13. Does step down treatment can completely discontinue ICS without increasing the risk of exacerbations ().

A. True

B. False

14. For CVA, patients with chronic cough who cannot perform bronchial provocation test clinically and have no features suggesting other causes of chronic cough can be considered for empirical treatment according to CVA, but further examination is required when the treatment is ineffective. ()

A. False

B. Ture

15. Poor symptom control of severe asthma, meet criteria when ()

A. ACT≥19, ACQ greater than 1.5

B. ACT≤19, ACQ less than 1.5

C. ACT≤19, ACQ greater than 1.5

D. ACT≥19, ACQ less than 1.5

16. The China Pulmonary Health Survey (CPH) study showed that the prevalence of asthma in the Chinese population aged 20 years and above using the asthma questionnaire ()

A.1.2%

B.4.2%

C.8.2%

D 10.2%

17. For asthma during pregnancy, should ICS be reduced or discontinued based on safety considerations? ()

A. Yes

B. No

Part II Multiple Choice Questions

18. Objective tests for variable airflow limitation in asthma include ()

A. After inhalation of bronchodilators, FEV1 increased by >12%, and the absolute value of FEV1 increased by >200 ml)

B. FEV1 increased by >12% compared with the baseline value after 4 weeks of anti-inflammatory treatment, and the absolute value of FEV1 increased by >200 ml (excluding respiratory tract infection).

C. Positive bronchial challenge test

D. Average daily diurnal variability or PEF weekly variability of peak expiratory flow

19. Asthma Treatment Goals ()

A. To achieve good control of asthma symptoms and maintain normal activity levels

B. Minimize exacerbations and deaths

C. Minimize irreversible damage to lung function

D. Minimize the risk of drug-related adverse reactions

20. How many ways are there to step up the treatment of asthma? ()

A. Escalation of maintenance therapy

B. Short-course booster therapy

C. Daily adjustment of treatment

21. Severe asthma includes: ()

A. Step 4 treatment maintains control, but step-down treatment will lose control

B. Step 4 treatment fails to maintain control and requires step 5 treatment

C. Uncontrolled asthma even with the above treatments

22. Severe asthma treatment drugs include ()

A. ICS and OCS, LABA, LTRA, LAMA,

B. Sustained release theophylline

C. Macrolide drugs

D. Biological drugs

23. What do you think the diagnosis of asthma is based on ()

A. Recurrent episodes of wheezing and shortness of breath, with or without chest tightness or cough, occur frequently at night and in the morning, and are often related to exposure to allergens, cold air, physical and chemical stimuli, upper respiratory tract infections, exercise, etc.

B. Chronic persistent asthma that is uncontrolled at the time of attack and partly, with scattered or diffuse wheezing in both lungs, prolonged expiratory phase

C. Can be relieved by treatment or spontaneously relieved

D. Have any of the objective tests for airflow limitation

E. Excluding wheezing symptoms caused by other diseases

24. Assessment of asthma symptom control, including assessing whether the patient has () in the past 4 weeks:

A. Daytime Asthma Symptoms

B. Waking up at night due to asthma

C. Use reliever medication

D. Activity limitation due to asthma

25. You think the CTVA diagnosis is based on: ()

A. Chest tightness as the only or main symptom, without wheezing, shortness of breath and other symptoms and signs of typical asthma

B. Possesses any of the objective tests for variable airflow limitation

C. Excluding chest tightness caused by other diseases

D. Anti-asthma treatment is effective

Appendix E Inhaler skill score assessment checklist

Inhaler skill score assessment checklist

MDI（ Ventolin, Ipratropium Bromide Solution for Inhalation ,Beclomethasone Dipropionate and Formoterol Inhalation Aerosol , Glycopyrronium Bromide and Formoterol Fumarate Inhalation Aerosol ）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open. Open the nozzle dust cap	①True ②False
start up	2	Shake vigorously to suspend the liquid evenly	① True ②False
exhale	3	Exhale as fully as possible	①True ②False
Bite	4	Lips closed to hold the mouthpiece	①True ②False
Inhale	5	While inhaling slowly and deeply, press on the bottom of the canister and continue to inhale	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False
repeat or finish	7	Cover the protective cap, gargle with ICS medicines	① True ②False
DPI（HandiHaler）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open. Open dust cap and nozzle	①True ②False
start up	2	Place the capsule in the central chamber, close the mouthpiece until you hear a click, keep the inhaler upright, press the pierce button all the way down, and release	① True ②False
exhale	3	Exhale as fully as possible and stay away from the mouth	①True ②False

Bite	4	Lips closed to hold the mouthpiece	①True ②False
Inhale	5	Take a quick, deep breath to rotate the capsule until no more air is drawn in	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False
repeat or finish	7	Pour out the used capsule after inhalation, close the mouthpiece and dust cap	① True ②False
DPI（Turbuhaler）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open. Unscrew and pull out the cap	①True ②False
start up	2	Take the straight device, hold the red handle part and the middle part of the dowel, rotate it to the end in one direction, and then rotate it to the end in the opposite direction, you will hear a clicking sound during this process	①True ②False
exhale	3	Exhale as fully as possible and stay away from the mouth	①True ②False
Bite	4	Hold the unit horizontally, with lips that wrap around the nozzle without blocking the vents	①True ②False
Inhale	5	Inhale quickly and forcefully until no more air is drawn in	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False
repeat or finish	7	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	① True ②False

DPI（Diskus）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open.	①True ②False
start up	2	Open dust cap and nozzle	①True ②False
exhale	3	Place the capsule in the central chamber, close the mouthpiece until you hear a click, keep the inhaler upright, press the pierce button all the way down, and release	①True ②False
Bite	4	Exhale as fully as possible and stay away from the mouth	①True ②False
Inhale	5	Lips closed to hold the mouthpiece	①True ②False
hold breath	6	Take a quick, deep breath to rotate the capsule until no more air is drawn in	①True ②False
repeat or finish	7	Cover the protective cap, gargle with ICS medicines	② True ②False
DPI（®Ellipta）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open	① True ②False
start up	2	Open the dust cap until you hear a click	①True ②False
exhale	3	Exhale as fully as possible and stay away from the mouth	①True ②False
Bite	4	Hold the device horizontally, lips wrapping the nozzle	①True ②False
Inhale	5	Inhale quickly and forcefully until no more air is drawn in	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False

repeat or finish	7	Turn off device	① True ②False
DPI（ Indacaterol Maleate and Glycopyrronium Bromide Powder for Inhalation, Hard Capsules ）Steps			
Prepare	1	Clean your mouth, sit upright and tilt your head back slightly to keep your airway open. Open dust cap and nozzle	①True ②False
start up	2	Take one capsule out of the package, put it in the central compartment, close the nozzle until you hear a click, press the piercing buttons on both sides firmly, press the piercing buttons all the way, and release	True ②False
exhale	3	Exhale as fully as possible and stay away from the mouth	①True ②False
Bite	4	lip wrap nozzle	①True ②False
Inhale	5	Take a quick, deep breath to rotate the capsule until no more air is drawn in	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False
repeat or finish	7	Pour out the used capsule after inhalation, close the mouthpiece and dust cap	①True ②False
SMI（ Tiotropium Bromide Inhalation Spray ）Steps			
Prepare	1	Clean your mouth, sit upright, tilt your head slightly back to keep the airway open, close the protective cover, turn the transparent base half a turn in the direction indicated by the arrow on the label until you hear a click, and fully open the dust cap	①True ②False
start up	2	Exhale as fully as possible	①True ②False
exhale	3	Lips wrap the mouthpiece, do not cover the vents	①True ②False

Bite	4	Point the device at the back of the throat and press the dosing button	①True ②False
Inhale	5	Inhale slowly and deeply for as long as possible until no more air is inhaling	①True ②False
hold breath	6	Move the mouthpiece away from your lips, hold your breath for as long as possible for 6 to 10 seconds and then exhale slowly	①True ②False
repeat or finish	7	Close the dust cap, suck again (2 clicks = 1 dose), repeat the steps	① True ②False

Appendix F Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
BPT	Bronchial Provocation Test
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	electronic Case Report Form
FeNO	Fractional exhaled nitric oxide
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
KPI	Key Performance Indicator
MCID	Minimum clinical important difference
MARS-A	Medication Adherence Report Scale for Asthma
PEF	Peak expiratory flow
PFT	Pulmonary Function Testing
PHL	Potential Hy's Law
PI	Principal investigator
QIP	Quality Improvement Program
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities

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