

Original Research**Pragmatic Evaluation of an Improvement Program for People Living With Modifiable High-Risk COPD Versus Usual Care: Protocols for the Cluster Randomized PREVAIL Trial**

Katherine Hickman^{1,2,3} Yasir Tarabichi⁴ Andrew P. Dickens⁵ Rachel Pullen⁵ Margee Kerr^{5,6} Amy Couper^{5,6} Alexander Evans⁶ James Gatenby⁶ Luis Alves^{7,8} Cono Ariti⁵ Mona Bafadhel⁹ Victoria Carter⁶ James Chalmers¹⁰ Rongchang Chen¹¹ Graham Devereux¹² M. Bradley Drummond¹³ J. Martin Gibson^{14,15,16} David M. G. Halpin¹⁷ MeiLan Han¹⁸ Nicola A Hanania¹⁹ John R. Hurst²⁰ Alan Kaplan^{5,21,22} Konstantinos Kostikas^{5,23} Barry Make²⁴ Douglas Mapel²⁵ Jonathan Marshall²⁶ Fernando Martinez²⁷ Catherine Meldrum²⁸ Marije van Melle^{5,29} Marc Miravittles³⁰ Tamsin Morris³¹ Hana Mullerova³² Ruth Murray⁶ Shigeo Muro³³ Clementine Nordon³² Jill Ohar³⁴ Wilson Pace^{35,36} Michael Pollack³⁷ Jennifer K. Quint³⁸ Anita Sharma³⁹ Dave Singh⁴⁰ Mukesh Singh^{41,42,43} Frank Trudo³⁷ Dennis Williams^{44,45} Tom Wilkinson^{46,47,48} Tonya Winders⁴⁹ David Price^{5,6,50}

¹ National Respiratory Audit Programme, Care Quality Improvement Department, Royal College of Physicians, London, England, United Kingdom

² Low Moor Medical Practice, Bradford, England, United Kingdom

³ West Yorkshire Integrated Care Board, Primary Care Respiratory Society, Wakefield, United Kingdom

⁴ Center for Clinical Informatics Research and Education, MetroHealth, Cleveland, Ohio, United States

⁵ Observational and Pragmatic Research Institute, Singapore, Singapore

⁶ Optimum Patient Care, Cambridge, United Kingdom

⁷ Epidemiology Research Unit, Institute of Public Health, University of Porto, Porto, Portugal

⁸ Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal

⁹ Faculty of Life Sciences and Medicine, King's Centre for Lung Health, School of Immunology and Microbial Science, King's College London, London, United Kingdom

¹⁰ Scottish Centre for Respiratory Research, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom

¹¹ Key Laboratory of Respiratory Disease of Shenzhen, Shenzhen Institute of Respiratory Disease, Shenzhen People's Hospital; Second Affiliated Hospital of Jinan University, First Affiliated Hospital of South University of Science and Technology of China, China

¹² Liverpool School of Tropical Medicine, Liverpool, United Kingdom

¹³ Division of Pulmonary Diseases and Critical Care Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

- ¹⁴ Salford Royal Hospital, Salford, United Kingdom
- ¹⁵ NorthWest EHealth Ltd., Manchester, United Kingdom
- ¹⁶ Diabetes and Metabolic Medicine, University of Manchester, Manchester, United Kingdom
- ¹⁷ College of Medicine and Health, University of Exeter Medical School, Exeter, United Kingdom
- ¹⁸ University of Michigan, Ann Arbor, Michigan, United States
- ¹⁹ Airways Clinical Research Center, Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Waco, Texas, United States
- ²⁰ Respiratory, University College London, London, United Kingdom
- ²¹ Airways Group of Canada, Stouffville, Ontario, Canada
- ²² University of Toronto, Toronto, Canada
- ²³ Respiratory Medicine Department, University of Ioannina, Ioannina, Greece
- ²⁴ Department of Medicine, National Jewish Health, Denver, Colorado, United States
- ²⁵ College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, United States
- ²⁶ BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom
- ²⁷ University of Massachusetts Chan Medical School, UMassMemorial Health, Worcester, Massachusetts, United States
- ²⁸ Pulmonary and Critical Care Medicine Division, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan, United States
- ²⁹ Connecting Medical Dots BV, Utrecht, the Netherlands
- ³⁰ Pneumology Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, CIBER of Respiratory Diseases, Barcelona, Spain
- ³¹ Medical and Scientific Affairs, AstraZeneca, London, United Kingdom
- ³² BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom
- ³³ Department of Respiratory Medicine, Nara Medical University, Nara, Japan
- ³⁴ Section on Pulmonary, Critical Care, Allergy and Immunology, Wake Forest University, Winston-Salem, North Carolina, United States

- ³⁵ DARTNet Institute, Aurora, Colorado, United States
- ³⁶ University of Colorado, Denver, Colorado, United States
- ³⁷ Global Patient Safety, BioPharmaceuticals, AstraZeneca, Wilmington, Delaware, United States
- ³⁸ School of Public Health, Imperial College London, London, United Kingdom
- ³⁹ Platinum Medical Centre, Chermeside, Queensland, Australia
- ⁴⁰ Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester University NHS Foundation Trust, Manchester, United Kingdom
- ⁴¹ Horse Fair Practice Group, Rugeley, Staffordshire, United Kingdom
- ⁴² Keele University Medical School, Staffordshire, United Kingdom
- ⁴³ Staffordshire Integrated Care System, Staffordshire, United Kingdom
- ⁴⁴ Allergy and Asthma Network, Vienna, Virginia, United States
- ⁴⁵ Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, United States
- ⁴⁶ Mymhealth Limited, London, United Kingdom
- ⁴⁷ National Institute for Health and Care Research Southampton Biomedical Research Centre, University of Southampton, Southampton, United Kingdom
- ⁴⁸ Faculty of Medicine, University of Southampton, Southampton, United Kingdom
- ⁴⁹ Global Allergy and Airways Patient Platform, Vienna, Austria
- ⁵⁰ Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

Address correspondence to:

David Price
 Observational and Pragmatic Research Institute
 22 Sin Ming Lane, #06-76, Midview City
 Singapore 573969
 Phone: +65 3105 1489
 Email: dprice@opri.sg

Running Head: Protocols for the PREVAIL Trial

Keywords: quality improvement; CONQUEST; high-risk; COPD; MACRE

Abbreviations: CONQUEST: Collaboration on Quality improvement initiative for achieving Excellence in Standards of COPD care; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cluster Randomized Trial; EMR: Electronic Medical Records; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled Corticosteroids; IPCRG: International Primary Care Respiratory Group; ITT: Intention to treat; MACE : major adverse cardiac event; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; MACRE: major adverse cardiovascular and respiratory events; OPC: Optimum Patient Care; OPGC: Optimum Patient Care Global; OPCR: Optimum Patient Care Research Database; OPRI: Observational and Pragmatic Research Institute; PREVAIL: PRagmatic EVAluation of an improvement program for people Living with modifiable high-risk COPD PCCs: primary care clusters; QIP: Quality Improvement Program; QS: Quality Standards; SCS: systemic corticosteroids; RCT: Randomized Controlled Trial; SABA: Short-acting beta-agonist; SAMA: Short-acting muscarinic antagonist

Funding Support: This trial will be conducted by Observational and Pragmatic Research International Ltd and was co-funded by Observational and Pragmatic Research International and AstraZeneca. No funding was received by the Observational and Pragmatic Research Institute Pte Ltd (OPRI) for its contribution.

Date of Acceptance: April 21, 2025 | **Published Online:** April 25, 2025

Citation: Hickman K, Tarabichi Y, Dickens AP, et al. Pragmatic evaluation of an improvement program for people living with modifiable high-risk COPD versus usual care: protocol for the cluster randomized PREVAIL trial. *Chronic Obstr Pulm Dis*. 2025; Published online April 24, 2025.

<https://doi.org/10.15326/jcopdf.2024.0564>

Abstract

Background:

The burden of COPD is well established, but opportunities for earlier diagnosis and improved management are still missed. Compared to the general COPD population, patients with a history of exacerbations and sub-optimal treatment ('modifiable high-risk') are at greater risk of future exacerbations and adverse health outcomes. To date there is no systematic approach for identifying and treating this patient group.

Methods:

Two cluster randomized controlled trials (CRTs) in the UK and US will assess the impact of a primary care-based quality improvement program (CONQUEST), compared to routine care. In each trial, 126 primary care clusters will be randomized 1:1 to intervention or control arms. Three groups of modifiable high-risk patients will be identified using electronic medical records: undiagnosed with potential COPD, newly diagnosed COPD and already diagnosed COPD. Eligible patients will be aged ≥ 40 years, have experienced ≥ 2 moderate/ ≥ 1 severe exacerbations in the prior 24 months, including ≥ 1 in the last 12 months, and not be prescribed inhaled triple therapy. Patients in the undiagnosed group will also be required to have a positive smoking history. Primary trial outcomes will be the annual rate of exacerbations and the annual rate of major adverse cardiac and respiratory events, comparing the quality improvement program against routine care.

Discussion:

These will be the first CRTs assessing such a comprehensive primary care-based COPD quality improvement program. Intention to treat analysis of trial outcomes after 24 months will inform its effectiveness in targeting the identification, assessment, treatment and follow-up of patients with modifiable high-risk COPD.

Trial registration: UK trial: ISRCTN15819828; US trial: NCT05306743

Introduction

The social, economic, and personal burdens resulting from chronic obstructive pulmonary disease (COPD) are well established^{1–3}, and national strategies such as those in the United States (US)⁴ and the United Kingdom (UK)⁵ have aimed to diagnose COPD earlier, improve management of the disease and increase awareness among the general population. Despite these campaigns and initiatives and the high prevalence of COPD in high-income countries, reports indicate up to 60% of cases are undetected^{6–8}, with many patients only receiving a diagnosis after admission to hospital for an acute exacerbation⁹ and/or having experienced a significant decline in lung function^{10,11}. This suggests that opportunities for earlier diagnosis may have been missed resulting in an increased risk of exacerbations and associated potential for increased risk of cardiovascular events, greater lung function decline, higher mortality rates, and increased healthcare costs^{10–18}. Three recent cross-sectional database studies in the UK, US, and Australia explored clinical management of patients with high-risk COPD, with all studies identifying opportunities for earlier identification of COPD, increased assessment of cardiovascular risk, optimization of inhaled therapy and referral for appropriate non-pharmacological treatment^{19–21}.

Primary care settings play a pivotal role in COPD care, serving as the first point of contact for patients presenting with symptoms, the primary location for diagnoses, and the central hub for long-term management of the condition. Even if diagnosed, many patients with COPD are at increased risk of future respiratory events and could benefit from improved management such as regular symptom assessment and counselling on medication adherence, inhaler technique, vaccination, and smoking cessation^{22–31}. There is a subgroup of patients, both diagnosed and undiagnosed with potential COPD, who are at greater risk of exacerbations and adverse events (due to a history of previous exacerbations, comorbidities or clinical characteristics), in whom there may be opportunities to modify that risk through earlier diagnosis and/or improved management and treatment^{32–36}. We have adopted the concept ‘modifiable high-risk’ to describe this subgroup; and introduced a quality improvement program designed to help this population in primary care settings.

The **C**ollaborati**N** on a **Q**uality Improvement Initiative to Achieve **E**xcellence in **S**tandards of COPD Care (CONQUEST) program uses routinely collected electronic medical records (EMRs) to identify undiagnosed and diagnosed modifiable high-risk patients and provides a clinical decision support tool for primary care professionals to guide their management, in alignment with expert opinion and national and international guidelines³⁷. CONQUEST is a

quality improvement program (QIP) embedded in primary care that is underpinned by four evidence-based quality standards (QS) that were specifically developed by expert pulmonologists. The QS integrate quality improvement into routine patient care by supporting healthcare systems to achieve a timely diagnosis, provide individualized disease assessment, optimize COPD pharmacological and non-pharmacological management and ensure appropriate follow-up³⁵. The CONQUEST QIP is novel in that, unlike previous studies focused largely on case-finding^{32–34,36,38–40}, it combines case-finding with identifying opportunities to optimize management. The scope of the CONQUEST QIP also extends beyond interventions involving case-finding with subsequent treatment⁴¹, by identifying both newly diagnosed and already diagnosed patients at increased risk of future exacerbations due to their exacerbation history^{11,42}, optimizing their management and monitoring them over a longer period. Previous COPD QIPs have improved guideline adherence, medication prescription and patients' inhaler technique^{43–45}. We anticipate that by identifying patients with modifiable high-risk COPD and focusing on their assessment, treatment and follow-up, the CONQUEST QIP will improve guideline adherence and patient health outcomes.

As a QIP designed for implementation in primary care settings, it is critical to assess whether the program makes an impact in these settings. The **PR**agmatic **EVA**luation of a quality **I**mprovement program for people **L**iving with modifiable high-risk COPD (PREVAIL) pragmatic cluster randomized trials, which are described in detail here, have been designed to answer this question. The aim of the PREVAIL trials is to evaluate the health outcomes resulting from CONQUEST QIP implementation in terms of COPD exacerbations and major adverse cardiac or respiratory events (MACREs), in both diagnosed and undiagnosed modifiable high-risk patients, compared to usual care.

Methods

Study design

The PREVAIL cluster randomized trials (CRTs) are two separate, but related, cluster randomized pragmatic trials - one conducted in the UK, the other in the US - that will test the effectiveness of the CONQUEST QIP in improving patient outcomes and determine its impact compared to usual care among primary care patients who are already diagnosed with COPD, and patients undiagnosed with potential COPD, who meet the modifiable high-risk criteria. Although the trials are independent of each other, they will follow the standardized protocol described in this manuscript.

As the CONQUEST QIP is a cluster-level behavioral intervention, the CRT design will avoid the logistic challenges and risk of contamination inherent in equivalent individually randomized trials. Primary care clusters (PCCs) will be the unit of randomization for the trials. PCCs in each country will be randomized 1:1 to either the intervention arm where the CONQUEST QIP will be delivered, or to the control arm where they will continue to deliver usual care until the end of the outcome evaluation period (**Figure 1**). The CONQUEST QIP will then be rolled out to PCCs in the control arm.

Primary care setting

The PREVAIL CRTs will be conducted within primary care settings in order to be generalizable, and more closely aligned with the needs of stakeholders (e.g., patients, practitioners, payers and institutions involved in public health)^{46–48}. In the UK, PCCs represent general practitioner practices (primary care organizations serving a list of registered patients), whereas in the US self-contained primary care teams (primary care practice personnel identifying as a team caring for a panel of patients⁴⁹) will form an individual cluster. This variation is required as primary care settings in the US vary from small independent practices to large clinics within an integrated health system⁴⁹.

In the UK, primary care respiratory leads, primary care respiratory networks and NHS research organizations will identify PCCs suitable for inclusion. PCCs who have opted to participate in the broader Optimum Patient Care QIP will also be invited to participate in PREVAIL. In the US, integrated healthcare systems will identify PCCs within their network that are suitable for inclusion. To be eligible for inclusion in the PREVAIL CRT, PCCs must function as a single randomization unit and have a sufficient number of patients meeting modifiable high-risk criteria, in accordance with sample size calculations. PCCs will be ineligible for inclusion if they are in the process of or planning to change their EMR system within the trial period and/or if they are currently engaged in other COPD-related research studies or QIPs. In both countries, the PREVAIL trial will be conducted in diverse geographical areas to maximize the generalizability of the study findings.

Participant eligibility criteria

Three subsets of modifiable high-risk patients will be included in the PREVAIL CRTs: undiagnosed with potential COPD, newly diagnosed COPD and already diagnosed COPD. Definitions for patient cohorts and related terms are outlined in **Table 1**. All patients will be ≥ 40 years old, have a history of COPD exacerbations (or COPD-like exacerbations if not in the already diagnosed patient group), have ≥ 24 months of EMR data available and have a clear

opportunity for optimization in disease management. COPD-like exacerbations in undiagnosed patients are identified as events analogous to a COPD exacerbation; episodes of respiratory symptoms treated with courses of antibiotics, steroids or both. Patients who are undiagnosed but with potential COPD will also have a positive smoking history.

Patients treated with any form of inhaled triple therapy involving LAMA, LABA and ICS, actively treated asthma, any other significant lung disease and/or active cancer (except for non-invasive skin cancer) will be excluded to ensure that patients receiving the QIP have modifiable disease and are able to participate in the intervention. Patients who do not provide permission to use their EMR data for research will also be excluded.

For PCCs randomized to the intervention arm, modifiable high-risk patients will be identified by applying CONQUEST patient identification algorithms to primary care EMR data covering a 24-month risk identification period. These algorithms are derived from previously validated tools, adapted to meet the specific requirements of the CONQUEST program^{38,50–52}.

Data source

There will be variations between UK and US PREVAIL data repositories because of different ethical and data management requirements. In the UK, structured and unstructured patient data will be obtained from EMRs using the Optimum Patient Care Research Database (OPCRD) (<https://www.opcrd.optimumpatientcare.org/>). The OPCRD was established in 2005 and comprises data for over 24 million patients. It has been approved by the UK National Health Service for clinical research use and is validated and frequently utilized for medical and health research^{51,53–57}.

In the US, the DARTNet Institute (<https://dartnet.info/>) will extract standardized structured EMR data from participating PCCs and provide the Observational and Pragmatic Research Institute (OPRI) with a limited data set. OPRI will house the data in a US cloud-based computing system that is compliant with The Health Insurance Portability and Accountability Act.

Intervention

A detailed description of the CONQUEST QIP has previously been published but in summary, it supports healthcare professionals in primary care in the identification and management of patients with modifiable high-risk COPD, structured around the four CONQUEST QS^{35,37}.

Figure 2 summarizes the program components, and outlines the activities undertaken and the support given to intervention PCCs during the trial. All considerations for assessment,

pharmacological or non-pharmacological management, or follow-up are based on current best practice guidelines and expert opinion at the time of program implementation and are detailed in the CONQUEST Clinical Decision Support package provided to healthcare providers. The package includes considerations for both pharmacological therapy and non-pharmacological management, such as pulmonary rehabilitation referral, vaccination uptake, smoking cessation advice and inhaler technique review where applicable.

All decisions about patient management are made entirely at the discretion of the treating clinicians and patients, who together negotiate the preferred course of action during consultations in the implementation and outcome evaluation phases of the trial.

Implementation of spirometry testing in undiagnosed patients and the provision of clinical consultations differs between the UK and the US based on healthcare system structure and logistics. For example, the clinical consultation during disease assessment is provided remotely by clinical pharmacists who then discuss treatment considerations with General Practitioners in the UK, and by appointed clinical providers working with primary care practitioners in US PCCs. However, the core components of the intervention are the same.

The implementation of the QIP at PCCs lasts 6 months, during this time the core components of the intervention (except ongoing patient follow-up and QIP feedback reports for PCCs) will be delivered.

Comparator

In the control arm of the PREVAIL CRTs, PCCs will continue to provide usual care until the end of the trial period.

Outcomes

All trial outcomes described below will be assessed over a 24-month period.

Primary outcomes

The primary outcomes are the annual rate of moderate or severe COPD exacerbations, and the annual rate of major adverse cardiac and respiratory events (MACRE). Moderate COPD exacerbations are defined as events requiring oral corticosteroids and/or a course of antibiotics within 3 days of a lower respiratory consultation that does not result in hospitalization; whereas severe COPD exacerbations are defined as events resulting in respiratory-related hospitalization or all-cause mortality.

MACRE extends the composite outcome of MACE (major adverse cardiac events), which has been used in many previous studies^{58–61}, to also include a respiratory component which better reflects the type of adverse events that patients with modifiable high-risk COPD are exposed to. In PREVAIL, MACRE encompasses incident heart failure diagnosis or heart failure hospitalization, non-fatal myocardial infarction, non-fatal ischemic stroke, all-cause mortality, severe COPD exacerbations and complicated exacerbations (requiring additional hospitalization or corticosteroids/antibiotics between 8-28 days after onset of initial exacerbation). MACRE will be analyzed as a composite measure and also disaggregated by individual components.

Secondary outcome

The secondary outcome is the annual systemic corticosteroid (SCS) dose used to treat exacerbations. SCS exposure will be measured as the average annual dose, in milligrams, of prednisolone taken via any systemic route. Use of SCS other than prednisolone will be converted to prednisolone equivalent dosing using UK or US formulary conversion tables^{62–64}.

Exploratory outcomes

The first exploratory outcome will be the annual rate of explanatory diagnoses, other than COPD, within the subset of initially undiagnosed patients with potential COPD who do not receive a COPD diagnosis following diagnostic case-finding. Explanatory diagnoses will include incident asthma, chronic heart failure, lung cancer, other chronic respiratory conditions, gastro-esophageal reflux disease and any others identified by the study team via analysis of secondary data. The second exploratory outcome will be the annual rate of unscheduled respiratory care events, defined as any event not constituting a formal COPD review i.e., respiratory-related emergency room attendances and hospitalizations except scheduled office/outpatient visits and, respiratory-related primary care attendances with no supporting COPD review code or record of dyspnea (modified Medical Research Council dyspnea scale⁶⁵) or disease-specific health-related quality of life (COPD Assessment Test⁶⁶) score. The rate of incident pneumonia cases will be explored, in light of potential increased use of inhaled corticosteroids (ICS) within the intervention arm; other ICS-related adverse events will not be explored as they are outside the scope and resources of the trials. Changes in lung function (spirometry) and disease-specific health-related quality of life (COPD Assessment Test) will also be assessed as exploratory outcomes.

Data management and statistical analysis

Data management

Data management procedures are standardized across the UK and US. Specifically, all data management procedures will be performed by senior data analysts who will continuously ensure the integrity, validity, and confidentiality of data collection and storage procedures through regular monitoring and periodic assessments of data quality. Data collections are checked for content (data structure and format), completeness (presence of key and optional data files) and continuity. Details of each data extraction and transfer will be logged to an administrative database, and data are made available for processing.

Sample size calculation

Sample size estimates for the primary analyses cohort are based on the primary objectives and all calculations account for the clustered nature of the trial design using appropriate formulas for event rates⁶⁷. Estimates are similar for both the UK and US studies and are indicative of the potential power to detect trial outcomes using primary care medical record data for patients with high-risk COPD, held in the Optimum Patient Care Research Database (OPCRD). Specifically, the conservative parameter estimates are based on a database snapshot of modifiable high-risk patients in 2015 from 514 primary care clusters with EMR data.

In each of the UK and US trials, it was estimated that enrolling 126 clusters with a mean of 12 modifiable high-risk patients would result in 90% power to detect a 30% reduction in the annual exacerbation rate, equivalent to a rate ratio of 0.7 (and 80% power to detect a 26% reduction [rate ratio of 0.74]). This is based on OPCRD data, with an estimated coefficient of variation between PCCs in this cohort of 0.56 and an annual exacerbation rate of 1.36 over a 24-month follow-up period ($\alpha=0.05$).

Based on the projected number of clusters, using OPCRD data, it was also estimated there would be 90% power to detect a 32% reduction, equivalent to a rate ratio of 0.68 (and 80% power to detect a 28% reduction [rate ratio of 0.72]) in the annual rate of MACRE events in patients with COPD. This is based on an estimated coefficient of variation between PCCs in this cohort of 0.56 and a control group annual MACRE rate over a subsequent 24-month period of 0.53 ($\alpha=0.05$).

Randomization and blinding of primary care clusters

To account for variation in important cluster-level characteristics, a stratified randomization approach will be adopted.

In the UK, PCCs will be stratified according to deprivation (Index of Multiple Deprivation (IMD) score 2019⁶⁸) and scale of opportunity for triple therapy (Quality Outcome Framework COPD list size – number of patients currently prescribed triple therapy). Stratification characteristics were selected based on their prognostic association with the primary outcomes, after confirmation of sufficient variation in national data to ensure different levels of risk between stratified PCCs. Based on OPCRd data, the median IMD score and median number of patient with COPD not prescribed triple therapy will be used as cut-points to create “high risk” and “low risk” groups for both characteristics, creating four strata: low/low, low/high, high/high and high/low.

In the US, PCCs will be stratified based on background exacerbation rates, into “high” and “low” groups based on the background COPD exacerbation profile within the PCCs in the preceding 12 months. The cut-off rate for the strata will be the median annual rate of exacerbations, based on available data in the US Optimum Patient Care Global (OPCG) research database.

Within each stratum, PCCs will be randomized at a ratio of 1:1 using permuted blocks of different sizes to receive either the CONQUEST QIP (intervention arm), or to continue to provide usual care (control arm). At the end of the outcome evaluation period, the CONQUEST QIP resources will be implemented in the control arm PCCs.

As the trial is evaluating a cluster-level behavioral intervention, it is not possible to blind the PCCs to the allocation arm. For practical reasons the operational study team will not be blinded to allocation, but the statistician analyzing the trial outcome data will be blinded.

Statistical analysis

All analyses will be conducted in accordance with a pre-specified statistical analysis plan. For the purpose of data analysis there will be three cohorts (**Figure 3**). The primary analysis cohort will comprise patients with already and newly diagnosed COPD. The secondary analysis cohort will solely comprise patients with already diagnosed COPD, whereas the exploratory analysis cohort will comprise patients who were initially identified as undiagnosed potential COPD.

A summary of outcomes cross matched to analysis cohorts is presented in **Table 2**, however all three cohorts will be used to examine the primary and secondary outcomes with variations in the cohorts used to assess exploratory outcomes. Data for all primary, secondary and exploratory outcomes will be analyzed using the intention-to-treat (ITT) principle. To minimize potential bias due to loss to follow-up, any modifiable high-risk patients identified in the control arm who die during the implementation or outcome evaluation period, and who already have a COPD diagnosis code, or where the cause of death is COPD, will be included in the ITT population, even if the patient is not reviewed during the eventual roll-out period.

Poisson regression models with gamma-distributed random effects to account for clustering at the PCC level will be fit to calculate the rate ratio comparing the rates of primary outcomes (dependent variables) between treatment arms (control vs CONQUEST QIP; independent variable), adjusted for main confounders.

All regression models will be adjusted for baseline covariates, such as smoking status, age, socio-economic status and sex, as well as the randomization stratification factors of deprivation and the proportion of COPD patients not on triple therapy. Covariates will be pre-specified in the Statistical Analysis Plan and included as fixed covariates where appropriate

An additional per-protocol analysis will assess the impact of the intervention using an independent variable that indicates the level of intervention implementation strength, using a pre-agreed set of indicators that describe the coverage and components of the final CONQUEST QIP. This indicator will be fully developed in parallel with the development of the final intervention package.

Process evaluation

Data will be collected throughout the QIP implementation phase, to determine the extent to which the intervention was delivered as intended, the length and content of assessment clinics, and whether it was delivered to the target population. These process data will provide additional information to inform the interpretation of the trial results and allow judgements on the likelihood of success if the QIP were implemented more widely.

Ethical approval

In the UK the PREVAIL CRT protocol has been approved by the Health Research Authority and the East Midlands – Derby Research Ethics Committee (REC 21/EM/0252) and by the Anonymized Data Ethics and Protocol Transparency Committee (ADEPT 1321). The trial will be performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology

Practice and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP/DSPP/42512) and with the ISRCTN registry (ISRCTN15819828). In the US, BRANY Institutional Review Board (IRB) serves as the single IRB (22-08-112) and the trial has been registered with the US National Institute of Health's National Library of Medicines international Clinical Trials database at clinicaltrials.gov (#NCT05306743).

Discussion

The aim of the PREVAIL CRTs is to evaluate the effectiveness of the CONQUEST QIP which focuses on identifying undiagnosed and diagnosed patients with modifiable-high risk COPD and once identified, improving COPD care in line with expert opinion and evidence-based guidelines. Prior investigations suggest that while case-finding methods can suitably identify patients with COPD, poor follow-up and suboptimal management may prevent improved patient outcomes^{23,32–34,38,39,69,70}. In this regard, the CONQUEST QIP is novel and has the potential to address these evidence-practice gaps because it combines case-finding with clinical decision tools to guide management. Additionally, the CONQUEST QIP has the potential to meet COPD research priorities identified by the International Primary Care Respiratory Group (IPCRG), such as having simple tools that enable the diagnosis and assessment of COPD in primary care settings, including those with limited access to resources, and managing patients who have COPD and comorbid conditions, including cardiovascular disease^{71,72}. Whilst ambitious in their proposed undertaking, the PREVAIL CRTs provide an opportunity to compare a wide range of health outcomes in patients with COPD being treated in primary care over a comparatively long time frame.

It is important to ensure the PREVAIL CRTs are pragmatically designed, and methodology is appropriate for assessing the stated outcomes. The PREVAIL CRTs scored 35 out of 45 on the PRECIS-2-PS tool⁷³; a tool used to identify where planned studies are on the pragmatic-explanatory continuum, with scores ranging from 9 (very explanatory) to 45 (very pragmatic) (**Figure 4**). Having a pragmatic study design ensures the proposed studies will examine the benefits of the CONQUEST QIP in real world primary care practice.

The CRT design is appropriate to evaluate the CONQUEST QIP as it is implemented at the PCC-level and aims to change care pathways for patients with modifiable high-risk COPD. CRTs are widely used to evaluate QIPs within healthcare settings, whereby the healthcare provider, rather than the individual patient, is the unit of randomization^{74–77}. The international

nature of the PREVAIL CRT will aid assessment of the external validity of the CONQUEST QIP, and the randomization of PCCs will enable the trials to assess the applicability of the QIP and clinical decision support tools to a diverse population of patients with modifiable high-risk COPD living in high income countries.

Having a 24-month lead in time prior to baseline randomization will help detect respiratory events in patients with undiagnosed potential COPD who have an increasing frequency of events prior to diagnosis. For example, in a US study, it was shown that in the 24 months prior to diagnosis, the mean number of exacerbations for patients with COPD was 2.04⁷⁸. A 24-month risk identification period will also better account for seasonal effects and potential temporary changes in detection, coding and management of COPD exacerbations due to the COVID-19 pandemic. The follow up period of at least 24 months will also allow for these factors and give a better estimate of the effects of the program on the risk of exacerbations and MACRE compared to the more common 52 weeks used by many clinical trials.

COVID-19 has had a global impact on clinical trials and research across diverse medical fields, with delays in subject enrollment, operational gaps in conducting trials and overall delays in projected timelines⁷⁹. It is reasonable to assume these challenges could also be experienced in the PREVAIL CRTs, and the additional difficulties of conducting a respiratory based study in the COVID-19 era must be considered⁸⁰. Respiratory-related considerations pertaining to the PREVAIL CRTs include the impact of COVID-19 on COPD exacerbation frequency in the risk identification period, ability and willingness of patients to attend spirometry, and the capacity of participating PCCs to commit to a QIP. Numbers of patients meeting the eligibility criteria will be monitored by the internal study team and if fewer than anticipated modifiable high-risk patients are identified due to lower baseline exacerbations rates than expected, protocol modifications will be discussed with the study team.

One of the criteria used to identify undiagnosed patients with potential COPD was a positive smoking history; while this maximized the potential yield of newly diagnosed COPD, the case-finding process would have missed undiagnosed COPD within non-smoking patients. As the trials target patients with the largest scope for optimization in terms of both pharmacological and non-pharmacological management, some patients may be omitted who require appropriate management relating to one of these components. The trial analysis will be based on EMR data in the UK and US, with algorithms extracting data from multiple clinical systems in each country. Use of a common data model⁸¹ to standardize the structure and content of extracted

EMR data will ensure that data in different formats can be processed and analyzed within the two countries; however, variation in clinicians' recording and coding of patient data means that outcomes may be under- or over-estimated. While within-country data variations will be addressed using the above approach, differences in the availability of recorded data in the UK and US precluded analysis of combined data from both countries.

The environmental impact of COPD inhaled therapy is a major concern for healthcare providers in the UK and US; metered dose inhalers accounted for approximately 3% of the NHS carbon footprint in 2019⁸², and 98% of all inhaler-related emissions in the US in 2022⁸³. As the PREVAIL trials have been designed to explore patient health outcomes associated with the quality improvement program, the trials do not include environmental outcomes. However, the licensing of new propellants is likely to change the carbon cost of inhalers considerably during the outcome evaluation period of the trials, rendering interpretation of any collected data during this period challenging.

If the CONQUEST QIP is shown to be effective in improving outcomes for patients with modifiable high-risk COPD, a post-hoc economic evaluation may be undertaken to explore the cost-effectiveness of the intervention. Furthermore, the logistics of implementing this program in routine clinical practice will be explored, by actively seeking feedback from healthcare professionals in the intervention arm PCCs and, in collaboration with steering committee members, considering ways of mitigating obstacles in the future.

Should the trials demonstrate successful implementation of the CONQUEST QIP in primary care and beneficial patient health outcomes, they will help to establish the role of automated modifiable high-risk patient identification and the value of optimizing therapy in this patient population. It will also provide a framework for COPD case-finding and quality improvement that can address opportunities for management in this common but often under-recognized and under-treated disease.

Acknowledgements

Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC). We would like to acknowledge Shay Soremekun of the Observational and Pragmatic Research Institute (OPRI), Singapore, and David Jones of Optimum Patient Care, Cambridge, United Kingdom for intellectual contribution to the trial design which supported the development of this publication. Writing, editorial support, and/or formatting assistance in the development of this manuscript was provided by Shilpa Suresh (MSc) of the Observational and Pragmatic Research Institute, Singapore.

Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors made a significant contribution to the work reported, whether that is in the study conception, design, or execution; acquisition of data, analysis, and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work. All authors have given approval for the submission of this article. The authors received no direct compensation related to the development of the manuscript.

Conflict of Interests

Katherine Hickman, Yasir Tarabichi, Martin Gibson, Catherine Meldrum, Graham Devereux, and Dennis Williams report no conflicts of interest.

Andrew P Dickens, Rachel Pullen, and Alexander Evans are employees of the Observational and Pragmatic Research Institute, which is a research collaborator of the CONQUEST initiative with Optimum Patient Care and AstraZeneca.

Margee Kerr and Amy Couper are contracted by the Observational and Pragmatic Research Institute, a research collaborator for the CONQUEST initiative, and by Optimum Patient Care Global, a co-funder of the CONQUEST initiative.

James Gatenby and Victoria Carter are employees of Optimum Patient Care Ltd, a co-funder of the CONQUEST initiative.

Luís Alves has served as an advisor or consultant for AstraZeneca, GlaxoSmithKline, and Merck Sharp & Dohme; served as a speaker or a member of a speakers' bureau for AstraZeneca, GlaxoSmithKline, BIAL, Viatris and Novartis Pharmaceuticals Corporation.

Con Ariti was an employee of the Observational and Pragmatic Research Institute, which is a research collaborator of the CONQUEST initiative with Optimum Patient Care and AstraZeneca.

Mona Bafadhel reports grants from AstraZeneca and personal fees and non-financial support from AstraZeneca, Chiesi, GlaxoSmithKline, and others from AlbusHealth, outside the submitted work.

James Chalmers has received research grants or consultancy fees from Astrazeneca, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Grifols, Insmmed, and Zambon.

Rongchang Chen has received grant support from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline; and reimbursement for advisory work and educational activities from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis.

M. Bradley Drummond has received grant support from the NIH, Boehringer-Ingelheim, Midmark, and Teva; consultancy fees from AstraZeneca, GlaxoSmithKline, Genentech, Stratos, Verona, and Takeda in the prior 18 months unrelated to this work.

David MG Halpin has received sponsorship to attend international meetings, and honoraria for lecturing, attending advisory boards and preparing educational materials from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Pfizer.

Nicola A. Hanania served as an advisor or consultant for AstraZeneca, GlaxoSmithKline, Sanofi, Genentech, Teva, Verona, Amgen and his institution received research grant support from AstraZeneca, GlaxoSmithKline, Sanofi, Genentech, and Teva.

John R Hurst has received personal payment and payment to his institution (UCL), including research grants, reimbursement for advisory work and educational activities, and support to attend meetings from pharmaceutical companies that make medicines to treat COPD, which include AstraZeneca, Boehringer Ingelheim, Chiesi, and Novartis.

Barry Make reports funding from the NHLBI for the COPDGene study; grants and medical advisory boards from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and Sunovion; personal fees for Douglas Mapel from Spiration and Shire/Baxalta; CME personal fees from WebMD, National Jewish Health, American College of Chest Physicians, Projects in Knowledge, Hybrid Communications, SPIRE Learning, Ultimate Medical Academy, Catamount Medical, Eastern Pulmonary Society, Catamount Medical Communications Medscape, Eastern VA Medical Center, Academy Continued Healthcare Learning, and Mt. Sinai Medical Center; royalties from Up-To-Date; medical advisory boards from Novartis, Phillips, Third Pole, Science 24/7, and Verno; and grants from Pearl, outside the submitted work.

Douglas Mapel has received grant funding from Boehringer Ingelheim Pharmaceuticals, GlaxoSmithKline, Sunovion; and consultancy fees from Boehringer Ingelheim Pharmaceuticals, Mylan, Theravance Biopharma, and Novartis.

Jonathan Marshall, Tamsin Morris, Hana Mullerova, Michael Pollack, and Frank Trudo are employees of AstraZeneca and hold stock and/or stock options in the company. AstraZeneca is a co-funder of the CONQUEST initiative.

Fernando Martinez has received personal fees and non-financial support from the American College of Chest Physicians, AstraZeneca, Boehringer Ingelheim, ConCert, Genentech, GlaxoSmithKline, Inova Fairfax Health System, Miller Communications, National Society for Continuing Education, Novartis, Pearl Pharmaceuticals, PeerView Communications, Prime Communications, Puerto Rico Respiratory Society, Chiesi, Sunovion, Theravance, Potomac, University of Alabama Birmingham, Physicians Education Resource, Canadian Respiratory Network, Teva, and Dartmouth; non-financial support from ProterrixBio, Gilead, Nitto, and Zambon; and personal fees from Columbia University, Integritas, MD magazine, Methodist Hospital Brooklyn, New York University, UpToDate, WebMD/MedScape, Western Connecticut Health Network, Patara/Respivant, PlatformIQ, American Thoracic Society, Rockpointe, Rare Disease Healthcare Communications, and France Foundation; grant support from NIH; and is a member of steering committees for Afferent/Merck, Biogen, Veracyte, Prometic, Bayer, Bridge Biotherapeutics, and ProMedior.

Marc Miravittles reports speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, TEVA, Spin Therapeutics, Palobiofarma SL, pH Pharma, Novartis, Sanofi, and Grifols and research grants from Grifols.

Shigeo Muro reported lecture and advisory fees from Novartis Pharma, GlaxoSmithKline, and AstraZeneca; lecture fees and grants from Boehringer Ingelheim; research grant from ROHTO Pharmaceutical and Kintetsu Cable Network, and grant and fund from Chugai Pharmaceutical, Ono Pharmaceutical, and Taiho Pharmaceutical.

Jill Ohar has participated in advisory boards for Sunovion Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Mylan, Verona, and Theravance and has received grant funding from Sunovion Pharmaceuticals Inc, TEVA, Gordon and Betty Moore Foundation, NIH sub-award, and Boehringer Ingelheim.

Jennifer Quint has been supported by institutional research grants from the Medical Research Council, NIHR, Health Data Research, GSK, BI, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Insmed, and Sanofi and received personal fees for advisory board participation, consultancy, or speaking fees from GlaxoSmithKline, Boehringer Ingelheim, Sanofi, Chiesi, and AstraZeneca.

Anita Sharma serves on advisory boards for Diabetes, Heart Failure and Osteoporosis for Novartis, Merck Sharp & Dohme and Boehringer Ingelheim, Eli Lilly, and Amgen.

MeiLan K. Han reports personal fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Cipla, Chiesi, Novartis, Pulmonx, Teva, Verona, Merck, Mylan, Sanofi, DevPro, Aerogen, Polarian, Regeneron, Amgen, UpToDate, Altesa Biopharma, Medscape, NACE, MDBriefcase, Integrity and Medwiz. She has received either in kind research support or funds paid to the institution from the NIH, Novartis, Sunovion, Nuaira, Sanofi, Astrazeneca, Boehringer Ingelheim, Gala Therapeutics, Biodesix, the COPD Foundation and the American Lung Association. She has participated in Data Safety Monitoring Boards for Novartis and Medtronic with funds paid to the institution. She has received stock options from Meissa Vaccines and Altesa Biopharma.

Alan Kaplan is a member of the advisory board of, or speakers bureau for, ALK, AstraZeneca, Belus, Boehringer Ingelheim, Covis, Eisai, GlaxoSmithKline, Idorsia, Merck Frosst, Moderna, Novo Nordisk, Novartis, Pfizer, Purdue, Sanofi, Teva, Trudel, and Valeo.

Dave Singh has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GlaxoSmithKline, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pulmatrix, Sanofi, Teva, Theravance Biopharma, and Verona Pharma

Mukesh Singh reports previously received fees from AstraZeneca, Boehringer Ingelheim, Cheisi, GlaxoSmithKline, Napp/Mundipharma, Pfizer, and Teva.

Tom Wilkinson has received personal fees from AstraZeneca, GlaxoSmithKline, Enanta, Epiendo, j&j, Novartis, Genentech, Synairgen, my mhealth, biomerieux, Rocheand Sanofi/Regeneron alliance. Research grants from AstraZeneca, Biomerieux, GlaxoSmithKline, my mhealth, synairgen, Janssen and Sanofi/Regeneron.

Tonya Winders has received personal fees from AstraZeneca, GlaxoSmithKline, Novartis, Genentech, and Sanofi/Regeneron alliance. Allergy & Asthma Network & Global Allergy & Airways Patient Platform has received funds for unbranded disease awareness and education from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Genentech, Viatriis, and Sanofi/Regeneron.

David Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatriis, Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatriis, Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatriis, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Viatriis, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme, Teva Pharmaceuticals; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Novartis, Teva Pharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

References

1. Trueman D, Woodcock F, Woodcock E. Estimating the economic burden of respiratory illness in the UK. Published online 2017. Accessed February 24, 2023. https://cdn.shopify.com/s/files/1/0221/4446/files/PC-1601_-_Economic_burden_report_FINAL_8cdaba2a-589a-4a49-bd14-f45d66167795.pdf?1309501094450848169
2. British Lung Foundation. Chronic Obstructive Pulmonary Disease (COPD) Statistics. blf.org.uk. 2012. Accessed February 24, 2023. <https://statistics.blf.org.uk/copd>
3. Centers for Disease Control and Prevention. COPD Costs. 2018. Accessed February 24, 2023. <https://www.cdc.gov/copd/infographics/copd-costs.html>
4. COPD National Action Plan. Published online 2018. Accessed February 24, 2023. <https://www.nhlbi.nih.gov/resources/copd-national-action-plan>
5. The NHS Long Term Plan. Published online 2019. Accessed February 24, 2023. <https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf>
6. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402-407. doi:10.1136/thx.2007.085456
7. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. *J Asthma*. 2006;43(1):75-80. doi:10.1080/02770900500448738
8. Bakerly ND, Cardwell G. The “missing millions”: Where do we find them? *Chron Respir Dis*. 2016;13(4):319-320. doi:10.1177/1479972316667362
9. Balcells E, Antó JM, Gea J, et al. Characteristics of patients admitted for the first time for COPD exacerbation. *Respir Med*. 2009;103(9):1293-1302. doi:10.1016/j.rmed.2009.04.001
10. Kostikas K, Price D, Gutzwiller FS, et al. Clinical impact and healthcare resource utilization associated with early versus late COPD diagnosis in patients from UK CPRD database. Published online May 2020.
11. Jones RCM, Price D, Ryan D, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. *Lancet Respir Med*. 2014;2(4):267-276. doi:10.1016/S2213-2600(14)70008-6
12. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med*. 2017;5(5):426-434. doi:10.1016/S2213-2600(17)30119-4
13. Crisan L, Wong N, Sin DD, Lee HM. Karma of Cardiovascular Disease Risk Factors for Prevention and Management of Major Cardiovascular Events in the Context of Acute

- Exacerbations of Chronic Obstructive Pulmonary Disease. *Front Cardiovasc Med*. 2019;6:79. doi:10.3389/fcvm.2019.00079
14. Halpin DMG, Decramer M, Celli B, Kesten S, Leimer I, Tashkin DP. Risk of nonlower respiratory serious adverse events following COPD exacerbations in the 4-year UPLIFT® trial. *Lung*. 2011;189(4):261-268. doi:10.1007/s00408-011-9301-8
 15. Larsson K, Janson C, Ställberg B, et al. Impact of COPD diagnosis timing on clinical and economic outcomes: the ARCTIC observational cohort study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:995-1008. doi:10.2147/COPD.S195382
 16. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events. A Post Hoc Cohort Analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2018;198(1):51-57. doi:10.1164/rccm.201711-2239OC
 17. Kerkhof M, Voorham J, Dorinsky P, et al. The Long-Term Burden of COPD Exacerbations During Maintenance Therapy and Lung Function Decline. *COPD*. 2020;Volume 15:1909-1918. doi:10.2147/COPD.S253812
 18. Halpin DMG, Decramer M, Celli BR, Mueller A, Metzendorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85-91. doi:10.1016/j.rmed.2017.04.013
 19. Halpin DMG, Dickens AP, Skinner D, et al. Identification of key opportunities for optimising the management of high-risk COPD patients in the UK using the CONQUEST quality standards: an observational longitudinal study. *The Lancet Regional Health - Europe*. 2023;29:100619. doi:10.1016/j.lanepe.2023.100619
 20. Kerr M, Tarabichi Y, Evans A, et al. Patterns of Care in the Management of High-Risk COPD in the US (2011-2019): An Observational Study for the CONQUEST Improvement Program. *Lancet Regional Health - Americas*. In Press.
 21. Evans A, Hancock K, Dickens AP, et al. Identifying opportunities for optimising the management of high-risk COPD patients in Australia: an observational study. In: *Poster Presentation*. ; 2023.
 22. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128-1138. doi:10.1056/NEJMoa0909883
 23. Halpin DMG, de Jong HJL, Carter V, Skinner D, Price D. Distribution, Temporal Stability and Appropriateness of Therapy of Patients With COPD in the UK in Relation to GOLD 2019. *EClinicalMedicine*. 2019;14:32-41. doi:10.1016/j.eclinm.2019.07.003
 24. Gruffydd-Jones K, Brusselle G, Jones R, et al. Changes in initial COPD treatment choice over time and factors influencing prescribing decisions in UK primary care: a real-world study. *npj Prim Care Resp Med*. 2016;26(1):16002. doi:10.1038/npjpcrm.2016.2
 25. Palli SR, Zhou S, Shaikh A, Willey VJ. Effect of compliance with GOLD treatment recommendations on COPD health care resource utilization, cost, and exacerbations

- among patients with COPD on maintenance therapy. *J Manag Care Spec Pharm.* 2021;27(5):625-637. doi:10.18553/jmcp.2021.20390
26. Restrepo R. Medication adherence issues in patients treated for COPD. *COPD.* 2008;Volume 3:371-384. doi:10.2147/COPD.S3036
 27. Blackstock FC, ZuWallack R, Nici L, Lareau SC. Why Don't Our Patients with Chronic Obstructive Pulmonary Disease Listen to Us? The Enigma of Nonadherence. *Ann Am Thorac Soc.* 2016;13(3):317-323. doi:10.1513/AnnalsATS.201509-600PS
 28. Fekete M, Pako J, Nemeth AN, Tarantini S, Varga JT. Prevalence of influenza and pneumococcal vaccination in chronic obstructive pulmonary disease patients in association with the occurrence of acute exacerbations. *J Thorac Dis.* 2020;12(8):4233-4242. doi:10.21037/jtd-20-814
 29. Ozlu T, Bulbul Y, Aydin D, et al. Immunization status in chronic obstructive pulmonary disease: A multicenter study from Turkey. *Ann Thorac Med.* 2019;14(1):75-82. doi:10.4103/atm.ATM_145_18
 30. Ghosh S, Anderson WH, Putcha N, et al. Alignment of Inhaled Chronic Obstructive Pulmonary Disease Therapies with Published Strategies. Analysis of the Global Initiative for Chronic Obstructive Lung Disease Recommendations in SPIROMICS. *Ann Am Thorac Soc.* 2019;16(2):200-208. doi:10.1513/AnnalsATS.201804-283OC
 31. Global Initiative for Chronic Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2024 Report.*; 2024. Accessed November 29, 2023. <https://goldcopd.org/2024-gold-report/>
 32. Make B, Dutro MP, Paulose-Ram R, Marton JP, Mapel DW. Undertreatment of COPD: a retrospective analysis of US managed care and Medicare patients. *Int J Chron Obstruct Pulmon Dis.* 2012;7:1-9. doi:10.2147/COPD.S27032
 33. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis.* 2014;9:889-904. doi:10.2147/COPD.S62750
 34. Bourbeau J, Sebaldt RJ, Day A, et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. *Can Respir J.* 2008;15(1):13-19. doi:10.1155/2008/173904
 35. Pullen R, Miravittles M, Sharma A, et al. CONQUEST Quality Standards: For the Collaboration on Quality Improvement Initiative for Achieving Excellence in Standards of COPD Care. *Int J Chron Obstruct Pulmon Dis.* 2021;16:2301-2322. doi:10.2147/COPD.S313498
 36. Halpin DM, Miravittles M, Metzendorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2891-2908. doi:10.2147/COPD.S139470
 37. Alves L, Pullen R, Hurst JR, et al. CONQUEST: A Quality Improvement Program for Defining and Optimizing Standards of Care for Modifiable High-Risk COPD Patients. *PROM.* 2022;Volume 13:53-68. doi:10.2147/PROM.S296506

38. Jordan RE, Adab P, Sitch A, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. *Lancet Respir Med*. 2016;4(9):720-730. doi:10.1016/S2213-2600(16)30149-7
39. Kaplan A, Thomas M. Screening for COPD: the gap between logic and evidence. *European Respiratory Review: An Official Journal of the European Respiratory Society*. 2017;26(143). doi:10.1183/16000617.0113-2016
40. Haroon S, Jordan R, Takwoingi Y, Adab P. Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. *BMJ Open*. 2015;5(10):e008133. doi:10.1136/bmjopen-2015-008133
41. Aaron SD, Vandemheen KL, Whitmore GA, et al. Early Diagnosis and Treatment of COPD and Asthma — A Randomized, Controlled Trial. *New England Journal of Medicine*. 2024;390(22):2061-2073. doi:10.1056/NEJMoa2401389
42. Halpin DMG, Healey H, Skinner D, Carter V, Pullen R, Price D. Exacerbation history and blood eosinophil count prior to diagnosis of COPD and risk of subsequent exacerbations. *European Respiratory Journal*. 2024;64(4). doi:10.1183/13993003.02240-2023
43. Terasaki J, Singh G, Zhang W, Wagner P, Sharma G. Using EMR to improve compliance with clinical practice guidelines for management of stable COPD. *Respir Med*. 2015;109(11):1423-1429. doi:10.1016/j.rmed.2015.10.003
44. Morganroth M, Pape G, Rozenfeld Y, Heffner JE. Multidisciplinary COPD disease management program: impact on clinical outcomes. *Postgrad Med*. 2016;128(2):239-249. doi:10.1080/00325481.2016.1129259
45. Markun S, Rosemann T, Dalla-Lana K, Steurer-Stey C. Care in Chronic Obstructive Lung Disease (CAROL): a randomised trial in general practice. *Eur Respir J*. 2018;51(5). doi:10.1183/13993003.01873-2017
46. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol*. 2009;62(5):499-505. doi:10.1016/j.jclinepi.2009.01.012
47. Seki T, Aki M, Kawashima H, et al. Electronic health record nested pragmatic randomized controlled trial of a reminder system for serum lithium level monitoring in patients with mood disorder: KONOTORI study protocol. *Trials*. 2019;20(1):706. doi:10.1186/s13063-019-3847-9
48. Murphy AW, Esterman A, Pilotto LS. Cluster randomized controlled trials in primary care: an introduction. *Eur J Gen Pract*. 2006;12(2):70-73. doi:10.1080/13814780600780627
49. Schottenfeld L, Petersen D, Peikes D, et al. Creating Patient-centred Team-based Primary Care. Published online March 2016. Accessed February 28, 2023. <https://www.ahrq.gov/sites/default/files/wysiwyg/ncepcr/tools/PCMH/creating-patient-centered-team-based-primary-care-white-paper.pdf>

50. Rothnie KJ, Müllerová H, Hurst JR, et al. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. *PLoS One*. 2016;11(3):e0151357. doi:10.1371/journal.pone.0151357
51. Kerkhof M, Voorham J, Dorinsky P, et al. Association between COPD exacerbations and lung function decline during maintenance therapy. *Thorax*. 2020;75(9):744-753. doi:10.1136/thoraxjnl-2019-214457
52. Health Data Research UK. Welcome to CALIBER! CALIBER. 2020. Accessed January 3, 2021. <https://www.caliberresearch.org/portal>
53. Magnussen H, Lucas S, Lapperre T, et al. Withdrawal of inhaled corticosteroids versus continuation of triple therapy in patients with COPD in real life: observational comparative effectiveness study. *Respir Res*. 2021;22(1):25. doi:10.1186/s12931-021-01615-0
54. Miravittles M, Sliwinski P, Rhee CK, et al. Changes in Control Status of COPD Over Time and Their Consequences: A Prospective International Study. *Arch Bronconeumol (Engl Ed)*. 2021;57(2):122-129. doi:10.1016/j.arbres.2020.06.003
55. Ming SWY, Haughney J, Ryan D, et al. A Comparison of the Real-Life Clinical Effectiveness of the Leading Licensed ICS/LABA Combination Inhalers in the Treatment for COPD. *Int J Chron Obstruct Pulmon Dis*. 2020;15:3093-3103. doi:10.2147/COPD.S263745
56. Voorham J, Baldi S, Santoro L, et al. Extrafine Beclometasone Dipropionate/Formoterol Fumarate vs Double Bronchodilation Therapy in Patients with COPD: A Historical Real-World Non-Inferiority Study. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2739-2750. doi:10.2147/COPD.S269287
57. Kerkhof M, Chaudhry I, Pavord ID, et al. Blood eosinophil count predicts treatment failure and hospital readmission for COPD. *ERJ Open Res*. 2020;6(4):00188-02020. doi:10.1183/23120541.00188-2020
58. Hermans WRM, Foley DP, Rensing BJ, et al. Usefulness of quantitative and qualitative angiographic lesion morphology, and clinical characteristics in predicting major adverse cardiac events during and after native coronary balloon angioplasty. *The American Journal of Cardiology*. 1993;72(1):14-20. doi:10.1016/0002-9149(93)90211-T
59. Reilev M, Pottgård A, Lykkegaard J, Søndergaard J, Ingebrigtsen TS, Hallas J. Increased risk of major adverse cardiac events following the onset of acute exacerbations of COPD. *Respirology*. 2019;24(12):1183-1190. doi:10.1111/resp.13620
60. White WB, Cooke GE, Kowey PR, et al. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. *Chest*. 2013;144(3):758-765. doi:10.1378/chest.12-2332
61. Armentaro G, Pelaia C, Cassano V, et al. Association between right ventricular dysfunction and adverse cardiac events in mild COPD patients. *Eur J Clin Invest*. 2023;53(2):e13887. doi:10.1111/eci.13887

62. National Institute for Health and Care Excellence. British National Formulary: Glucocorticoid therapy. <https://bnf.nice.org.uk/treatment-summary/glucocorticoid-therapy.html>
63. USPNF. United States Pharmacopeia (US) and the National Formulary (NF). Purchase USP-NF. Accessed February 28, 2023. <https://www.uspnf.com/purchase-usp-nf>
64. Margulies P. Corticosteroid Comparison Chart. Published online February 20, 2020. Accessed April 12, 2023. https://www.nadf.us/uploads/1/3/0/1/130191972/adrenal_hormone_replacement_protocol_and_quick_guide.pdf
65. Fletcher CM. The clinical diagnosis of pulmonary emphysema; an experimental study. *Proc R Soc Med*. 1952;45(9):577-584.
66. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *European Respiratory Journal*. 2009;34(3):648-654. doi:10.1183/09031936.00102509
67. Hayes RJ, Moulton L. *CLUSTER RANDOMISED TRIALS*. Second. CHAPMAN & HALL CRC; 2022.
68. National Statistics. English Indices of Deprivation 2019. Published online September 2019. Accessed February 28, 2023. <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019>
69. Lambe T, Adab P, Jordan RE, et al. Model-based evaluation of the long-term cost-effectiveness of systematic case-finding for COPD in primary care. *Thorax*. 2019;74(8):730-739. doi:10.1136/thoraxjnl-2018-212148
70. Haroon S, Adab P, Griffin C, Jordan R. Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial. *Br J Gen Pract*. 2013;63(606):e55-62. doi:10.3399/bjgp13X660788
71. Abdel-Aal A, Lisspers K, Williams S, et al. Prioritising primary care respiratory research needs: results from the 2020 International Primary Care Respiratory Group (IPCRG) global e-Delphi exercise. *NPJ Prim Care Respir Med*. 2022;32(1):6. doi:10.1038/s41533-021-00266-4
72. Pinnock H, Østrem A, Rodriguez MR, et al. Prioritising the respiratory research needs of primary care: the International Primary Care Respiratory Group (IPCRG) e-Delphi exercise. *Prim Care Respir J*. 2012;21(1):19-27. doi:10.4104/pcrj.2012.00006
73. Norton WE, Loudon K, Chambers DA, Zwarenstein M. Designing provider-focused implementation trials with purpose and intent: introducing the PRECIS-2-PS tool. *Implement Sci*. 2021;16(1):7. doi:10.1186/s13012-020-01075-y
74. Machline-Carrion MJ, Soares RM, Damiani LP, et al. Effect of a Multifaceted Quality Improvement Intervention on the Prescription of Evidence-Based Treatment in Patients at High Cardiovascular Risk in Brazil: The BRIDGE Cardiovascular Prevention Cluster Randomized Clinical Trial. *JAMA Cardiol*. 2019;4(5):408. doi:10.1001/jamacardio.2019.0649

75. Walker D, Otieno P, Butrick E, et al. Effect of a quality improvement package for intrapartum and immediate newborn care on fresh stillbirth and neonatal mortality among preterm and low-birthweight babies in Kenya and Uganda: a cluster-randomised facility-based trial. *The Lancet Global Health*. 2020;8(8):e1061-e1070. doi:10.1016/S2214-109X(20)30232-1
76. Scales DC. A Multifaceted Intervention for Quality Improvement in a Network of Intensive Care Units: A Cluster Randomized Trial. *JAMA*. 2011;305(4):363. doi:10.1001/jama.2010.2000
77. Wallace MB, Crook JE, Thomas CS, Staggs E, Parker L, Rex DK. Effect of an endoscopic quality improvement program on adenoma detection rates: a multicenter cluster-randomized controlled trial in a clinical practice setting (EQUIP-3). *Gastrointestinal Endoscopy*. 2017;85(3):538-545.e4. doi:10.1016/j.gie.2016.07.042
78. Yawn BP, Wollan P, Rank M. Exacerbations in the pre- and post-COPD diagnosis periods. *Pragmat Obs Res*. 2013;4:1-6. doi:10.2147/POR.S41778
79. Sathian B, Asim M, Banerjee I, et al. Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal J Epidemiol*. 2020;10(3):878-887. doi:10.3126/nje.v10i3.31622
80. Taylor-Cousar JL, Maier L, Downey GP, Wechsler ME. Restarting Respiratory Clinical Research in the Era of the Coronavirus Disease 2019 Pandemic. *Chest*. 2021;159(3):1173-1181. doi:10.1016/j.chest.2020.11.001
81. Hallinan CM, Ward R, Hart GK, et al. Seamless EMR data access: Integrated governance, digital health and the OMOP-CDM. *BMJ Health Care Inform*. 2024;31(1). doi:10.1136/bmjhci-2023-100953
82. Tennison I, Roschnik S, Ashby B, et al. Health care's response to climate change: a carbon footprint assessment of the NHS in England. *The Lancet Planetary Health*. 2021;5(2):e84-e92. doi:10.1016/S2542-5196(20)30271-0
83. Tirumalasetty J, Miller SA, Prescott HC, et al. Greenhouse Gas Emissions and Costs of Inhaler Devices in the US. *JAMA*. 2024;332(12):1017-1019. doi:10.1001/jama.2024.15331

Table 1: Study specific definitions for patient cohorts and terminology

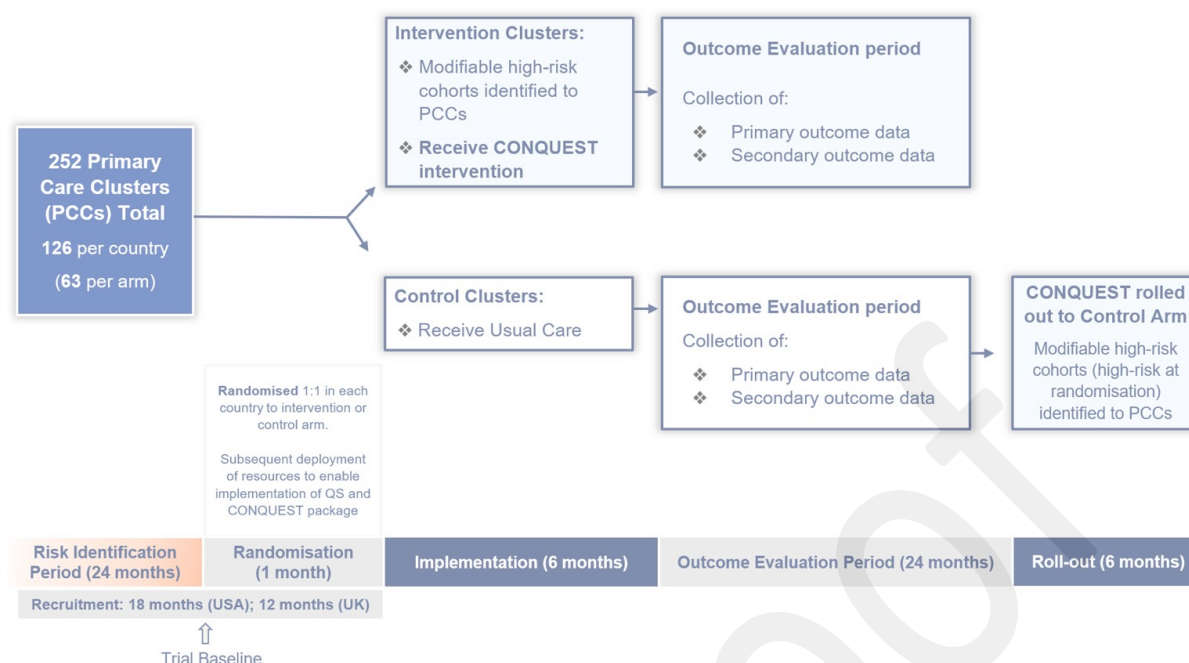
Term	Definition
Modifiable high-risk patient	Patients with COPD (or potential COPD) who have had ≥ 2 moderate or ≥ 1 severe exacerbations in the last 24 months with at least one exacerbation occurring in the last 12 months of the time period used and, whose medical records indicate there is scope for optimization of their management.
Potential undiagnosed COPD	Patients without a COPD diagnosis (ever) recorded in their EMR at trial baseline, who were current or ex-smokers with either ≥ 10 years smoking duration or ≥ 10 pack years smoking history.
Newly diagnosed COPD	Undiagnosed patients with potential modifiable high-risk COPD who receive a COPD diagnosis, irrespective of confirmatory spirometry, within the trial implementation period.
Already diagnosed COPD	Patients with a recorded diagnosis of COPD, irrespective of confirmatory spirometry, at any point in their history at trial baseline.
COPD exacerbation	A significant worsening in respiratory symptoms in people with COPD (or an event analogous to a COPD exacerbation in people with suspected but undiagnosed COPD) that requires a change in treatment or management.
Moderate exacerbation	Required a prescription of OCS and/or a course of antibiotics within 3 days of a lower respiratory consultation that does not result in hospitalization.
Severe exacerbation	An exacerbation resulting in a respiratory-related hospitalization or death.
Complicated exacerbation	A severe COPD exacerbation OR A moderate COPD exacerbation involving any of the following: <ul style="list-style-type: none"> • additional acute course(s) of corticosteroids and/or respiratory antibiotic between 8 and 28 days after the initial event • further record of moderate/severe COPD exacerbation between 8 and 28 days after the start of the initial event
Risk identification period	The 24 months prior to randomization where PCC electronic medical record (EMR) data will be retrospectively searched to identify undiagnosed patients with potential COPD and, patients with already diagnosed COPD who meet the modifiable high-risk criteria. The term 'trial baseline' is used to describe the end of this 24-month period, immediately prior to randomization.
Implementation period	The intervention implementation period runs for 6 months during which time the CONQUEST Quality Improvement program is implemented in intervention arm PCCs. This includes invitation of modifiable high-risk cohorts for assessment and clinical decision support prompted consultations to initiate optimization of COPD management. Control arm PCCs continue with standard care.
Outcome Evaluation period	Intervention arm clusters: The outcome evaluation period starts at the end of the 6-month CONQUEST implementation period in the intervention arm. During

	<p>the outcome evaluation period PCCs in the CONQUEST arm continue to receive the remaining components of the intervention.</p> <p>Control arm clusters: The outcome evaluation period will start 6 months after recruitment of a PCC into the control arm. During the outcome evaluation period control arm practices will continue to administer usual care for COPD.</p>
<p>Abbreviations: COPD: chronic obstructive pulmonary disease; EMR: electronic medical records; OCS: oral corticosteroids; PCC: primary care cluster</p>	

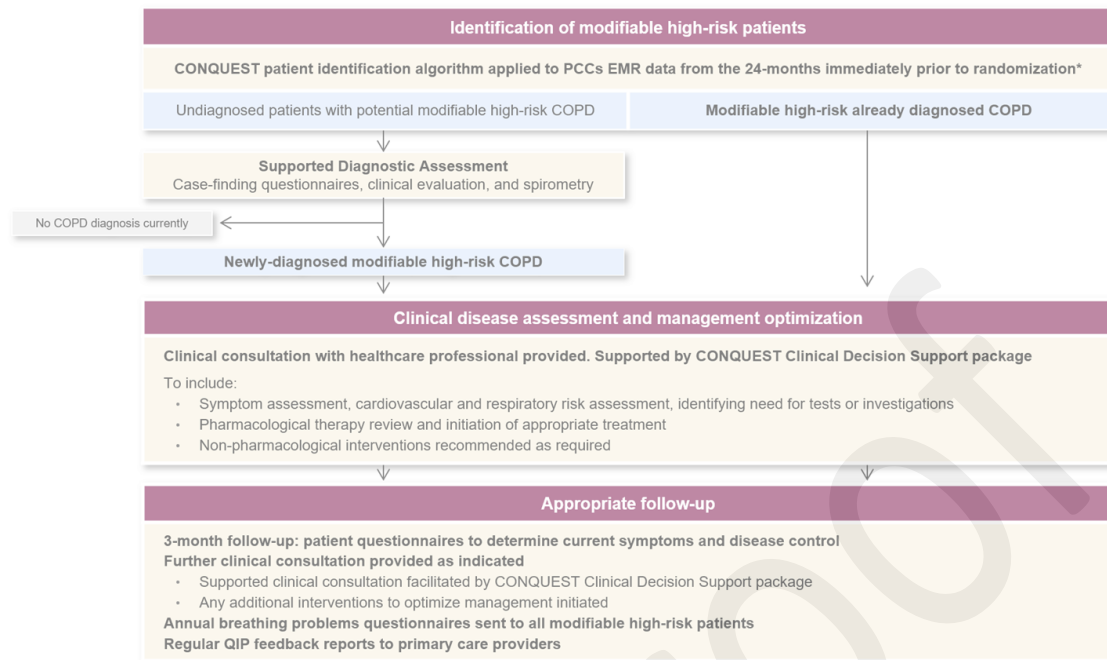
Pre-proof

Table 2: PREVAIL CRT outcomes and analysis cohorts

Outcomes	Primary analysis cohort – Already diagnosed and newly diagnosed patients	Secondary analysis cohort – Already diagnosed patients	Exploratory analysis cohort – all initially undiagnosed patients with potential COPD
Primary outcomes			
The annual rate of moderate or severe COPD exacerbations	✓	✓	✓
The annual rate of major adverse cardiac or respiratory events. Presented:			
In composite	✓	✓	✓
Disaggregated by components	✓	✓	✓
Secondary outcomes			
The annual systemic corticosteroid dose used to treat exacerbations	✓	✓	✓
The annual rate of unscheduled respiratory care events	✓	✓	✓
Exploratory outcomes			
The rate of explanatory diagnoses, other than COPD.			✓ [†]
Change in lung function (spirometry)	✓	✓	✓
Change in disease-specific quality of life (COPD assessment test)	✓	✓	
Abbreviations: COPD: chronic obstructive pulmonary disease.			
† The subset of all initially undiagnosed patients with potential COPD who do not receive a COPD diagnosis following the diagnostic case-finding exercise			

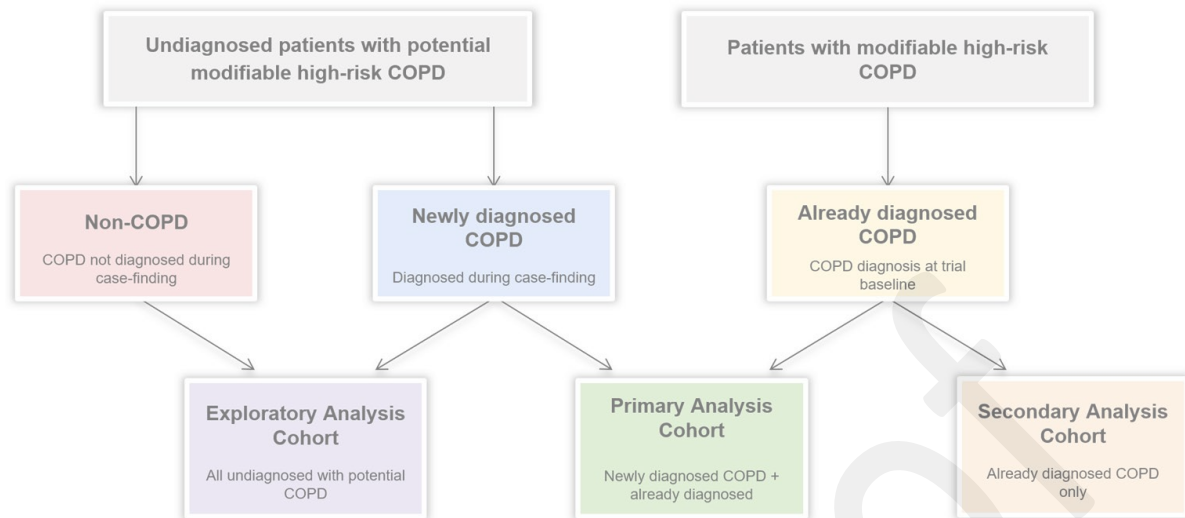
Figure 1 – Overview of PREVAIL CRT Design and Time Periods for the UK and US

Abbreviations: PCCs = Primary Care Clusters; QS = Quality Standards; CONQUEST = Collaboration N on a Quality Improvement Initiative to Achieve Excellence in Standards of COPD Care

Figure 2 – PREVAIL Intervention: CONQUEST QIP Components

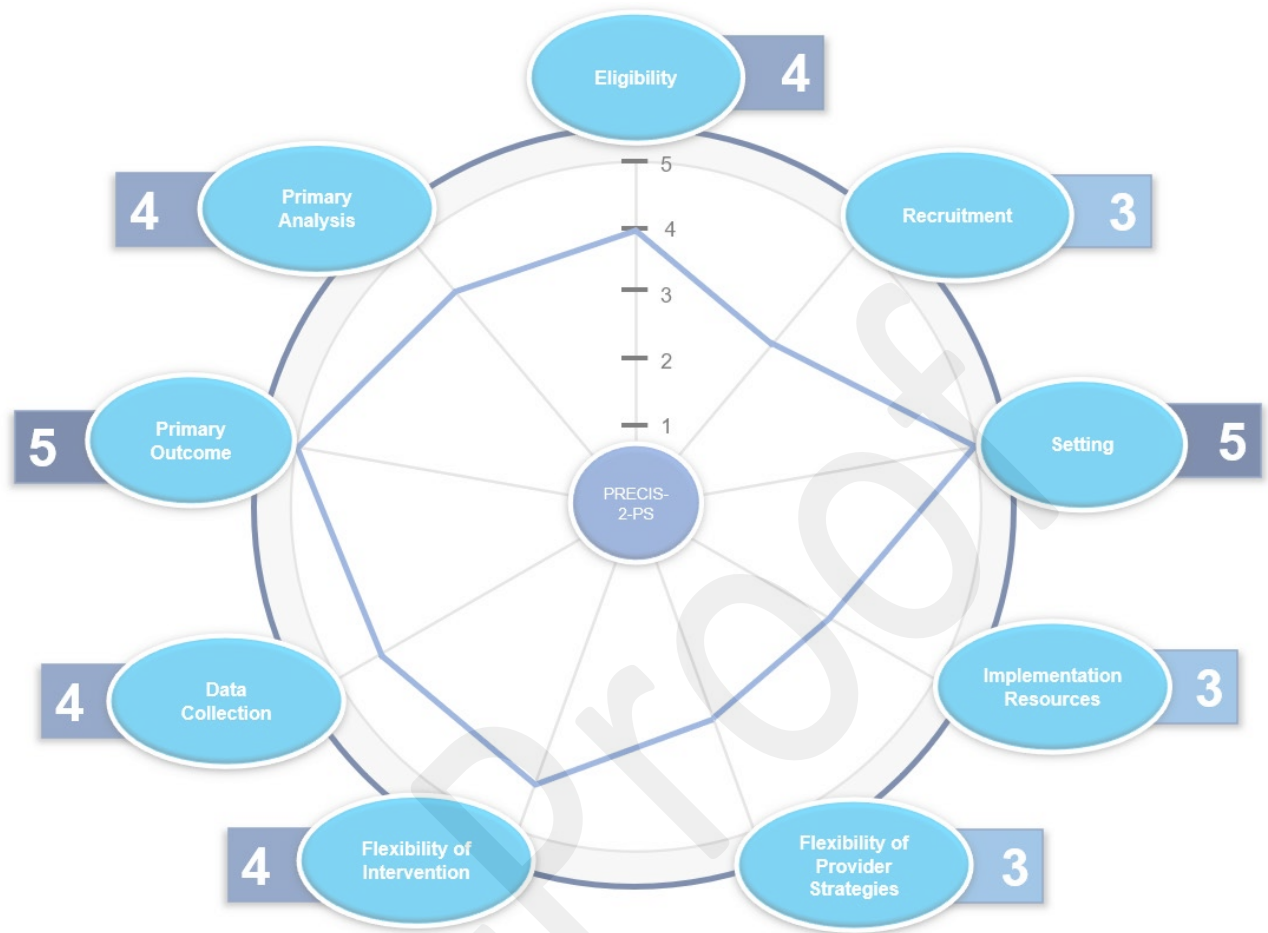
Abbreviations: CONQUEST = Collaboration on Quality improvement initiative for achieving Excellence in Standards of COPD care; COPD = Chronic Obstructive Pulmonary Disease; EMR = electronic medical record; PCCs = primary care clusters; QIP = quality improvement program; QS = quality standard

*In control PCCs modifiable high-risk patients will be identified at the end of the outcome evaluation period based on the 24-months EMR data immediately prior to randomization

Figure 3 – Composition of the Analysis Cohorts for the PREVAIL CRTs

Abbreviations: COPD = chronic obstructive pulmonary disease; CRT = cluster randomized trial

**Figure 4 – Pragmatic explanatory continuum indicator summary-2 (PRECIS-2)
Provider Strategies scoring of the PREVAIL trial.**



Each parameter is scored on a scale of 1 to 5, with lower scores being more aligned with observational studies and higher scores more representative of a pragmatic trial. As depicted, the PREVAIL CRT scored 35 out of 45 on the PRECIS-2-PS scale indicating it favors a pragmatic design.