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Variation in patient pathways and hospital admissions for exacerbations of COPD: linking the National COPD Audit with CPRD data

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Declaration of originality

I, Philip W Stone, hereby certify that the work presented in this thesis is my own and all information presented from other works is properly referenced.

Philip W Stone

Copyright declaration

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Abstract

The aim of this thesis was to link secondary care data from a UK national audit of chronic obstructive pulmonary disease (COPD) care with primary care data from a database of UK electronic health records (EHRs) to explore how variations in patient pathways through healthcare across England affect hospital admissions for acute exacerbations of COPD (AECOPD). This aim was achieved through 6 objectives: (i) a systematic review of the literature on validation of AECOPD definitions in EHRs; (ii) determination of predictors of referral to pulmonary rehabilitation from general practice; (iii) a comparison of the quality of COPD primary care in each UK country, as currently only Wales is assessed; (iv) determination of whether the COPD Best Practice Tariff (BPT) pay-for-performance scheme improves patient outcomes; (v) assessment of the utility of NEWS2 as a severity score measure in AECOPD admissions; (vi) linkage of secondary care audit data with primary care EHR data to explore how management of patients with COPD affects AECOPD hospital admissions.

A summary of the key results is as follows. Firstly, although few studies have validated AECOPD definitions, a validated AECOPD definition was found in a systematic search of the literature that could be used in subsequent objectives. Secondly. while generally appropriate patients appear to be prioritised for PR referral, women were less likely to be considered for referral than men. Thirdly, England, Scotland, and Northern Ireland had substantially lower proportions of patients with confirmed airways obstruction and referrals to pulmonary rehabilitation than Wales. This suggests that completing primary care audits solely in Wales is leading to improvements in, at least, the recording of care that are not happening in the rest of the UK. Fourthly, the combination of interventions financially incentivised by the COPT BPT were not associated with an improvement in 30-day mortality or readmission. One component of the BPT, specialist review, was associated with 31% lower odds of inpatient mortality. Fifthly, NEWS2 was a poor predictor of length of hospital stay, requirement for NIV, and inpatient mortality, with AUC values of 0.7 or less for each outcome. Sixth and finally, 80% of patients admitted for AECOPD had contact with their GP in the 2 weeks prior to admission, suggesting that these admissions could not have been avoided. 86% of admissions were clinically appropriate. Contact with primary care did not appear to affect admission appropriateness. Receipt of a discharge care bundle was associated with receipt of best practice care, however this association appeared to derive from already having received those items of care in secondary care.

Power was limited in the final analyses making it difficult to draw firm conclusions, however COPD discharge care bundles do not appear to be leading to improvements in key patient outcomes.

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Chapter 1. Background

1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterised by respiratory symptoms such as breathlessness, cough, or sputum production, and airflow limitation due to damage to the airway and/or alveoli(1,2). It is estimated that 1.2 million people in the UK have diagnosed COPD, making it the second most common lung disease in terms of diagnoses(3). UK healthcare costs related to COPD are estimated at £1.8 billion annually(4) and in 2013 COPD was the 4th and 5th most common cause of death for men and women, respectively(5). The UK has the 12th highest mortality rate for COPD in the world, and the 3rd highest in Europe(3).

COPD develops when the lungs become damaged and inflamed as a result of long-term inhalation of a harmful substance(6–8) – roughly 90% of cases are due to tobacco smoking(9), however air pollution and occupational exposures are also risk factors(1,8). The airflow obstruction that characterises COPD is not fully reversible, and is usually progressive in the long term(7). There is no simple diagnostic test for COPD with diagnosis being a clinical judgement based on historical exposures, physical examination, and confirmation of airflow obstruction through spirometry(7).

1.1.1 Diagnosis

A post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of <0.7 indicates persistent airflow obstruction(1), though there is some debate as to whether the lower limit of normal (LLN) (the bottom 5% of the healthy population for a given age and gender) should be used instead of the fixed ratio of 0.7(10,11). There is concern that using a fixed ratio will under diagnose COPD in younger patients and over diagnose COPD in older patients as the FEV_1/FVC ratio naturally declines with age(11,12). Several studies have compared the fixed ratio and LLN, with many finding that using the LLN appears to underestimate prevalence of COPD, especially in older patients(13–15). There are also large studies that have found little difference between use of either the fixed ratio or the LLN(16,17), with one also assessing the combination of FEV_1/FVC ratio and FEV_1 percent of predicted, and finding the combination of the two was more strongly associated with patient outcomes then the FEV1/FVC ratio alone using either cut-off(16). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therefore recommends using the fixed 0.7 cut-off due to its simplicity and the recommendation that COPD diagnosis should come not only from evidence of airways obstruction via spirometry, but also through assessment of symptoms and historical exposures(12).

In the UK, NICE guidelines(18) suggest suspecting diagnosis of COPD in individuals over 35 years old who have a risk factor for COPD, such as history of smoking, and one or more of the symptoms that characterise the disease (breathlessness, cough, or sputum production). Post-bronchodilator spirometry is then used to calculate the FEV_1/FVC ratio, with a ratio less than 0.7 indicating airway obstruction. A chest X-ray and full blood count will also be performed as part of the diagnostic process to rule out alternative diagnoses. Assessment of the severity of COPD will be done through the Medical Research Council (MRC) dyspnoea scale (**Table 1**), a questionnaire to assess breathlessness(1,18), and GOLD stage (**Table 2**), a classification of the severity of airflow limitation, derived using post-bronchodilator FEV_1(1). More recently GOLD has been expanded to include a combination of symptoms and exacerbations, with less emphasis purely on lung function(12).

Table 1. *Medical Research Council (MRC) dyspnoea scale*

MRC Grade	Degree of breathlessness
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 metres or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

From the NICE guideline for COPD (NG115)**(18)**, adapted from Fletcher et al, 1959**(19)**.

Table 2. *Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. For patients with FEV_1/FVC < 0.7.*

GOLD Stage	Post-bronchodilator FEV_1 percent of predicted
1 – Mild	≥ 80%
2 – Moderate	50 – 79%
3 – Severe	30 – 49%
4 – Very severe	< 30%

Adapted from the GOLD Pocket Guide(1) and NICE guideline for COPD (NG115)**(18)**.

1.1.2 Management of stable COPD

The primary aim of management of COPD is to relieve symptoms and reduce the risk of disease flare-ups(12). The first stage of COPD treatment is to identify and reduce exposure to the risk factor,

most commonly tobacco smoke. Patients should be offered both counselling and pharmacotherapy (nicotine replacement therapy, varenicline, or bupropion) to maximise their chances of successfully stopping smoking(12,18). The pneumococcal vaccination and an annual influenza vaccination should also be offered to patients to reduce the likelihood of a lower respiratory tract infection that could lead to a substantial worsening of symptoms(18).

Pulmonary rehabilitation is another beneficial intervention that has been shown to improve dyspnoea, fatigue, quality of life, and exercise capacity in individuals with COPD(20,21). Pulmonary rehabilitation is a comprehensive programme of care for people with chronic respiratory disease that includes an initial patient assessment followed by exercise training, education, and behaviour change exercises(1,18,22). Programmes are tailored to the needs of each individual participant, based on their initial assessment, and aim to maximise a patient's autonomy by improving their physical and mental health and installing long-term healthy behaviours(18,22). Pulmonary rehabilitation will typically be offered to patients with an MRC grade of 3 or more, but it is not suitable for patients that are unable to walk who have recently suffered a heart attack(18).

If all of the aforementioned therapies have been offered and patients are still struggling with breathlessness then inhalers will be prescribed(7,23). Initially patients will be offered either a short-acting beta2 agonist (SABA) or short-acting muscarinic antagonist (SAMA) to take as required. If the patient is still struggling with breathlessness then in addition to the SABA/SAMA, a patient will be offered a combination inhaler: a combined long-acting beta2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhaler if their condition does not have asthmatic features; or a combined LABA and inhaled corticosteroid (ICS) inhaler if their condition has asthmatic features (asthmatic features would be defined as a previous diagnosis of asthma or atopy or a substantial variation in FEV_1 over time). If the patient still has symptoms that are affecting their quality of life or they suffer 1 severe or 2 moderate disease flare-ups within a year, then that patient's GP should consider prescribing triple therapy (LAMA + LAMA + ICS)(18). The management described here is that recommended by NICE in the UK, which itself has been influenced by recommendations from both GOLD(12) and the European Respiratory Society (ERS) and American Thoracic Society (ATS)(24).

Smoking cessation, influenza vaccination, and pulmonary rehabilitation are prioritised before the prescription of inhaled therapies because these three interventions represent "high-value" care. These interventions are considered "high-value" because they are cost effective, providing a benefit to large number of patients, whereas inhalers only benefit patients with more severe symptoms. The "high-value" interventions also provide benefits beyond treatment of a patient's COPD; for example, smoking cessation will reduce the risk of developing other comorbidities, providing future NHS cost

savings. Prioritising these “high-value” interventions before inhaled therapies therefore allows the NHS to maximise the health benefits derived from its limited healthcare budget(25,26).

1.1.3 Acute exacerbations of COPD

Many patients with COPD experience episodes of sustained worsening or a flare-up in symptoms termed an acute exacerbation of COPD (AECOPD), or simply ‘exacerbation’(7), which can require hospitalisation when particularly severe(18). During an exacerbation, symptoms will typically last 1 to 2 weeks, however some symptoms may persist longer and 20% of patients will not have recovered to their pre-exacerbation state after 8 weeks(1,27). Frequent exacerbations are associated with increased mortality(28) and a decrease in lung function(29) and quality of life(30). Patients with more frequent exacerbations have a faster decline in lung function and increased mortality(28,29). Some exacerbations legitimately require hospitalisation, for example those that require oxygen or non-invasive ventilation (NIV), however other hospitalisations are potentially avoidable(7).

AECOPD is one of the most common reasons for emergency hospital admission in England with approximately 115,000 admissions annually(31). Data from the 2018/19 national audit of AECOPD admissions found an inpatient mortality of 3.6% and 10.2% of admissions required NIV(32). AECOPD hospitalisations are very costly to healthcare services(33–35), costing an estimated average of £1,868 per admission in England(36), and as high as an average of $44,909 for the most severe admissions in the US(35).

Exacerbations are usually caused by a viral infection, most commonly the human rhinovirus(37,38) (the cause of the common cold), however bacterial infections and air pollution may also contribute to exacerbations(1). Exacerbations due to viral infection are often severe and can lead to hospital admissions. This explains the seasonal nature of COPD exacerbations and highlights the importance of the seasonal influenza vaccine for individuals with COPD(1).

Diagnosis of AECOPD is a clinical judgement and treatment will depend on the severity of the exacerbation. In a mild exacerbation, a patient will be able to manage their condition at home with increased use of a SABA or SAMA inhaler. During a moderate exacerbation, a patient will require treatment with oral corticosteroids and/or antibiotics (where this is evidence of a bacterial infection), which they can receive from their GP. In severe exacerbations, where a patient experiences a rapid decline in their condition, they will be admitted to hospital. To aid appropriate treatment of an exacerbation, it is recommended that admitted patients receive a chest X-ray, a measure of blood oxygen levels, an electrocardiogram (to rule out any cardiac causes), a full blood

count, and a sputum culture if the sputum is purulent. Oxygen will be prescribed to patients if their arterial blood gas is below the individual's target range. Where a patient has persistent hypercapnic (elevated blood CO_2 concentration) respiratory failure despite receiving optimal medical treatment, treatment with NIV is recommended(18).

Non-invasive ventilation, as the name suggests, refers to a device that assists a patient with their breathing without the requirement for a endotracheal tube or tracheostomy(39). This is generally achieved using positive pressure ventilation through either a face mask, helmet, or nasal mask(39). Systematic reviews of the use of NIV in the management of hypercapnic respiratory failure due to AECOPD have found that it reduces the risk of mortality by 46% and the risk of requirement for endotracheal intubation by 65%(40). Use of NIV is also associated with reduced length of hospital stay and reduced incidence of complications(40).

Before a patient is discharged from hospital due to AECOPD, the British Thoracic Society (BTS) recommends that the medical team complete a checklist of best practice care, known as a discharge bundle. The specific items of care to complete on a COPD discharge bundle are(41):

- a review of medication and check of inhaler technique
- provision of a self-management plan and emergency drug pack, where appropriate
- an offer of support to achieve smoking cessation
- an assessment and referral for pulmonary rehabilitation
- arrangement of follow-up

The aim of the BTS COPD discharge bundle is to improve patient self-management and post-discharge care in order to reduce COPD readmissions. Each intervention of the bundle was chosen based on evidence that it improves outcomes for patients with COPD(42): inhalers are often used incorrectly(42,43) and assessing technique provides an opportunity to ensure patients are maximising the benefit from their medication; self-management education is associated with a reduction in admissions(42,44) and allows patients to feel more in control of their condition; smoking cessation is a cost-effective intervention(42,45) associated with reduced decline in lung function(18,42,46,47); pulmonary rehabilitation is associated with improvements in exercise capacity, quality of life(42,48) and hospital admissions(42,49); and follow-up was included to assess whether patients may require readmission as 50% of readmissions occur during the 38 days following discharge(42,50). Whilst each of the elements of the care bundle have been extensively investigated and shown to improve a number of different outcomes, few studies have evaluated the efficacy of the COPD discharge bundle as a whole(51).

1.2 Electronic health records

Electronic health records (EHRs) (also known as electronic medical records (EMRs)) are digital versions of patient notes and have been widely adopted in the NHS(52–54). Routinely collected EHRs are increasingly used as a source of data for epidemiological research(55). This increase in use has even lead to the development of research guidelines specifically for routinely-collected EHRs(56). To enable consistent recording and easy analysis of data; patient characteristics, symptoms, diagnoses, procedures, and results are generally stored in these databases using a specific clinical coding scheme.

One commonly used clinical coding scheme is the World Health Organisation's (WHO) International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)(57). As an example, in ICD-10 clinical terminology, AECOPD is represented using the code "J44.1". In the NHS, in secondary care, ICD-10 codes are used to record diagnoses and Office of Population Censuses and Surveys classification of surgical operations and procedures (OPCS-4) codes(58) are used to record interventions and surgical procedures(52). In primary care, Read codes(59) have historically been used to record all clinical events, however from April 2018 onwards GP practices have been transitioning to the new and more comprehensive SNOMED CT clinical terminology(53,54).

1.2.1 Read codes

Read codes have been used by the NHS since 1985 to record clinical terms related to patients in electronic General Practice databases(53). Read codes can code very detailed information on diagnosis, but also detail on symptoms, examinations, procedures, referrals, administration, prescriptions, and occupations and social information(59). Read codes have a hierarchical structure and each subsequent character of a code adds further detail about the location of that condition within the hierarchy(60). All version 2 Read codes consist of 5 bytes or characters, and full-stops (.) indicate that no further progression within the hierarchy is required. Each code carries its own distinct meaning but may also act as a 'parent' code for more detailed variations on the same concept. For example, H31.. (chronic bronchitis) has the parent codes H3... (chronic obstructive pulmonary disease) and H.... (respiratory system diseases). The number of possible 'child' codes descending from each parent varies from one clinical area to another.

1.2.2 SNOMED CT

NHS Digital describes SNOMED CT as "the most comprehensive and precise clinical health terminology product in the world"(54). It is the result of a three-year project to merge version 3 Read codes (also known as Clinical Terms Version 3 (CTV3)) and the previous version of the SNOMED

clinical terminology, SNOMED RT(61). While SNOMED CT was originally an acronym for SNOMED Clinical Terms, it is now considered a brand name(61). SNOMED CT introduces a "concept ID" to link equivalent and synonymous terms, making identifying clinical events much simpler. For example, the concept ID for "common cold" will identify many terms synonymous with the common cold that otherwise have their own unique ID.

1.3 Clinical audit

The purpose of clinical audit is to check that healthcare is provided according to standards, show patients and care providers the quality of care being provided, and highlight where improvements to care could be made(62). There are more than 30 national audits in the UK to examine care quality for common conditions. These audits are commissioned and managed by the National Clinical Audit and Patient Outcomes Programme (NCAPOP) and collect and analyse data from clinicians in participating trusts to give a national representation of care quality for audited conditions(62). Most of the national audits collect data for England and Wales, however some of the audits additionally include Scotland and Northern Ireland(62). As well as providing a national view of care quality, these audits can provide individual trusts with information on their performance relative to the rest of the country or their local region.

National clinical audit has been found(63) to improve communication between colleagues and other medical professionals, improve patient care, lead to increased professional satisfaction, and improve data recording. However, downsides to national audit are increased workload for clinicians, feelings of diminished clinical ownership (such as feeling unable to provide personalised care), and fears of litigation or the audit being used as an exercise to apportion blame(63).

Data collection for the national clinical audits has historically been a snapshot of care, collecting data for a specified period only, however many of the NCAPOP audits are now implementing continuous data collection, producing large databases of prospectively-collected care data(64). These data differ from EHRs in that they are not routinely collected but require additional collection and entry. This has the advantage of providing greater and more specific detail than would be available from routinely collected data, however it comes at the expense of an increased burden on clinicians.

1.3.1 National Asthma and COPD Audit Programme (NACAP)

The National Asthma and COPD Audit Programme (NACAP) (previously called the National COPD Audit Programme, prior to the addition of asthma to the audit on 1st March 2018(65)) is one of the NCAPOP audits and comprises a number of workstreams that aim to follow the journey of patients

through their diagnosis and treatment of COPD, highlighting instances where best practice care is not being received(65). The four key workstreams are(65):

- **Primary care audit** – an audit of the care received by COPD patients in Welsh general practice (66). Primary care audits have only been completed in Wales so far due to concerns over the confidentiality of patient primary care data in England(67).
- **Secondary care organisational audit** – an audit of the services and staff available in participating hospitals that admit COPD patients (68). The audits have all been in England and Wales. Scotland participated in the 2018/19 audit but has since opted out of participation in further audits.
- **Secondary care clinical audit** – an audit of the care received by COPD patients during a hospitalisation for AECOPD (69). The secondary care clinical participation is the same as for the organisational audit, having included at least England and Wales in all audits completed so far.
- **Pulmonary rehabilitation audit** – an audit of pulmonary rehabilitation services in England and Wales (70).

1.4 Variation in patient care in the UK

Even with the national clinical audit highlighting good care and areas for improvement, there are still significant disparities between regions of England for quality of care and outcomes in people with COPD. The 2nd Atlas of variation(71) in risk factors for healthcare and respiratory disease found that between English CCGs there was:

- 4-fold variation in mortality
- 18-fold variation in referral to pulmonary rehabilitation
- 5.6-fold variation in the rate of emergency admission to hospital for COPD
- 3.7-fold variation in 30-day readmission
- 8-fold variation in the proportion of patients receiving NIV during hospital admission

The recommendations from the Atlas of variation are that greater effort needs to be made to follow the evidence-based best practice care for COPD and better communication is required between primary and secondary care(71).

1.5 Thesis rationale

In this thesis I seek to investigate how quality of COPD care varies by patient characteristics and location within the UK for both primary and secondary care, and how the interaction between primary and secondary care affects patient outcomes. Where areas of care appear to be lacking, I then also make recommendations on how delivery of care could be improved to reduce the variation in care.

Before starting analyses, I complete a systematic search of the literature to find validated definitions of AECOPD in EHR databases. These valid definitions of AECOPD are then used in analysis of the NACAP primary care audit to examine predictors of referral to pulmonary rehabilitation from primary care. This provides insight into which patients may require targeting for receipt of this important intervention and offers potential insight into why rates of referral differ 18-fold across England.

Thirdly, I replicate the NACAP primary care audit in the Clinical Practice Research Datalink (CPRD) research database of primary care EHRs to determine its representativeness and compare care quality between the UK countries. Fourthly, I move on to secondary care and examine whether the Best Practice Tariff pay-for-performance scheme is producing the desired improvements to patient care and outcomes.

Fifthly, I examine the suitability of the revised National Early Warning Score (NEWS2) as a method to categorise AECOPD admissions by severity. If NEWS2 can accurately predict AECOPD severity it will serve as a useful covariate in future analyses of AECOPD admissions to provide adjustment for AECOPD severity. Finally, in my sixth objective I link primary care data from CPRD with NACAP secondary care clinical audit data to explore how management of COPD in primary care affects management in secondary care and vice versa, and how management of care in primary and secondary care together affects patient outcomes. This linkage between primary and secondary care data provides the best detail to date on the full patient pathway of people with COPD and allows me to thoroughly investigate causes of variation in AECOPD admissions.

A visualisation of the flow between the objectives of this thesis is shown in **Figure 1** and the thesis aim and objectives are summarised in section **1.6** below.

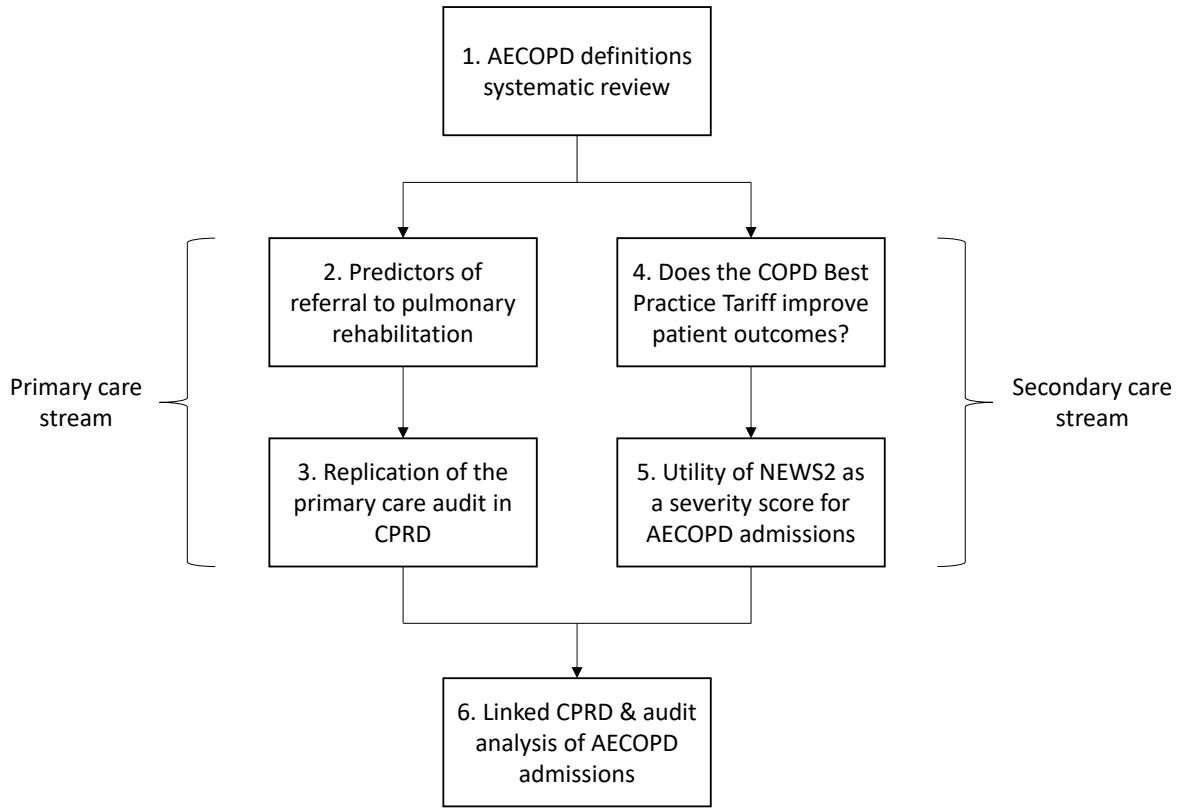

Figure 1. *Flowchart of thesis objectives.*

1.6 Aim and Objectives

1.6.1 Aim

To link secondary care AECOPD data from the clinical audit component of the National Asthma and COPD Audit Programme (NACAP) with primary care data from the Clinical Practice Research Datalink (CPRD) to explore how variations in patient pathways through healthcare across England affect hospital admissions for acute exacerbations of COPD (AECOPD).

1.6.2 Objectives

To address the specified aim, the following objectives were completed:

1. Complete a systematic review of the literature on validation of AECOPD definitions in electronic health records. This will ensure an accurate definition of AECOPD can be used in subsequent work.

2. Determine predictors of referral to pulmonary rehabilitation from general practice. This will identify possible reasons for variation in referral for this important element of COPD care and highlight patients that may require targeting to increase referrals.

3. Replicate the 2017 NACAP Welsh primary care audit in Welsh and then all UK CPRD practices and compare outcomes to determine if the Welsh CPRD population is representative of Wales, and if it is, if care received by Welsh COPD patients is representative of the care received in the rest of the UK. As there is no UK-wide primary care audit this will demonstrate the suitability of Wales as a sample population for national audit.

4. Determine if the COPD Best Practice Tariff (BPT) improves patient outcomes. This will help determine if the BPT pay-for-performance scheme is having the desired improvement to patient care.

5. Assess the utility of NEWS2 as a severity score for AECOPD admissions. If NEWS2 can predict AECOPD outcomes it will be a useful tool to risk categorise AECOPD admissions.

6. Link secondary care data from the clinical audit component of the National Asthma and COPD Audit Programme with CPRD primary care data, then explore how management of patients with COPD and patient pathways vary across England, and how this affects and is impacted by AECOPD hospital admissions.

Chapter 2. Validation of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) recording in electronic health records: a systematic review

2.1 Introduction

In this thesis I study the treatment that patients receive prior to and after experiencing an AECOPD using data from EHRs. Therefore, it is essential to use an accurate definition of AECOPD to reduce any misclassification bias that could lead to a reduction in any measure of effect. Rothnie et al. have carried out studies to validate the recording of AECOPD in both primary(72) and secondary(73) care in England, and Rimland et al.(74) have published a protocol for a systematic review of the validation of COPD in healthcare databases. However, the systematic review from Rimland et al.(74) has not yet been published and there is currently no available review of the validation of AECOPD definitions in EHRs.

Diseases and other clinical events in EHRs are commonly defined using 'codelists' of relevant clinical codes from a particular clinical terminology, such as ICD-10. Guidelines(75,76) have been produced to give researchers advice on how best to generate these codelists, with the aim of producing reusable and shareable definitions for all variables in a study. Repositories(77–79) have also been created to enable researchers to further share their codelists but these appear underutilised.

Therefore, in this chapter I complete a systematic literature review of studies that validate definitions of AECOPD in EHRs. Not only is this beneficial for subsequent chapters of this thesis, enabling usage of an accurate definition of AECOPD in EHRs, but it provides a useful resource for other researchers studying AECOPD in EHRs. It may also help to provide consistency between future studies if they utilise the recommended AECOPD definitions. This consistency will aid comparability between studies and disease monitoring (e.g., prevalence and incidence). An accurate disease definition is particularly important in disease monitoring as different disease definitions may give dramatically different pictures of healthcare utilisation, making it harder to allocate funds to disease areas where increased funding is required most. A recommended AECOPD code definition may also be useful as a list of preferred terms for clinicians to use when recording AECOPD in EHRs.

2.1.1 Objective

The primary objective of this systematic review is to provide an overview of the methods and findings of studies that validate AECOPD definitions used in EHRs and administrative claims databases. The target population are people that experience an AECOPD. The intervention measured

(index test) is the AECOPD detection algorithm with the comparison group being the reference standard used to confirm AECOPD diagnosis. This means that studies included in this review may use different reference standards – this is to ensure capture of all validation studies. The outcome is the validity of the AECOPD detection algorithm. These can be studies in any country, using any clinical coding scheme, in any EHR database. Required details in included studies are:

- The database and type of EHRs used
- The algorithm used to detect the AECOPD
- The reference standard used to validate the AECOPD
- The estimated validity of the AECOPD detection algorithm

2.2 Methods

MEDLINE and EMBASE (via the Ovid interface) were searched using keywords and MeSH terms(80,81) related to 'exacerbation of COPD', 'electronic health records' or 'administrative claims database', and 'validation', including any relevant synonyms. The full search strategy can be found in **Appendix A**. The search strategy used to detect the validation terms was guided by a strategy developed by Benchimol et al.(82) and strategies used in similar reviews(74,83–86) of validation studies in EHR databases. The reference lists of retrieved articles were also searched.

2.2.1 Eligibility criteria

All studies written in English published between 1st January 1990 and 30th September 2019 that validated an AECOPD definition in EHRs were considered. The specific inclusion criteria of the study were:

- Data originates from an EHR or administrative claims database where data are routinely collected.
- The AECOPD detection algorithm is compared against a reference or gold standard definition (such as a questionnaire completed by a physician to confirm the diagnosis).
- There must be a measure of validity (positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, c-statistic, etc.) or sufficient information to be able to calculate one.
- Studies were excluded if they only looked at COPD diagnosis rather than specifically AECOPD.

2.2.2 Data management and synthesis

Articles identified by the search strategy were stored in the reference management package EndNote (Clarivate Analytics, Philadelphia, Pennsylvania, USA) and duplicate articles removed. Unique article titles and abstracts were then loaded in to Rayyan(87) and screened by two independent reviewers. If either reviewer thought the inclusion criteria were met, then the articles were included in full-text review. Articles selected for full-text review were then independently screened by both reviewers for inclusion in the review with disagreement between reviewers resolved by consensus or arbitration by a third reviewer. Reasons for study exclusion were recorded. The full text articles were read, and both reviewers independently extracted study details and assessed risk of bias. These data were stored in a pre-formatted Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) form. The data extracted from included studies were:

- Study details (title, first author, year of publication, DOI)
- Study aim/research question
- EHR database used
- Population (location, time period)
- Type of algorithm(s) used to detect AECOPD (e.g. clinical coding scheme)
- Algorithm(s) used to detect AECOPD (e.g. the list of clinical codes used)
- Reference/gold standard the algorithm(s) was compared against
- Measure(s) of validity calculated (e.g. PPV)
- Result(s) of validity measure(s)
- Prevalence of AECOPD
- Information to calculate validity (where available: true positives, false positives, true negatives, false negatives)

The primary outcome measure sought was the validity of the AECOPD detection algorithm.

The quality and risk of bias in individual studies was assessed using QUADAS-2(88), a quality assessment tool for diagnostic accuracy studies. QUADAS-2 was tailored to this specific review using a recommended reporting checklist developed by Benchimol et al.(82) for use in validation studies of health administrative data. The tailored QUADAS-2 risk of bias assessment can be found in **Appendix B**. Where multiple validations were reported in a study, quality of reporting and risk of bias was assessed for each validation. Results from the review were combined in a narrative synthesis with information presented in the text and in tables to summarise study details, the algorithms used to validate AECOPD in EHRs, the reference standard used to validate the algorithm, the validity of the algorithms, and the risk of bias in studies.

Where studies have validated algorithms in similar databases that use the same clinical terminology, the methods and results of the validations were compared to assess the best algorithm to use when using that clinical terminology. Where studies were sufficiently homogeneous and have been carried out in similar populations using similar reference standards, bivariate random-effects regression was used to calculate summary measures of sensitivity and specificity(89) or PPV and NPV(90) (where no sensitivity and specificity values are provided). Where this meta-analysis was possible, publication bias was determined visually using a funnel plot of the of the standard error against the measure of effect for each study and statistically using Egger's test. Asymmetries between the left and right sides of a funnel plot, such as most studies falling on just the left or right side of the plot, may indicate publication bias. In Egger's test, which is a type of regression analysis, a statistically significant difference from 0 for the intercept term (known as the bias) indicates publication bias(91).

2.2.3 Protocol registration

The protocol for this review was registered on PROSPERO: International prospective register of systematic reviews (registration number: CRD42019130863)(92). The protocol is published in BMJ Open(93).

2.3 Results

Out of 2406 articles found by the search strategy, 7 met the inclusion criteria and were included in the review (**Figure 2**). 4 of the studies were in US hospitals, 2 in English national patient databases, and one in the Danish National Patient Registry (**Table 3**). The clinical terminology used by the studies was either ICD-9, ICD-10, or Read codes (**Table 3**). The patient definition varied between studies with some using a broader definition, including patients ≥25 years(94), and others were more selective, including patients ≥55 years old(95). It should be noted that the Pu et al.(96) study is a conference abstract rather than a journal article and has therefore not been through peer review. However, as sufficient detail was included to allow for assessment, it was included in this review.

The risk of bias for each study is shown in **Table 4**. Only the assessment of secondary care (ICD-10) algorithms in the English Hospital Episode Statistics (HES) database from the second Rothnie et al(73) study had a low risk of bias for all domains assessed. This means that validity in the other studies may be overestimated. The Ginde(95), Stein 2010(97), first Rothnie(72), and Pu(96) studies did not provide sufficient detail to be able to assess whether the reference standard used would be likely to introduce bias to the study. The reference standard used in the Thomsen(98) and Stein 2012(94) studies was at risk of bias because the reference standard was not interpreted without

knowledge of the index test result, which could have influenced classification. The Thomsen(98) study was also at high risk of bias for flow and timing as busy hospitals were unable to return details from the patient record. These busier hospitals may have had more severe cases. The Stein 2012(94) study was at risk of bias for patient selection as patients that were transferred were excluded. Again, these excluded patients could have been more severe cases. Finally, the second Rothnie study that validated primary care Read code definitions against HES ICD-10 code definitions had high risk of applicability concerns because it was not compared against the gold standard of physician confirmation.

The four studies in US hospitals(94–97) all performed validations on ICD-9 codes (**Table 5**). All studies validated similar ICD-9 codes, and the single AECOPD code of 491.21 provided the best PPV in all studies, ranging between 74% and 100%. Stein et al, 2012(94) also assessed sensitivity of the 491.21 ICD-9 code and compared it with other algorithms. However, they found that it was not as sensitive as using codes for a primary diagnosis of COPD or a secondary diagnosis of COPD with a primary diagnosis of respiratory failure (12.3% vs. 24.3%).

The studies in Danish(98) and English(73) hospitals both used ICD-10 codes (**Table 6**). Both studies validate variations of J44 COPD codes, however the Thomsen(98) study validates using PPV and the Rothnie(73) study validates using sensitivity. Thomsen et al.(98) finds that using a J44 parent code as primary diagnosis gives the best PPV, although all three algorithms they test provide good PPVs. Rothnie et al.(73) find that a COPD code (J44.9) as the primary diagnosis or an AECOPD (J44.0 or J44.1) or LRTI (J22) as either primary or secondary diagnosis codes provides the best sensitivity. This algorithm with high sensitivity from Rothnie et al.(73) is similar to the Thomsen et al.(98) algorithm with high PPV and is therefore likely to represent a good compromise between high sensitivity and high PPV.

The two Rothnie et al. studies validated the use of Read codes in English primary care (**Table 7**). The second study uses the same definitions as the first but instead validates the algorithms against a different reference standard. Rothnie et al.(72) validated their algorithms using PPV and sensitivity and found that the best compromise between the two measures was found when combining their algorithms with a PPV >75%. This combined algorithm included, prescription of antibiotics and oral corticosteroids for 5-14 days, a symptom (dyspnoea, cough, or sputum) with a prescription of antibiotics or oral corticosteroid, a lower respiratory tract infection, or an AECOPD code, and gave a PPV of 85.5% and sensitivity of 62.9%.

Due to the limited number of studies and absence of full data on true and false positive and negatives, quantitative synthesis of results was not possible.

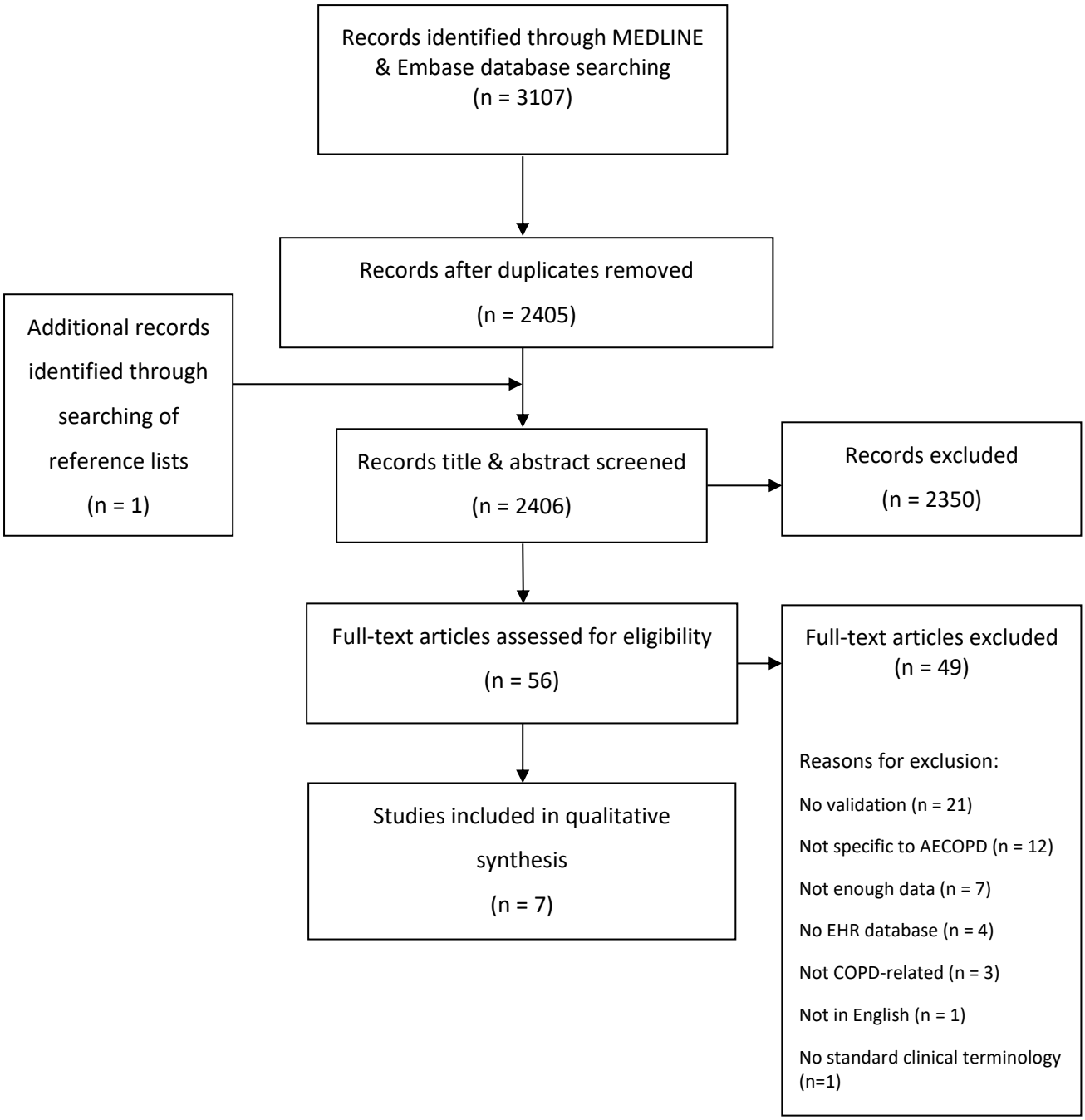

Figure 2. *PRISMA flowchart for validation of acute exacerbation of COPD definitions in electronic health records systematic review*

Table 3. *Summary of studies included in validation of acute exacerbation of COPD definitions in electronic health records systematic review*

Author, year, country, period	Population characteristics	Data source	Code type
Ginde et al., 2008 (95), USA, July 2005 – June 2006	Patients ≥55 years visiting emergency department	Unspecified EHR database from two US hospitals	ICD-9-CM
Stein et al., 2010 (97), USA, 2000 – 2006	Patients ≥40 years with ICD-9-CM code for AECOPD	National Inpatient Sample (NIS)	ICD-9-CM
Thomsen et al., 2011 (98), Denmark, January 2008 – December 2008	Patients ≥30 years with hospital discharge diagnosis for COPD	Danish National Patient Registry (DNPR) discharge codes from 34 Danish hospitals	ICD-10
	Patients with hospital discharge diagnosis for acute respiratory failure or pneumonia without code for COPD	DNPR discharge codes from 34 Danish hospitals	ICD-10
Stein et al., 2012 (94), USA, November 2005 – October 2006	Patients ≥25 years with hospital admission	Discharge codes from 2 hospitals in Chicago, USA	ICD-9-CM
Rothnie et al., 2016 (72), UK, January 2004 – August 2013	COPD patients ≥35 years	CPRD	Read and Product codes
	COPD patients ≥35 years with additional material provided by GP	CPRD	Read and Product codes
Rothnie et al., 2016 (73), UK, January 2004 – March 2014	COPD patients ≥35 years	HES	ICD-10
	COPD patients ≥35 years	CPRD	Read and Product Codes
Pu et al., 2017 (96), USA, 2012 – 2014	Patients discharged with ICD-9 code for AECOPD	Hospital database	ICD-9

Table 4. *QUADAS-2 risk of bias table for studies included in validation of acute exacerbation of COPD definitions in electronic health records systematic review*

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ginde et al., 2008 (95)	☺	☺	?	☺	☺	☺	☺
Stein et al., 2010 (97)	☺	☺	?	☺	☺	☺	☺
Thomsen et al., 2011 (98) **(PPV)**	☺	☺	☹	☹	☺	☺	☺
Thomsen et al., 2011 (98) **(NPV)**	☺	☺	☹	☹	☺	☺	☺
Stein et al., 2012 (94)	☹	☺	☹	☺	☺	☺	☺
Rothnie et al., 2016 (72)	☺	☺	?	☹	☺	☺	☺
Rothnie et al., 2016 (73) **(HES/ICD-10)**	☺	☺	☺	☺	☺	☺	☺
Rothnie et al., 2016 (73) **(CPRD/Read)**	☺	☺	☺	☺	☺	☺	☹
Pu et al., 2017 (96)	☺	☺	?	☺	☺	☺	?

☺ = Low risk of bias

☹ = High risk of bias

? = Unclear risk of bias

Table 5. *ICD-9 validation studies of acute exacerbation of COPD definitions*

Study	Algorithm (codes)	Gold standard reference	N	PPV	NPV	Sensitivity	Specificity
Ginde et al., 2008 (95)	491.2x	Consensus by two emergency physicians from abstracted chart data	181	100 (98-100)	-	-	-
	492.8	Consensus by two emergency physicians from abstracted chart data	4	75 (19-99)	-	-	-
	496	Consensus by two emergency physicians from abstracted chart data	15	60 (32-84)	-	-	-
	491.2x, 492.8, or 496	Consensus by two emergency physicians from abstracted chart data	200	97 (93-99)	-	-	-
Stein et al., 2010 (97)	491.21 (Obstructive chronic bronchitis with acute exacerbation) primary diagnosis	Primary diagnosis recorded in physician notes	Sample of 200	74	-	-	-
	491.x, 492.x, or 496 (Chronic airway obstruction, not elsewhere classified) primary diagnosis	Primary diagnosis recorded in physician notes		62	-	-	-

	491.0 (Simple chronic bronchitis), 491.1 (Mucopurulent chronic bronchitis), 491.21 (Obstructive chronic bronchitis with acute exacerbation), 491.22 (Obstructive chronic bronchitis with acute exacerbation), 491.8 (Other chronic bronchitis), 491.9 (Unspecified chronic bronchitis), 492.0 (Emphysematous bleb), 492.8 (Other emphysema), 493.22 (Chronic obstructive asthma with acute exacerbation), or 496 (Chronic airway obstruction, not elsewhere classified) primary diagnosis OR 518.81 (Acute respiratory failure), 518.82 (Other pulmonary insufficiency not elsewhere classified), or 518.84 (Acute and chronic respiratory failure) primary diagnosis AND 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, or 496 secondary diagnosis	Primary diagnosis recorded in physician notes		60	-	-	-
Stein et al., 2012 (94)	Primary diagnosis of COPD (490, 491.x, 492.x, 493.22, 496) OR primary diagnosis of respiratory failure (518.81, 518.82, 518.84, 799.1) and secondary diagnosis of COPD (age >=25)	Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation;	50	81.2	93.9	24.7	99.5

		and hospitalisation for one of these respiratory symptoms					
	Primary diagnosis of COPD (491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, 496) OR primary diagnosis of respiratory failure (518.81, 518.82, 518.84) and secondary diagnosis of COPD (age >=40)	Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms	46	85.4	93.9	24.3	99.7
	Primary diagnosis of COPD: 491.x, 492.x, 496 (age>=40)	Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms	29	85.6	93.2	14.5	99.8
	Primary diagnosis of AECOPD: 491.21 (age>=40)	Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms	20	97.2	93	12.3	100
Pu et al., 2017 (96)	491.21 (AECOPD)	Chart review	620	91 (88-93)	31 (27-35)	57 (54-61)	76 (70-81)

Table 6. *ICD-10 validation studies of acute exacerbation of COPD definitions*

Study	Algorithm(s)	Gold standard reference	N	PPV	NPV	Sensitivity	Specificity
Thomsen et al., 2011 (98)	PPV: J44 (COPD) primary or secondary diagnosis	Physician review of patient medical records	1581	92 (91-93)	-	-	-
	PPV: J44 (COPD) as primary diagnosis	Physician review of patient medical records	1223	93 (92-95)	-	-	-
	PPV: J44 (COPD) as secondary diagnosis, acute respiratory failure or pneumonia as primary diagnosis	Physician review of patient medical records	358	87 (84-91)	-	-	-
	NPV: Pneumonia (J13-J18) or acute respiratory failure (J96) without J44	Physician review of patient medical records	1546	-	81 (79-83)	-	-
	NPV: Pneumonia (J13-J18) without J44	Physician review of patient medical records	1432	-	82 (80-84)	-	-
	NPV: Acute respiratory failure (J96) without J44	Physician review of patient medical records	114	-	59 (49-68)	-	-
Rothnie et al., 2016 (73) **(HES/ICD-10)**	Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell	Hospital discharge summary	40	-	-	87.5 (72.4-94.9)	-
	Specific AECOPD code (J44.0 or J44.1) or COPD code (J44.9) in any position in any FCE during spell	Hospital discharge summary	40	-	-	85.0 (69.6-93.3)	-
	Specific AECOPD code (J44.0 or J44.1) in any position or LRTI code (J22) or	Hospital discharge summary	40	-	-	85.0 (69.6-93.3)	-

	COPD code (J44.9) in the first position in any FCE during spell						
	Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell	Hospital discharge summary	40	-	-	77.5 (61.3-88.2)	-
	Specific AECOPD code (J44.0 or J44.1) in any position in any FCE during spell	Hospital discharge summary	40	-	-	77.5 (61.3-88.2)	-
	Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell	Hospital discharge summary	40	-	-	65.0 (48.5-78.6)	-

Table 7. *Read code validation studies of acute exacerbation of COPD definitions*

Study	Algorithm(s)	Gold standard reference	N	PPV	NPV	Sensitivity	Specificity
Rothnie et al., 2016 (72)	Oral corticosteroid (OCS) prescription	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	1152	73.0 (69.5-76.5)	-	30.2 (25.8-34.6)	-
	Antibiotic prescription	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	5840	60.9 (59.0-62.9)	-	71.1 (66.8-75.4)	-
	Oral corticosteroid and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	823	79.3 (75.8-82.9)	-	24.5 (20.4-28.6)	-
	Exacerbation Symptom definition (increase in 2 or more of: dyspnoea, cough, sputum)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	142	64.8 (56.2-73.3)	-	2.6 (1.1-4.0)	-
	Exacerbation Symptom definition and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	88	89.8 (82.9-96.7)	-	2.2 (0.9-3.6)	-

	Exacerbation Symptom definition and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	57	93.0 (85.6-100.0)	-	1.8 (0.6-3.1)	-
	Exacerbation Symptom definition and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	48	97.9 (94.5-100.0)	-	1.7 (0.5-2.9)	-
	Lower respiratory tract infection (LTRI) code (excluding pneumonia)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	1745	79.6 (76.9-82.3)	-	23.0 (19.2-26.8)	-
	LTRI code and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	1558	81.4 (78.7-84.1)	-	19.9 (16.3-23.5)	-
	LTRI code and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	393	88.3 (84.4-92.2)	-	12.0 (9.3-14.7)	-
	LTRI code and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	371	88.1 (84.1-92.1)	-	11.4 (8.8-14.0)	-

	AECOPD code	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	885	96.0 (94.5-97.6)	-	25.1 (20.9-29.2)	-
	AECOPD code and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	638	96.9 (95.4-98.3)	-	18.2 (14.6-21.8)	-
	AECOPD code and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	423	96.5 (94.5-98.4)	-	17.5 (13.8-21.2)	-
	AECOPD code and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians	377	96.8 (95.0-98.6)	-	16.0 (12.6-19.5)	-
Rothnie et al., 2016 (72) (subset with additional patient data)	Oral corticosteroid (OCS) prescription	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	367	72.2 (66.5-77.9)	-	22.7 (16.1-29.2)	-
	Antibiotic prescription	Review of GP questionnaires and other relevant material from patient notes by two	2245	61.3 (58.3-64.3)	-	63.4 (55.4-71.4)	-

		respiratory physicians (with additional information provided by GPs)					
	Oral corticosteroid and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	251	79.7 (73.5-85.8)	-	18.6 (12.4-24.7)	-
	Exacerbation Symptom definition (increase in 2 or more of: dyspnoea, cough, sputum)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	83	63.9 (52.7-75.0)	-	2.1 (0.1-4.0)	-
	Exacerbation Symptom definition and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	50	94.0 (88.0-100.0)	-	2.1 (0.1-4.0)	-
	Exacerbation Symptom definition and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with	36	94.4 (86.8-100.0)	-	1.6 (0.1-3.2)	-

		additional information provided by GPs)					
	Exacerbation Symptom definition and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	31	100.0 (88.8-100.0)	-	1.6 (0.1-3.2)	-
	Lower respiratory tract infection (LTRI) code (excluding pneumonia)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	693	82.8 (78.8-86.9)	-	24.7 (18.8-30.7)	-
	LTRI code and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	621	84.5 (80.6-88.5)	-	20.6 (15.2-26.0)	-
	LTRI code and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with	142	93.0 (88.3-97.6)	-	12.4 (7.8-16.9)	-

		additional information provided by GPs)					
	LTRI code and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	129	92.2 (87.1-97.4)	-	10.8 (6.7-15.0)	-
	AECOPD code	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	350	98.3 (96.9-99.6)	-	26.8 (19.7-33.9)	-
	AECOPD code and oral corticosteroid prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	236	99.2 (98.1-100.0)	-	18.6 (12.4-24.7)	-
	AECOPD code and antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with	155	98.1 (96.0-100.0)	-	17.0 (10.8-23.2)	-

		additional information provided by GPs)					
	AECOPD code and oral corticosteroid & antibiotic prescription (on the same day)	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	140	98.6 (96.8-100.0)	-	15.5 (9.7-21.2)	-
Rothnie et al., 2016 (72) (subset with additional patient data - combined algorithms)	Algorithms 5, 6, 8, or 12: Symptom definition with prescription of antibiotic or OCS; or LRTI; or AECOPD code	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)		88.1 (85.3-90.8)	-	51.6 (44.1-59.0)	-
	Algorithms 3, 5, 6, 8, or 12: Prescription of antibiotics and OCS for 5-14 days; or Symptom definition with prescription of antibiotic or OCS; or LRTI code; or AECOPD code	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)		85.5 (82.7-88.3)	-	62.9 (55.4-70.4)	-
	All algorithms combined	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with		63.8 (61.0-66.6)	-	88.1 (82.9-93.4)	-

		additional information provided by GPs)					
Rothnie et al., 2016 (73) **(CPRD/Read)**	AECOPD hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell		50.2 (48.5-51.8)	-	4.1 (3.9-4.3)	-
	AECOPD identified using validated algorithm and hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell		43.3 (42.3-44.2)	-	5.4 (5.1-5.7)	-
	AECOPD hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell		49.0 (47.3-50.6)	-	4.6 (4.5-4.9)	-
	AECOPD identified using validated algorithm and hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell		38.5 (37.6-39.4)	-	5.5 (5.2-5.9)	-

	AECOPD hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell		45.9 (44.2-47.6)	-	4.7 (4.4-4.9)	-
	AECOPD identified using validated algorithm and hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell		37.2 (36.3-38.1)	-	5.7 (5.4-6.0)	-

2.4 Discussion

Unfortunately, due to the low number of studies validating AECOPD detection algorithms in commonly used clinical terminologies, a formal quantitative synthesis of validation results has not been possible. However, it is possible to provide a recommendation on the best AECOPD detection algorithms based on currently available validation studies (**Table 8**). The best algorithm to use for EHR databases using ICD-9 is the single AECOPD diagnosis code recommended by Stein et al.(94). The best algorithm to use for ICD-10 databases is either an AECOPD or LRTI diagnosis code in any position or a COPD diagnosis in the primary diagnosis position, as recommended by Rothnie et al.(73). The best algorithm to use for Read codes is either an LRTI or AECOPD diagnosis, a prescription for COPD-specific antibiotics and oral corticosteroids for 5-14 days, or two or more respiratory symptoms (dyspnoea, cough, sputum) combined with a prescription for antibiotics and oral corticosteroids on the same day; as recommended by Rothnie et al.(72).

Table 8. *Recommended algorithm for detecting acute exacerbation of COPD in electronic health records using ICD-9, ICD-10, or Read codes*

Clinical terminology	Algorithm	PPV (%)	Sensitivity (%)
ICD-9	AECOPD diagnosis code (491.21)	97	12
ICD-10	Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in primary diagnosis position	-	88
Read V2	Any of: • a medical diagnosis of LRTI or AECOPD • a prescription of COPD-specific antibiotic combined with OCS for 5–14 days • a record of two or more respiratory symptoms of AECOPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day.	86	63

The aim of this piece of work was to find validated definitions of AECOPD, but details on all COPD definitions available in code repositories and published literature (including those that have not been validated) can be found in the BREATHE phenotype library(99–101). The unvalidated definitions found by BREATHE include some very broad codelists and, in some cases, codes that appear inappropriate, such as asthma codes. However, generally the codelists found by BREATHE have substantial overlap with the codeslists found in this systematic review.

2.4.1 Limitations

One potential issue with validation studies is publication bias – a detection algorithm found to have an undesirable validity may be less likely to be published. Validity may also be calculated in a population with a higher prevalence of the condition than would be found in the general population to produce a greater PPV. Publication bias can be difficult to assess but studies that provide information on prevalence can be checked to ensure it matches that of the general population. Unfortunately, only one study provided information on AECOPD prevalence, so the PPVs derived from the included studies may not be comparable. There may also be an issue with reuse of algorithms in different EHR databases. While many databases use the same clinical terminology and could therefore share detection algorithms, it is possible that a detection algorithm for one database may not have the same level of validity in another database. This will be particularly true for databases with data quality improvement programmes where coding will be much more accurate compared with those without such programmes. Another limitation is that some AECOPDs may be managed at home by patients using a rescue pack of antibiotics and oral corticosteroids; this may be those with less severe symptoms. These exacerbations will not be recorded in EHR databases as the patient will not visit a doctor in either primary or secondary care.

2.4.2 Conclusion

While it is possible to recommend the algorithms in **Table 8** based on current available data, it is conceivable that better AECOPD detection algorithms exist and further validation in other databases using the same clinical terminology could be helpful.

Chapter 3. Methods

This chapter describes the sources of data used in subsequent chapters, the processes required to work with these data sources, and how the variables studied were defined.

3.1 Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD) is a UK government-owned database of primary care EHRs available for research(102). It is a not-for-profit service, funded by the Medicine and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR)(102). CPRD was created in June 1987, initially called the Value Added Medical Products (VAMP) Research Databank(103,104). It then became the General Practice Research Database (GPRD) when it was donated to the Department of Health in 1994(103,104). Finally it gained its current title of the Clinical Practice Research Datalink (CPRD) in April 2012 when it became a joint venture between the MHRA and the NIHR(105–107).

Every month CPRD receives routinely-collected EHR data from GP practices all over England, Wales, Scotland, and Northern Ireland that have agreed to contribute to the database(108). Data are pseudonymised (a random ID is generated for each patient and potentially identifiable information is stripped from the data – e.g. birth year is provided rather than date of birth) before being transferred to CPRD to ensure patient confidentiality.

3.1.1 CPRD GP Online Data (GOLD)

All practices that contribute to CPRD's original database, CPRD GP On Line Data (GOLD), use the Vision software package – a software package developed by In Practice Systems Ltd. (INPS) for GP surgeries to manage patient EHRs(109,110). The clinical terminology used to record information in the Vision software, and therefore within CPRD GOLD, is Read version 2(108). The Read clinical terminology, named after its creator Dr. James Read, contains over 250,000 codes (many of which are synonyms) which represent(59):

- Diseases
- History and symptoms
- Examination findings and signs
- Diagnostic procedures
- Preventative, operative, therapeutic, and administrative procedures

- Drugs and appliances
- Occupations and social information

The August 2018 cut of CPRD GOLD contains data from 304 current general practice clinics in the UK, covering 2.6 million active (currently contributing data) patients (3% of UK population)(111). CPRD GOLD additionally includes data for over 15 million historic patients that no longer contribute new data to the database, either due to death or transfer to another practice that does not contribute to CPRD. Patients in CPRD GOLD are representative of the UK population with regard to age, sex, and ethnicity(102,108). Information included within the data CPRD provide are: demographics (birth year, sex, weight, etc.), symptoms and signs, tests, diagnoses, immunisations, prescriptions and interventions, lifestyle information (e.g. smoking and alcohol status), and referrals to secondary care(102).

3.1.1.1 Variable definitions

COPD

In analyses using CPRD GOLD (**Chapter 5**), COPD was defined using the same validated(112) Read V2 codes that were used to define COPD in the NACAP primary care audit(113). In the validation study(112) these codes were found to have a positive predictive value (PPV) of 86.5%(112). The full COPD codelist is provided in **Appendix C**.

Other CPRD GOLD variable definitions can be found in the Methods section of the relevant chapter.

3.1.2 CPRD Aurum

The newer and larger database provided by CPRD is CPRD Aurum(114), named after the Latin word for gold. CPRD Aurum data are similar to CPRD GOLD data, however the data are provided by GP practices that use the Egton Medical Information System (EMIS) Web EHR software package instead of Vision(115). As of May 2018, CPRD Aurum contains data from 459 English practices with data for 12,813,335 patients, including 4,490,473 currently registered patients(115). CPRD Aurum does not include any GP practices from the other UK countries in the May 2018 release(115). The clinical terminology used by EMIS Web is a mixture of SNOMED CT codes, Read Version 2 codes mapped to SNOMED CT, and EMIS-specific codes that have been mapped to SNOMED CT where possible(115).

3.1.2.1 Variable definitions

CPRD Aurum data are only used in **Chapter 8**. Variable definitions specific to that chapter can be found in **8.3.3**.

3.1.3 CPRD Linked datasets

In addition to primary care data, CPRD can provide other data that have been linked to CPRD GOLD or CPRD Aurum for the purpose of epidemiological research(102). These linked data include: Hospital Episode Statistics (HES) (which includes admission, outpatient, Accident and Emergency (A&E), and diagnostic imaging data from secondary care providers), death registration data from the Office for National Statistics (ONS), cancer data from Public Health England (PHE), Mental Health Dataset (MHDS) data, and deprivation data(116).

Currently linkage of CPRD data with other datasets is limited to English practices that have consented to participate in the linkage scheme(116). In the August 2018 cut (set 16) of CPRD GOLD, 8,890,821 patients are eligible for linkage (57% of all current and historic patients)(111).

3.1.3.1 Deprivation: Index of Multiple Deprivation (IMD)

While there is a choice of deprivation measures available from CPRD, the most commonly used measure of deprivation is the Index of Multiple Deprivation (IMD). IMD is a measure of relative deprivation between Lower-layer Super Output Areas (LSOAs) in England(117), which are small areas of the country with a mean population of 1500 and a minimum population of 1000(118). IMD is calculated using 7 "domains" to indicate deprivation within an area: income, employment, education, health, crime, barriers to housing & services, and living environment(117). Each LSOA is then ranked from most to least deprived, and data provided by CPRD show the quintile, decile, or vigintile of a patient's LSOA. It should be noted that IMD cannot be used to determine how deprived an area is (just its relative deprivation), how deprived a person in that area might be, how affluent an area is, to compare English LSOAs with areas in other UK countries, or to measure changes in deprivation over time.

3.1.3.2 Office for National Statistics (ONS) death registration data

The gold standard for recording of death in England is ONS death registration data. It is a legal requirement for all deaths in England and Wales to be registered therefore data are very complete and it is the source from which official national mortality statistics are derived(119).

Most information entered into the registry is normally supplied by an informant (usually a close relative of the deceased) and cause of death is obtained from a Medical Certificate of Cause of Death (MCCD) completed by a medical practitioner when the death is certified. Cause of death is recorded using WHO ICD-10 codes which allows for international comparisons. The cause of death is coded using automated software or highly trained coders and the accuracy of automated coding is checked regularly. Completeness checks are conducted on the registry to ensure all death registrations are received and further checks are carried out before finalisation of the annual mortality dataset(119).

Mortality data provided by CPRD includes date of death, date of death registration, and cause of death (ICD-10 code).

3.1.3.3 Hospital Episode Statistics (HES)

The Hospital Episode Statistics (HES) database contains data on all hospital admissions, A&E attendances, and outpatient appointments at English NHS hospitals (120). This includes data on patients that are resident outside of England and also patients that are treated privately but in an NHS hospital(120).

HES Admitted Patient Care (APC)

HES APC captures data on inpatient and day case admissions. Data provided include admission date, discharge date, primary diagnosis (coded using ICD-10), secondary diagnoses, specialists seen, and procedures performed (coded using OPCS-4)(116).

HES Accident & Emergency (A&E) data

HES A&E comprises records of patient care in the Accident & Emergency department of English hospitals. Data provided include reason for attendance, outcome of attendance, waiting time, source of referral, A&E diagnosis, and A&E treatment (prescriptions not included)(116).

3.1.4 Accessing CPRD data

In order to gain access to CPRD data, first an application and protocol must be completed and sent to the Independent Scientific Advisory Committee (ISAC) for Medicines & Healthcare products Regulatory Agency (MHRA) Database Research(121,122). This form makes a formal request to use CPRD data and describes in detail the study you wish to complete.

3.1.4.1 Codelists

An important stage in the study design process is the completion of 'codelists' to define the exposures, outcomes, and covariates to be used in the study. These codelists can be ones generated previously by other researchers and shared in a clinical code repository such as ClinicalCodes.org(77), CALIBER(78), or CPRD @ Cambridge(79). Variables in this thesis have been defined using previously available lists from the 3 code repositories mentioned previously, or where no codelists have been available, new codelists were generated. Where no previous codelists have been available, the search process involved searching the Read (for CPRD GOLD) or SNOMED CT (for CPRD Aurum) clinical terminology dictionary for terms of interest, similar to the process used to find literature in a systematic review. The specific process used to generate codelists in this thesis is that described by Watson et al.(76). This Watson et al.(76) method involves searching for all relevant

terms related to the disease of interest, then performing an automated exclusion screen of the found terms to remove definite erroneous terms, and then finally a manual check of each found term for its suitability for inclusion. The codelist will then be checked by a clinician or other individual with suitable expertise in the area to confirm the included terms are appropriate.

For example, the COPD codelist was created by searching the CPRD medical code dictionary for terms relating to COPD, emphysema, or airway obstruction. The precise search terms used were (* is a wildcard character that represents either nothing or any character or combination of characters):

- *copd*
- *chronic obstructive pulmonary disease*
- *emphysema*
- *airway obstruction*
- *airway obstrucn*
- *emphysematous*
- *chronic obstructive airways*
- *chronic obstructive*

All terms in the CPRD medical code dictionary were converted to lower case prior to the search to avoid issues with case. The list of returned Read/SNOMED CT codes was then screened to remove any obviously incorrect codes. For codelists using SNOMED CT codes, the SNOMED Concept ID of each returned code was used to find any synonym codes in the CPRD medical code dictionary. This provisional codelist was then screened by a clinician (one of my supervisors) to remove any inappropriate codes, producing the final codelist for use in analysis.

Another method to generate codelists for CPRD Aurum is to match previously generated CPRD GOLD codelist Read V2 codes with SNOMED CT codes using the code mapping provided by CPRD. This matched-mapping method was used in my CPRD Aurum codelist production to ensure CPRD GOLD and CPRD Aurum codelist definitions were as similar as possible.

3.1.4.2 Data download

Once the protocol has been approved by CPRD's ISAC, researchers are able to login to CPRD's secure webserver to download their cohort. To do this a one-time password (OTP) generating USB key is required to be held by a user so that CPRD can verify that only the approved user is accessing CPRD data. This process is similar to using a card reader or mobile phone application to validate access to online banking. Once a user has access to the CPRD secure webserver, they will use a virtual desktop client to upload their cohort defining codelist (in the case of this thesis, the COPD codelist defined in

3.1.1.1) to download a list of pseudonymised IDs for patients that meet the researcher's cohort definition. That list of patient IDs is then used to download all events for those patients in the individual files of CPRD GOLD or CPRD Aurum. These files are often split into multiple parts due to very large volume of data they contain.

3.1.5 Dataset building and cleaning

CPRD GOLD and CPRD Aurum comprise multiple tab-delimited text files, often broken into multiple parts, that need to be linked using unique identifiers. The relationships between the files that comprise CPRD GOLD and CPRD Aurum are shown in **Figure 3** and **Figure 4**, respectively.

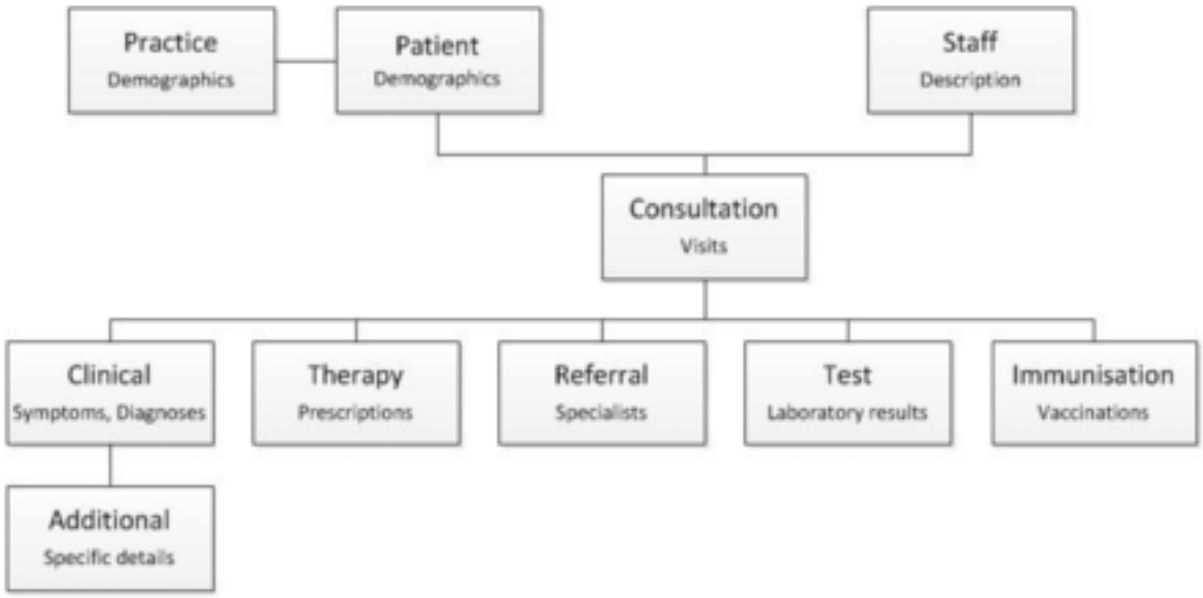

Figure 3. *CPRD GOLD data structure*

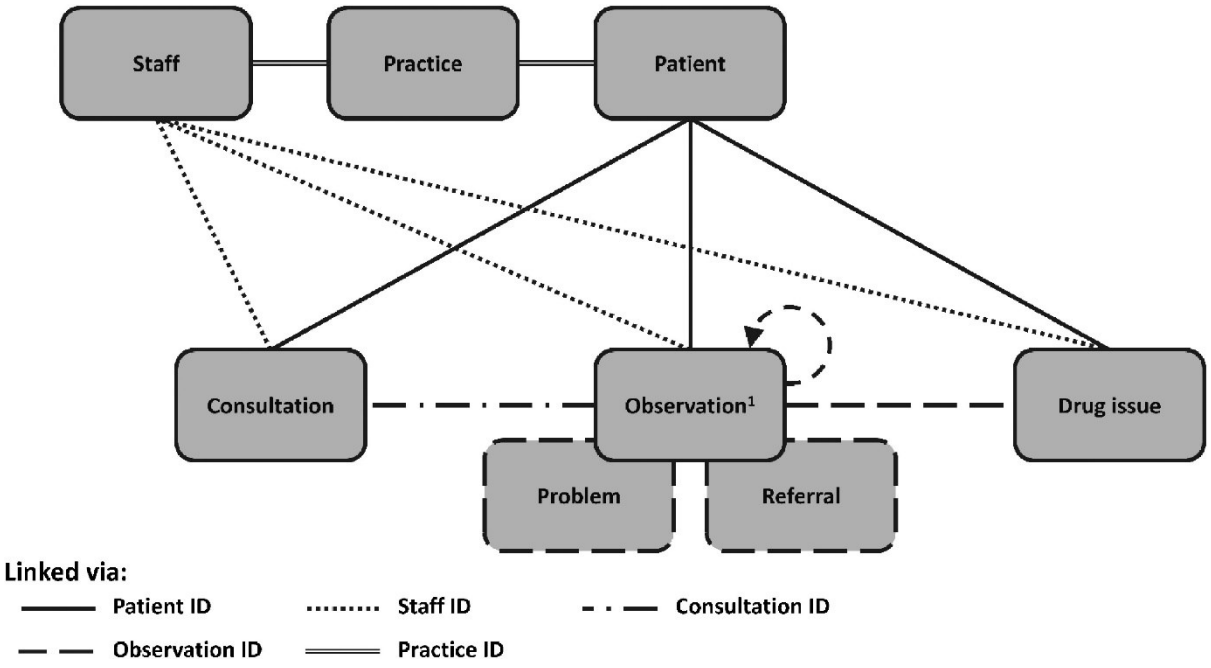

Figure 4. *CPRD Aurum data structure*

In order to generate the necessary dataset for analysis, text files downloaded from CPRD GOLD need to be first imported into Stata (StataCorp, College Station, TX, USA) (versions 15 and 16 were used in this thesis) and combined (where in multiple parts) and saved in Stata format. Data formatting can then be applied to the raw data as detailed in the CPRD GOLD or CPRD Aurum (as appropriate) Data Specification(123). Patients who do not meet CPRD's acceptable patient definition (only available in CPRD GOLD) (**Table 9**) will then be removed from the cohort to ensure data are up to research standard.

Table 9. *CPRD GOLD acceptable patient definition. Adapted from Herrett et al.(108)*

- No empty or invalid first registration date
- No empty or invalid current registration date
- Presence of a record for a year of birth
- A first registration date on or after their birth year
- A current registration date on or after their birth year
- Any transferred out reasons include a transferred out date
- Any transferred out dates include a transferred out reason
- Any transferred out dates are on or after their first registration date
- Any transferred out dates are on or after their current registration date
- A current registration date on or after their first registration date
- A gender of Female, Male, or Indeterminate
- An age of less than 116 at end of follow-up
- No recorded health care episodes in years prior to birth year
- At least one recorded health care episode with an event date
- Not temporarily registered

As only year of birth is available for adults in the CPRD databases, all patients analysed in this thesis using CPRD data were assumed to be born on the 1st of July for the purpose of determining age. Age was defined as that at the end of follow-up. Data were removed from analyses if any of the following impossible chronologies were detected:

- First registration year was before year of birth
- Current registration year was before year of birth
- Current registration date was before first registration date
- Year of transferring out of practice was before year of birth
- Transfer out date was before current registration date
- Year of death was before year of birth
- Date of death was before first registration date
- Date of death was before current registration date

3.1.6 Ethical approval

The use of CPRD data in **Chapter 5** and **Chapter 8** was approved by CPRD's ISAC (protocol: 18_194). The accepted protocol is included in **Appendix D**.

3.2 National Asthma and COPD Audit Programme (NACAP)

In this thesis I use data from both the NACAP primary care and COPD secondary care clinical audits. The two audit datasets are described below.

3.2.1 NACAP Primary Care Audit

The primary care audit, published in December 2017(34), is a cross-sectional study of all 82,696 people with COPD currently registered at 407 general practices in Wales (94% of all Welsh practices). It examined the quality of care received in the 2 years prior to the audit date of 31/03/2017, specifically observing (i) demographics, (ii) quality of diagnosis, (iii) assessment of severity, (iv) quality of treatment, and (v) equitable care.

The dataset was generated following a direct extraction from general practice patient record systems in June 2017 by NHS Wales Informatics Service (NWIS). No identifying information was collected from practices, with identifiable information being pseudonymised at source. Data were only extracted for patients with a diagnosis of COPD, defined in **3.2.1.2**. Data were not extracted for patients who had opted-out of usage of their pseudonymised data for audit or other analysis. Practice participation in the audit was on an opt-in basis and all practices in Wales were eligible. The primary care audit was conducted in Wales only because concerns over patient confidentiality prevented data collection from English practices (67,124).

3.2.1.1 Linked data

Welsh Index of Multiple Deprivation (WIMD)

Socioeconomic status (SES) in the primary care audit was defined using the 2014 Welsh Index of Multiple Deprivation (WIMD). WIMD is the Welsh equivalent of the English IMD, a measure that ranks the relative deprivation between small areas (or neighbourhoods). Values for WIMD are derived by assessing the income, employment, health, education, access to services, community safety, physical environment, and housing in an LSOA(125). WIMD data were provided by NWIS split in to 5 categories: 10% most deprived, 10-20% most deprived, 20-30% most deprived, 30-50% most deprived, and 50% least deprived. Category of WIMD was derived using the patient's home post code.

3.2.1.2 Variable definitions

COPD population

The COPD population was defined as those alive, registered, and aged at least 35 years on the audit date of 31st March 2017 with a validated(112) diagnosis of COPD in their primary care EHR prior to

the audit date. The Read V2 codes comprising the validated COPD diagnosis are provided in **Appendix C** (the 5-byte Read codes). COPD diagnosis codes were not counted where a subsequent resolved code was found before the end of the audit period.

Audited variables

Thirteen comorbidities (asthma, bronchiectasis, coronary heart disease, diabetes, heart failure, hypertension, lung cancer, stroke, osteoporosis, anxiety, depression, severe mental illness, and painful condition) were included in the primary care audit and defined as any Read code ever for the disease (see codelists from the audit resources(113) and **Appendix E**) in the patient's record without a subsequent disease resolved code. The exception to this was painful condition, which was defined as a record of ≥4 analgesic or anti-epileptic (in the absence of an epilepsy diagnosis) prescriptions in the 12 months preceding the audit date.

There are fourteen queries that make up the audit(113) (each query was defined using codelists that are published in the audit resources(113) and provided in **Appendix F**. Queries in bold represent key components of care):

1. **Proportion of patients with a post-bronchodilator FEV_1/FVC ratio < 0.7 (latest ever recorded before the audit date).**
2. **Proportion of patients with a chest X-ray 6 months prior to, or within 6 months of first COPD diagnosis.**
3. **Proportion of patients with an MRC score recorded in the year preceding the audit date.**
4. Proportion of patients with FEV_1 percent-predicted recorded in the year preceding the audit date.
5. **Proportion and status of patients asked about tobacco smoking in the year preceding the audit date.**
6. Proportion of patients with 0, 1, or 2 or more exacerbations in the year preceding the audit date (using both GP recorded codes and validated codes (lower respiratory tract infection, oral corticosteroid, and antibiotic codes)(72)).
7. Proportion of patients with an oxygen saturation level of 92% or less who have had arterial blood gas measurement or referral for home oxygen assessment.
8. Proportion of patients who have been prescribed an inhaler who have had their inhaler technique assessed in the year preceding the audit date.
9. **Proportion of patients who have had the influenza immunisation between 1st August 2016 and 31st March 2017.**

10. **Proportion of patients recorded as a current smoker in the 2 years preceding the audit date who have had a referral to a behavioural change intervention *and* had a stop smoking drug prescribed.**
11. **Proportion of (non-exempted) patients referred to pulmonary rehabilitation in the 3 years preceding the audit date with:**
    a. **an MRC score of 3-5.**
    b. any MRC score.
12. Proportion of patients on each type of inhaled therapy (LAMA, LABA, ICS, and their combinations (e.g. LABA & LAMA, triple therapy, etc.)) in the 6 months preceding the audit date.
13. Proportion of patients screened for, or diagnosed with, depression or anxiety in the 2 years preceding the audit date.
14. Proportion of patients on oxygen therapy in the 6 months preceding the audit date.

Where variables have been generated for events 'in the year preceding the audit date' this is defined as the 15-month period prior to 31st March 2017 to allow GPs sufficient time to complete their yearly review of the patient.

FEV_1/FVC values were cleaned by dividing values greater than 1 by 100 and any remaining values less than 0.2 or greater than 1 were excluded. MRC grade recorded in the past year and smoking status recorded in the past year were considered recorded if the patient had an MRC grade or smoking status in their patient record in the 15 months prior to the audit date. Both MRC grade and smoking status were the most recent available in the patient record. Smoking status was categorised as current smoker, ex-smoker, or never smoker (the Read codes used to define each category are shown in both the audit resources(113) and **Appendix F**).

The number of exacerbations in the past year was calculated using the validated method of detecting AECOPD in UK primary care electronic health records found in **Chapter 2**(72). This defines an exacerbation as either an exacerbation code, a prescription for oral corticosteroids and antibiotics on the same day, or a code for an LRTI. Any of these events occurring within 14 days of each other is considered part of the same exacerbation. This algorithm was used to find the number of exacerbations for each patient in the year prior to the audit date, and was categorised as 0, 1, 2, or >2 exacerbations. Four practices did not contribute data to this variable due to missing LRTI data.

Inhaled therapy regimen was defined based on prescriptions that the patient had received in the 6 months prior to the audit date. Triple therapy was defined as a prescription for a combined long-

acting β adrenoceptor agonist (LABA) & inhaled corticosteroid (ICS) and a long-acting muscarinic antagonist (LAMA) inhaler on the same day. LABA & LAMA therapy was defined as a prescription for a LABA and LAMA inhaler on the same day. Other inhaler prescriptions were defined as the most commonly received inhaler prescription (ICS, LABA, LABA & ICS, or LAMA).

Receipt of the seasonal influenza immunisation was considered true if the patient had a record of the immunisation in the preceding 01/08/2016 to 31/03/2017.

3.2.1.3 Ethical approval

The Healthcare Quality Improvement Partnership (HQIP) is data controller for the National Clinical Audit and Patient Outcomes Programme (NCAPOP) projects. An HQIP Extended Output Scope form was completed for the audit data set used in this analysis (**Appendix G**). Formal approval from the HQIP Data Access Request Group (DARG)(126) was not required as the dataset uses de-identified pseudonymised data for a purpose deemed to be in line with primary audit data collection.

3.2.2 NACAP Secondary Care Clinical Audit

3.2.2.1 2017 data extract

The secondary care clinical audit component of the National Asthma and COPD Audit Programme consists of a continuous (from 1st February 2017) clinical audit of the majority of patients admitted to hospitals in England and Wales with AECOPD(69). All acute hospitals in England and Wales are eligible to participate (Scotland joined the audit in 2018), and out of 197 eligible hospitals, 182 (92%) participated in data collection. Data are gathered from patient case notes and entered in to a secure audit tool, with particular focus on gathering detailed information on whether a patient has been reviewed by a specialist, prescribed oxygen, whether NIV is required, lung function (via spirometry), whether smoking cessation services have been offered, and a discharge bundle offered(69). Data are collated and pseudonymised by Crown Informatics before being made available to researchers for analysis(127). The first report on these prospective data was published in 2018 including analysis for patients discharged between commencement of the audit and 13/09/2017(69).

3.2.2.2 Linked data (outcomes report)

In 2019, a follow-up report was published. In this, longer-term outcomes – 30- and 90-day mortality and readmission – of the admissions included in the original audit report were assessed. All patients admitted to audit-participating hospitals for AECOPD on or after 01/02/2017 and discharged by 13/09/2017 had details of their admission linked with mortality data from the ONS(128) and admissions data from HES APC(120) or the Patient Episode Database for Wales (PEDW)(129). The data linkage was performed by NHS Digital (application reference: DARS-NIC-349273-T3L4K-v3.7)

and NHS Wales Informatics Service (NWIS) (application reference: 29892); national opt-outs were upheld. The pseudonymised linked data were sent via secure file transfer to Imperial College London for analysis.

Details on HES and ONS mortality data are as previously described in **3.1.3**.

Patient Episode Database for Wales (PEDW)

The patient Episode Database for Wales (PEDW) is the Welsh equivalent of England's Hospital Episode Statistics (HES).

3.2.2.3 2019 data extract

The 2019 extract of NACAP secondary care audit data includes admissions discharged between 01/10/2018 and 30/09/2019 and contains similar data to the 2017 extract. However, the revised National Early Warning Score (NEWS2)(130) has replaced the Dyspnoea, Eosinopenia (low eosinophil count), Consolidation, Acidaemia and atrial Fibrillation Score (DECAF)(131) as a measure of exacerbation severity. NEWS2 was recorded on arrival to hospital in A&E and is available for 89% of admissions in the 2019 extract.

3.2.2.4 Variable definitions

There a very few derived variables in the clinical audit as most variables are entered directly into the dataset.

Deprivation

Deprivation (English/Welsh/Scottish Index of Multiple Deprivation) is derived using the patient's home post code. This derivation is performed by Crown Audit so that identifying post code data does not need to leave Crown Audit's secure servers, and quintile of national IMD can be delivered to researchers requesting the dataset.

Wait-time variables

The following wait-times are calculated as follows by using the time of day (in minutes) values and dividing subtraction results by 60 to get a wait-time in hours:

$$Time\ from\ arrival\ to\ admission = Admission\ time - Arrival\ time$$

$$Time\ from\ admission\ to\ specialist\ review = Specialist\ review\ time - Admission\ time$$

$$Time\ from\ arrival\ to\ NIV = Time\ of\ NIV - Arrival\ time$$

3.2.2.5 Data cleaning

The clinical audit dataset is cleaned by removing:

- Overseas patients
- Patients with an invalid NHS number
- Admissions with an arrival time after their admission time
- Admissions with a discharge date before their admission date
- Admissions with a respiratory specialist review before their arrival time
- Admissions with a respiratory specialist review after discharge
- Admissions that received NIV before their arrival time
- Admissions that received NIV after discharge
- Admissions with a discharge date before their arrival date
- Admissions with respiratory specialist review wait times ≤-24 hours (24 hours prior to admission) (less than this is considered unrealistic)

3.2.2.6 Ethical approval

The audit operates under Section 251 approval from the Confidentiality Advisory Group (CAG) of the Health Research Authority (HRA). The reference number is CAG-8-06(b)/2013. This approval also grants the Royal College of Physicians permission to link audit data to externally held sources of data (using patient identifiable data items) for derivation of longer-term outcomes of the patient cohort. A record of the approval can be found at: https://www.hra.nhs.uk/about-the-hra/our-committees/section-251/cag-advice-and-approval-decisions (April 2013 onwards; non research). The data sharing agreement with NHS digital (DARS-NIC-349273-T3L4K-v3.7) also permits publication of aggregated patient data in peer-reviewed journals. Additional approval for this specific project was sought from HQIP following NACAP processes through an Extended Output Scope form. (**Appendix H** for analysis of the COPD BPT using the outcomes data and **Appendix I** for analysis of NEWS2 using the 2019 audit extract).

Chapter 4. Predictors of referral to pulmonary rehabilitation from primary care

4.1 Introduction

Having completed a systematic review of the literature on validated definitions of AECOPD in EHRs and having described the data sources used in this thesis; in this chapter I begin my investigation into the variation in COPD care in the UK by determining the predictors of referral to pulmonary rehabilitation from primary care for COPD patients as rates of referral remain low. Results from this chapter have been published in the International Journal of Chronic Obstructive Pulmonary Disease(132).

Pulmonary rehabilitation (PR) has been shown to improve dyspnoea, fatigue, quality of life, and exercise capacity in individuals with COPD(20,21). The quality of evidence for these benefits has been declared such that no further randomised controlled trials (RCTs) comparing PR and usual care are required to demonstrate its benefits(20,133).

While the strength of evidence for the benefits of PR is high and the referral criteria are well defined(18,134,135), the proportion of patients being referred to PR remains low. A systematic review(136) of rates of referral to PR in 10 different countries found referral rates of less than 35% in 93% of included studies. In the UK, roughly half of PR referrals are from primary care(70,137); however, between 2004 and 2014 only 9% of eligible COPD patients in England were referred to PR from primary care(138). In Wales, the picture is better with 35% of eligible patients referred in 2015(139) and 50% in 2017(66). However, that still leaves half of all eligible COPD patients without access to this important intervention.

4.2 Aim

No large studies of predictors of referral to PR have previously been completed therefore in this chapter I use NACAP primary care audit data to determine the patient characteristics associated with referral to PR. This serves to identify individuals that require better targeting in primary care and may offer some explanation on why rates of referral to PR are so low.

4.3 Methods

4.3.1 Database/population

The dataset used for this chapter is the NACAP primary care audit, described in **3.2.1** and the published audit report(66).

4.3.2 Variables

The outcome of the analysis – Referral to PR – was defined as any COPD patient with a Read code in their patient record indicating referral to PR in the 3 years prior to the audit date (01/04/2014 to 31/03/2017) (same definition as audit query 11a shown in **3.2.1.2**). Variable definitions and Read codes used to define pulmonary rehabilitation referral and all other events in the patient record can be found in **3.2.1.2** and in **Appendix F**, respectively. The thirteen comorbidities described in **3.2.1.2** and age, gender, WIMD, presence of an MRC grade in the last year (query 3), MRC grade, presence of smoking status in the last year (query 5), smoking status, number of exacerbations in the last year (query 6), inhaled therapy regimen (query 12), and influenza vaccination (query 9) (all as described in **3.2.1.2**) were used as potential predictors of referral to PR. A directed acyclic graph (DAG) or causal diagram showing the relationship between potential predictors and referral to PR is shown in **Figure 5**. Patients aged under 35 years, and without any events recorded in their patient file in the past 4 years were excluded.

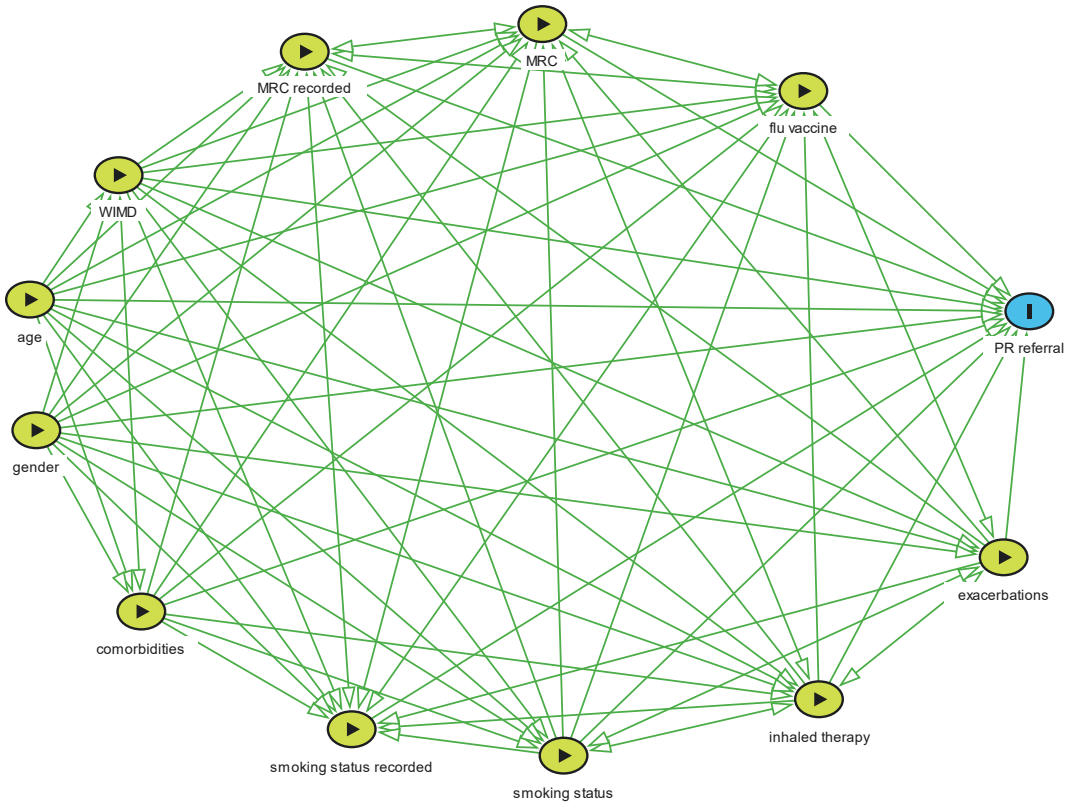

Figure 5. *Directed acyclic graph (DAG) or causal diagram showing exposures and their relationship to receipt of a referral to pulmonary rehabilitation from primary care. Generated using DAGitty(140).*

4.3.3 Statistical analysis

All data management and statistical analyses were performed using Stata 15 (StataCorp, College Station, TX, USA). Data were first summarised using means and proportions, where appropriate. Age was discretised to produce a categorical variable as its relationship with PR referral was non-linear (as determined by the likelihood ratio test). Where variables had no more than 5% missing data, complete-case analysis was used; otherwise, additional missing data categories were added to preserve sample size. To account for clustering of patients at practice level, mixed-effects logistic regression (*xtlogit* command, *re* option) was used to investigate the association between each of the twenty-three exposures and referral to PR with a random intercept for each practice. Odds ratios with 95% confidence intervals were generated for each exposure.

After univariate analyses, predictors of referral to PR were determined using mixed-effects logistic regression. The model was built using backward stepwise regression, adding significant and then removing non-significant variables until there were no further changes in significance. A p-value of <0.05 was regarded as statistically significant. Significance of categorical variables was tested using the likelihood ratio test.

Multicollinearity of predictors included in the final model was assessed using the Stata *collin* command. A variance inflation factor (VIF) of 10 was defined as indicating problematic multicollinearity. All variables had VIFs below 10 indicating multicollinearity was not an issue in the final model. Odds ratio graphs were generated using *coefplot*(141), a user generated command to produce forest plots.

I hypothesised that certain groups of patients would be more likely to refuse PR than others, so therefore completed a sensitivity analysis that additionally included patients that were exception reported for PR (declining PR will remove a patient from the denominator) as if they were referred. This would demonstrate that a GP has considered the patient's suitability for PR and then either deemed them unsuitable, offered them PR and they declined, not had a PR programme available to refer them to, or referred them. This therefore changes the outcome to *considered for PR* rather than *referred for PR* in the sensitivity analysis.

4.4 Results

A total of 13,297 people (16%) with COPD were referred from primary care for PR (**Table 10**). Patients with an MRC grade of 3 or higher, patients with 2 or more exacerbations, and patients on triple therapy had the highest proportion of PR referrals. Patients with an MRC grade of 1 had the lowest proportion of PR referrals.

In univariate analysis, coronary heart disease (p<0.001), heart failure (p=0.023), bronchiectasis (p<0.001), depression (p<0.001), anxiety (p<0.001), osteoporosis (p<0.001), painful condition (p<0.001), MRC recorded in the last year (p<0.001), and influenza immunisation (p<0.001) were all significantly associated with greater odds of referral to PR. Being female (p=0.011), having had a stroke (p=0.015), and having asthma (p=0.001) were significantly associated with lower odds of referral to PR. Older, more deprived, patients with a higher MRC grade, ex-smokers relative to current smokers, patients with more exacerbations in the last year, and patients on greater levels of inhaled therapy had greater odds of being referred to PR (**Table 11**).

In multivariate analysis, the variables included in the final model and independently associated with referral to PR were age (p<0.0001), gender (p=0.0031), deprivation (p=0.0061), diabetes (p=0.0001), asthma (p=0.0001), bronchiectasis (p<0.0001), depression (p=0.0019), painful condition (p=0.0003), MRC grade recorded in the last year (p<0.0001), MRC grade (p<0.0001), smoking status (p<0.0001), number of exacerbations in the last year (p<0.0001), inhaled therapy prescription (p<0.0001), and influenza vaccination (p<0.0001). Relative to patients under 60 years old, patients 70 years or older had lower odds of referral to PR. Women had 7% lower odds of referral than men (OR: 0.93 [95% CI: 0.89 – 0.98]). Relative to the 50% least deprived patients, the 20% most deprived patients had lower odds of referral to PR. Patients with diabetes, asthma, or a painful condition had 10% (OR: 0.90 [95% CI: 0.85 – 0.95]), 9% (OR: 0.91 [95%CI: 0.87 – 0.95]), and 11% (OR: 0.89 [95% CI: 0.84 – 0.95]), respectively, lower odds of referral to PR, and patients with bronchiectasis or depression had 34% (OR: 1.34 [95% CI: 1.22 – 1.48]) and 8% (OR: 1.08 [95% CI: 1.03 – 1.14]), respectively, higher odds of referral. Patients with an MRC grade recorded in the last year had more than twice (OR: 2.68 [95% CI: 2.52 – 2.85]) the odds of referral. Ex-smokers had 41% higher odds (OR: 1.41 [95% CI: 1.34 – 1.49]) of referral than current smokers. Patients with a higher MRC grade, more exacerbations in the last year, or on higher levels of inhaled therapy had higher odds of referral to PR than those with a lower MRC grade, fewer exacerbations, or on lower levels of inhaled therapy, respectively (**Table 11/Figure 6)**.

Table 10. *Characteristics of patients referred and not referred for pulmonary rehabilitation*

	Not referred for PR (%) N = 69,399	Referred for PR (%) N = 13,297
Age (years)		
35–59	11,598 (85.8%)	1,922 (14.2%)
60–64	7,615 (81.5%)	1,729 (18.5%)
65–69	10,842 (81.3%)	2,492 (18.7%)
70–74	12,406 (81.8%)	2,754 (18.2%)
75–80	10,579 (82.7%)	2,221 (17.4%)
≥80	16,359 (88.3%)	2,179 (11.8%)
Gender	**N = 69,396**	**N = 13,297**
Male	34,877 (83.6%)	6,857 (16.4%)
Female	34,519 (84.3%)	6,440 (15.7%)
Welsh Index of Multiple Deprivation (WIMD)	**N = 68,736**	**N = 13,207**
10% most deprived	18,156 (83.3%)	3,650 (16.7%)
10–20% most deprived	16,459 (83.8%)	3,179 (16.2%)
20–30% most deprived	13,851 (83.9%)	2,666 (16.1%)
30–50% most deprived	12,000 (84.7%)	2,172 (15.3%)
50% least deprived	8,270 (84.3%)	1,540 (15.7%)
Comorbidities		
Diabetes	15,732 (84.2%)	2,953 (15.8%)
Hypertension	36,610 (84.0%)	6,978 (16.0%)
Coronary heart disease	27,381 (82.8%)	5,673 (17.2%)
Stroke	7,320 (84.9%)	1,303 (15.1%)
Heart failure	6,180 (83.0%)	1,263 (17.0%)
Lung cancer	1,626 (84.6%)	295 (15.4%)
Asthma	29,203 (84.4%)	5,419 (15.7%)
Bronchiectasis	3,062 (77.6%)	884 (22.4%)
Depression	20,451 (82.3%)	4,410 (17.7%)
Anxiety	20,829 (82.7%)	4,351 (17.3%)
Severe mental illness[A]	5,403 (83.8%)	1,045 (16.2%)
Osteoporosis	8,751 (82.1%)	1,906 (17.9%)
Painful condition[B]	8,521 (81.5%)	1,929 (18.5%)
MRC grade recorded in the past year	39,290 (78.0%)	11,111 (22.1%)
MRC grade (latest recorded)		
1	9,741 (96.2%)	388 (3.8%)
2	28,829 (91.4%)	2,724 (8.6%)
3	14,221 (70.7%)	5,881 (29.3%)
4	7,665 (67.6%)	3,679 (32.4%)
5	1,674 (74.4%)	575 (25.6%)
Not recorded	7,269 (99.3%)	50 (0.7%)

Smoking status recorded in the past year	52,474 (81.9%)	11,575 (18.1%)
Smoking status (latest recorded)	**N = 66,422**	**N = 13,182**
Current smoker	22,219 (85.1%)	3,879 (14.9%)
Ex-smoker	34,770 (81.0%)	8,164 (19.0%)
Never smoker	9,433 (89.2%)	1,139 (10.8%)
Exacerbations in the past year	**N = 68,969**	**N = 13,164**
0	42,540 (89.1%)	5,184 (10.9%)
1	12,456 (83.0%)	2,561 (17.1%)
2	5,725 (77.2%)	1,687 (22.8%)
>2	8,248 (68.9%)	3,732 (31.2%)
Inhaled therapy treatment (last 6 months)		
Not on inhaled therapy	24,852 (91.2%)	2,410 (8.8%)
ICS	4,105 (91.4%)	388 (8.6%)
LABA	1,843 (88.8%)	232 (11.2%)
LABA & ICS	13,843 (84.7%)	2,508 (15.3%)
LAMA	9,060 (83.1%)	1,839 (16.9%)
LABA & LAMA	1,300 (76.5%)	399 (23.5%)
Triple therapy	14,396 (72.3%)	5,521 (27.7%)
Influenza vaccination	44,345 (81.2%)	10,257 (18.8%)

Notes: [A]Severe mental illness: schizophrenia, bipolar, and other psychotic illness. [B]Painful condition: 4 or more prescriptions of analgesics or antiepileptics (in the absence of an epilepsy diagnosis) in the past year. Proportions shown are row percentages.

Abbreviations: PR, pulmonary rehabilitation; MRC, Medical Research Council; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

Table 11. *Odds ratios for referral to pulmonary rehabilitation from primary care by patient characteristics*

	Odds ratio (95% CI)	
	Crude	**Adjusted**
Age (years)		
35–59	1	1
60–64	1.37 (1.27 – 1.48)	1.02 (0.93 – 1.10)
65–69	1.41 (1.32 – 1.51)	0.96 (0.89 – 1.04)
70–74	1.35 (1.27 – 1.45)	0.87 (0.80 – 0.94)
75–79	1.26 (1.18 – 1.35)	0.76 (0.70 – 0.82)
≥80	0.79 (0.73 – 0.84)	0.51 (0.47 – 0.55)
Gender		
Male	1	1
Female	0.95 (0.92 – 0.99)	0.93 (0.89 – 0.98)
Welsh Index of Multiple Deprivation (WIMD)		
10% most deprived	1.14 (1.05 – 1.23)	0.85 (0.78 – 0.93)
10–20% most deprived	1.11 (1.03 – 1.20)	0.89 (0.82 – 0.97)
20–30% most deprived	1.09 (1.01 – 1.18)	0.94 (0.86 – 1.03)
30–50% most deprived	1.01 (0.93 – 1.09)	0.94 (0.86 – 1.03)
50% least deprived	1	1
Comorbidities		
Diabetes	1.01 (0.96 – 1.05)	0.90 (0.85 – 0.95)
Hypertension	0.99 (0.95 – 1.03)	
Coronary heart disease	1.16 (1.11 – 1.20)	
Stroke	0.92 (0.87 – 0.98)	
Heart failure	1.08 (1.01 – 1.15)	
Lung cancer	0.91 (0.80 – 1.03)	
Asthma	0.93 (0.89 – 0.97)	0.91 (0.87 – 0.95)
Bronchiectasis	1.61 (1.49 – 1.75)	1.34 (1.22 – 1.48)
Depression	1.20 (1.15 – 1.25)	1.08 (1.03 – 1.14)
Anxiety	1.14 (1.09 – 1.18)	
Severe mental illness[A]	0.97 (0.90 – 1.04)	
Osteoporosis	1.20 (1.13 – 1.27)	
Painful condition[B]	1.21 (1.15 – 1.28)	0.89 (0.84 – 0.95)
MRC grade recorded in the past year	4.22 (4.01 – 4.44)	2.68 (2.52 – 2.85)
MRC grade (latest recorded)		
1	1	1
2	2.54 (2.27 – 2.84)	2.26 (2.01 – 2.54)
3	12.26 (10.98 – 13.68)	11.45 (10.20 – 12.85)
4	14.32 (12.79 – 16.03)	14.11 (12.50 – 15.92)
5	9.81 (8.49 – 11.34)	10.71 (9.14 – 12.55)
Not recorded	0.18 (0.13 – 0.24)	0.43 (0.31 – 0.59)

Smoking status recorded in the past year	2.27 (2.15 – 2.41)	
Smoking status (latest recorded)		
Current smoker	1	1
Ex-smoker	1.39 (1.33 – 1.45)	1.41 (1.34 – 1.49)
Never smoker	0.70 (0.66 – 0.76)	1.06 (0.98 – 1.16)
Exacerbations in the past year		
0	1	1
1	1.76 (1.66 – 1.85)	1.22 (1.15 – 1.30)
2	2.61 (2.45 – 2.78)	1.52 (1.42 – 1.64)
>2	4.13 (3.93 – 4.35)	1.85 (1.74 – 1.96)
Inhaled therapy treatment (last 6 months)		
Not on inhaled therapy	0.44 (0.41 – 0.47)	0.81 (0.75 – 0.88)
ICS	0.45 (0.40 – 0.50)	0.70 (0.61 – 0.80)
LABA	0.59 (0.50 – 0.68)	0.72 (0.61 – 0.85)
LABA & ICS	0.88 (0.82 – 0.94)	0.97 (0.89 – 1.05)
LAMA	1	1
LABA & LAMA	1.54 (1.36 – 1.76)	1.22 (1.05 – 1.40)
Triple therapy	2.06 (1.93 – 2.19)	1.39 (1.29 – 1.49)
Influenza vaccination	1.94 (1.86 – 2.03)	1.25 (1.18 – 1.32)

Notes: Adjusted results represent odds ratios of independent predictors of pulmonary rehabilitation referral included in the final model. [A]Severe mental illness: schizophrenia, bipolar, and other psychotic illness. [B]Painful condition: 4 or more prescriptions of analgesics or antiepileptics (in the absence of an epilepsy diagnosis) in the past year.

Abbreviations: CI, confidence interval; MRC, Medical Research Council; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist

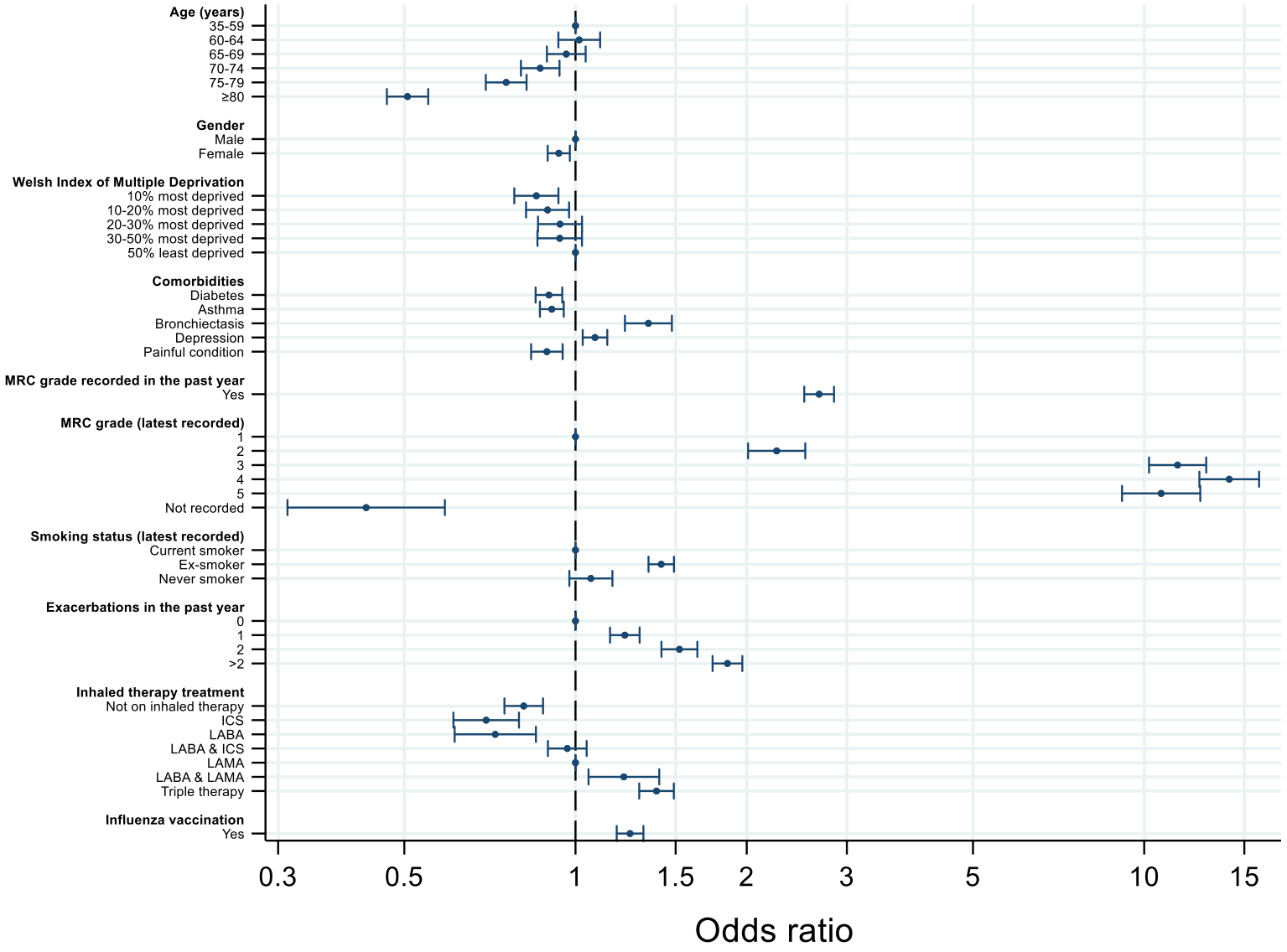

Figure 6. *Plot showing odds ratios with 95% confidence intervals for the independent predictors of referral to pulmonary rehabilitation from primary care*

4.4.1 Sensitivity analysis

The variables independently associated with consideration for PR were age (p<0.0001), gender (p<0.0001), lung cancer (p=0.0235), asthma (p<0.0001), MRC grade recorded in the last year (p<0.0001), MRC grade (p<0.0001), smoking status (p<0.0001), number of exacerbations in the last year (p<0.0001), inhaled therapy prescription (p<0.0001), and influenza vaccination (p<0.0001). Odds of consideration for PR were similar to odds of referral to PR for comorbid asthma, having an MRC grade recorded in the last year, the specific MRC grade, number of exacerbations in the last year, prescribed inhaled therapy, influenza vaccination, and women still had 8% lower odds (OR: 0.92 [95% CI: 0.88 – 0.95]) of consideration for PR than men (**Table 12**/**Figure 7**). Unlike in the referral analysis, patients over 60 years old had higher odds of consideration for PR than those under 60, and people with comorbid lung cancer had 17% higher odds (OR: 1.17 [95% CI: 1.02 – 1.34]) of consideration for PR than those without lung cancer. Different to the referral analysis, people with comorbidities of diabetes, bronchiectasis, depression, or painful condition did not have significantly different odds of consideration for PR. Deprivation was not a significant factor for consideration for PR. Ex-smokers were not significantly more likely (OR: 1.02 [95% CI: 0.98 – 1.07]) to be considered for PR than current smokers, however never smokers did have 28% lower odds (OR: 0.72 [95% CI: 0.67 – 0.77]) of consideration for PR than current smokers.

Table 12. *Odds ratios for consideration for pulmonary rehabilitation in primary care by patient characteristics*

	Odds ratio (95% CI)	
	Crude	**Adjusted**
Age (years)		
35–59	1	1
60–64	1.55 (1.46 – 1.64)	1.17 (1.08 – 1.26)
65–69	1.66 (1.58 – 1.75)	1.21 (1.13 – 1.30)
70–74	1.72 (1.64 – 1.81)	1.24 (1.16 – 1.33)
75–79	1.90 (1.80 – 2.00)	1.36 (1.26 – 1.46)
≥80	1.48 (1.41 – 1.55)	1.25 (1.17 – 1.35)
Gender		
Male	1	1
Female	0.92 (0.89 – 0.94)	0.92 (0.88 – 0.95)
Welsh Index of Multiple Deprivation (WIMD)		
10% most deprived	1.36 (1.28 – 1.44)	
10–20% most deprived	1.28 (1.21 – 1.36)	
20–30% most deprived	1.16 (1.10 – 1.24)	
30–50% most deprived	1.09 (1.03 – 1.16)	
50% least deprived	1	
Comorbidities		
Diabetes	1.16 (1.12 – 1.20)	
Hypertension	1.15 (1.12 – 1.18)	
Coronary heart disease	1.22 (1.18 – 1.25)	
Stroke	1.08 (1.03 – 1.13)	
Heart failure	1.32 (1.25 – 1.38)	
Lung cancer	1.05 (0.96 – 1.16)	1.17 (1.02 – 1.34)
Asthma	0.79 (0.76 – 0.81)	0.80 (0.76 – 0.84)
Bronchiectasis	1.27 (1.19 – 1.36)	
Depression	1.07 (1.04 – 1.11)	
Anxiety	1.01 (0.98 – 1.04)	
Severe mental illness[A]	0.96 (0.91 – 1.01)	
Osteoporosis	1.25 (1.19 – 1.30)	
Painful condition[B]	1.29 (1.23 – 1.35)	
MRC grade recorded in the past year	6.40 (6.18 – 6.63)	7.42 (7.02 – 7.83)
MRC grade (latest recorded)		
1	1	1
2	2.08 (1.96 – 2.21)	1.71 (1.60 – 1.83)
3	20.13 (18.83 – 21.53)	29.62 (27.36 – 32.05)
4	17.87 (16.62 – 19.23)	30.79 (28.16 – 33.66)
5	11.29 (10.12 – 12.60)	25.03 (21.78 – 28.77)
Not recorded	0.05 (0.04 – 0.06)	0.24 (0.19 – 0.29)

Smoking status recorded in the past year	2.70 (2.60 – 2.81)	
Smoking status (latest recorded)		
Current smoker	1	1
Ex-smoker	1.21 (1.17 – 1.25)	1.02 (0.98 – 1.07)
Never smoker	0.58 (0.55 – 0.61)	0.72 (0.67 – 0.77)
Exacerbations in the past year		
0	1	1
1	1.80 (1.73 – 1.87)	1.24 (1.18 – 1.31)
2	2.52 (2.39 – 2.66)	1.43 (1.33 – 1.54)
>2	3.96 (3.78 – 4.15)	1.61 (1.51 – 1.71)
Inhaled therapy treatment (last 6 months)		
Not on inhaled therapy	0.39 (0.37 – 0.40)	0.72 (0.67 – 0.77)
ICS	0.40 (0.37 – 0.44)	0.73 (0.66 – 0.81)
LABA	0.65 (0.58 – 0.71)	0.81 (0.71 – 0.92)
LABA & ICS	0.74 (0.70 – 0.78)	0.90 (0.83 – 0.96)
LAMA	1	1
LABA & LAMA	1.64 (1.47 – 1.83)	1.35 (1.17 – 1.56)
Triple therapy	2.01 (1.91 – 2.12)	1.45 (1.36 – 1.55)
Influenza vaccination	1.95 (1.89 – 2.01)	1.18 (1.13 – 1.24)

Notes: Adjusted results represent odds ratios of independent predictors of pulmonary rehabilitation referral included in the final model. [A]Severe mental illness: schizophrenia, bipolar, and other psychotic illness. [B]Painful condition: 4 or more prescriptions of analgesics or antiepileptics (in the absence of an epilepsy diagnosis) in the past year.

Abbreviations: CI, confidence interval; MRC, Medical Research Council; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist

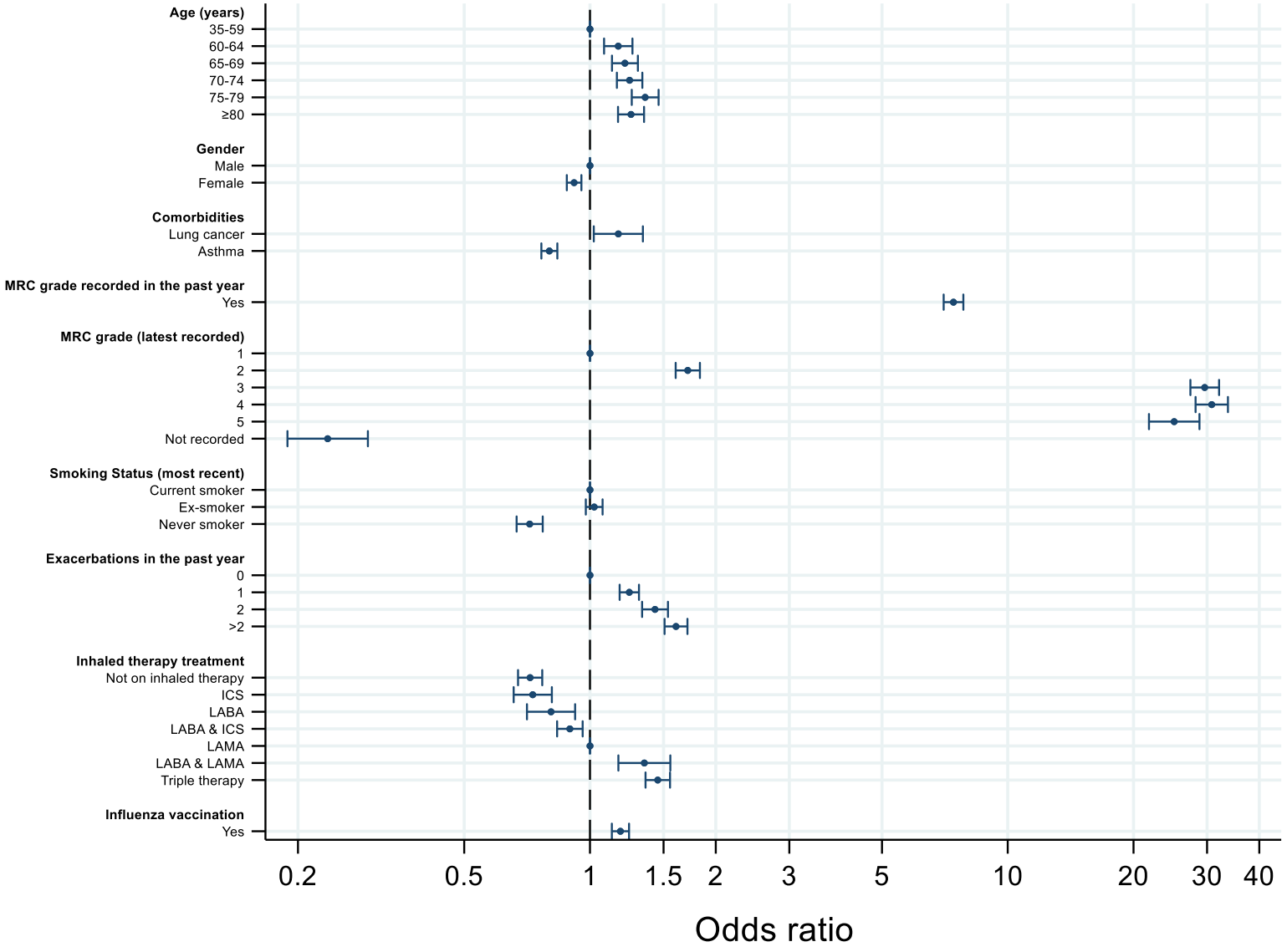

Figure 7. *Plot showing odds ratios with 95% confidence intervals for the independent predictors of* ***consideration*** *for pulmonary rehabilitation from primary care*

4.5 Discussion

In this chapter, I have found that people with COPD with a comorbidity of depression or bronchiectasis, an MRC grade recorded in the last year, a higher MRC grade, more exacerbations in the past year, on higher levels of inhaled therapy, vaccinated for influenza, or who were an ex-smoker had greater odds of referral to PR. These results are encouraging as they seem to indicate that people with more severe symptoms are being appropriately prioritised. From a service delivery perspective, it was interesting to observe that where markers of high-quality care for COPD patients were recorded, a greater proportion of patients were referred. For example, where MRC grade had been recorded, patients had an influenza vaccine, or were prescribed either LABA & LAMA or triple therapy compared to LAMA monotherapy they were significantly more likely to be referred. These results suggest that patients are more likely to be referred from general practices that offer higher quality healthcare. However, as clustering of patients within practices was adjusted for using a random intercept for each general practice, this may simply be a sign of greater engagement with primary care, thus providing more opportunities to discuss PR. The finding that people with an MRC grade ≥3 were more than 10 times more likely to be referred to PR than MRC grade 1 patients was unsurprising given that current guidelines recommend PR referral for any COPD patient with an MRC grade ≥3(18). The finding that ex-smokers were more likely to be referred than current or never smokers is potentially concerning as current smokers can benefit from pulmonary rehabilitation in parallel with smoking cessation treatment.

I also found that people with COPD who were older (≥70 years), female, more deprived, or had a comorbidity of diabetes, asthma or painful condition were less likely to be referred to pulmonary rehabilitation. It is concerning to find that these groups appear to be missing out on best practice care. It is possible older people are less likely to be referred due to their increased comorbidity and frailty. The most deprived people with COPD may be less likely to be referred than the least deprived due to them being more likely to refuse PR or poorer engagement with primary care. Emerging evidence for rehabilitation in participants with asthma(142–146) should encourage referral for those with comorbid asthma. There is some logic to the finding that people with a comorbidity of painful condition were less likely to be referred as NICE guidance(18) proposes that significant orthopaedic limitations may well limit participation in PR, although this has not been established in the literature.

It was surprising to find that women were less likely to be referred than men. Reduced access for women has previously been reported in the UK audit for cardiac rehabilitation(147), but there is no obvious reason for it. It may be that women are more likely to refuse PR, however the ‘consideration for PR’ sensitivity analysis similarly found that women were less likely to be considered for PR. It is

there is an unconscious bias against women which exists in treatment of COPD as well as diagnosis(148,149).

It was also interesting to note in the *considered for PR* sensitivity analysis that people ≥70 years old were more likely to be considered for PR despite being less likely to receive a referral. This suggests older people are more likely to decline, be unsuitable for, or not live near an available PR programme. Current smokers being no less likely to be considered for PR than ex-smokers, but being less likely to receive a referral suggests that current smokers are more likely to refuse PR. And the finding that deprivation is not a significant factor in consideration for PR suggests that more deprived patients may be more likely to refuse or not have access to an available PR programme. People with a comorbidity of lung cancer being more likely to be considered for PR but no more likely to be referred is likely a consequence of the Quality and Outcomes Framework (QOF) pay-for-performance scheme. QOF financially incentivises the referral of suitable people with COPD to PR. However, as the bonus payment is proportional to the proportion of suitable people referred to PR, GPs have a financial incentive to record unsuitable people as such so that the denominator used in the bonus payment calculation is as small as possible (making it easier to refer a large proportion of eligible patients). This means that a person with lung cancer that is unsuitable for PR will likely be swiftly recorded as such by their GP, and this record would include them in the *considered for PR* group.

4.5.1 Comparisons with previous studies

Although several previous studies have investigated uptake of PR (for those referred), only one study has previously quantitatively examined patient factors associated with referral. Li et al.(150) studied 88 patients hospitalised with COPD and found that patients with hypertension and more respiratory-related hospital bed days in the last 3 years were more likely to be referred for PR. They also found that anxiety and possibly depression were associated with greater likelihood of referral but only present unadjusted results. If both hospital bed days in the last 3 years and number of exacerbations in the last year can be considered proxies for disease severity, this current study and the Li et al.(150) study both highlight disease severity and depression as important factors in referral. The different results found by Li et al.(150) could simply reflect the low power of their study or differing priorities between primary and secondary care.

4.5.2 Strengths & limitations

The strength of this study comes from its size. It examines referral for 82,696 people with COPD from 94% of Welsh practices, making it the largest study to examine factors associated with PR referral to date. This large sample has enabled adjustment for multiple variables in analyses, something that would not have been possible in the only previous study(150) of predictors of PR

referral. Using nearly all individuals with COPD in Wales also ensures that results from this analysis are generalisable to a typical COPD population found in primary care.

The analysis is not without its limitations though. The definition of referral to PR was from primary care so it is not possible to say that this represents the characteristics of all COPD patients being referred to PR, as patients referred from secondary care may have substantially different traits. Another weakness of the analysis is that it is limited to Wales, which is likely a more homogenous population than the rest of the UK. WIMD is not a perfect definition of SES, as it only signifies the deprivation of an area in which a person lives, not how deprived a person is. This will likely bias results towards the null hypothesis for SES as the deprivation of a local population will appear more homogenous. The NACAP primary care audit data that was used is also quite limited in the data that it contains relative to a patient's full primary care record. Further details on the severity of a patient's condition, such as spirometry results, and details on the availability of PR programmes would have been useful additional potential predictors to examine.

In analyses, the general practice was used as a random intercept in the mixed-effects logistic regression models to account for clustering of patients within practices, but there is a possibility of clustering at the GP level too. Clustering at the GP level is likely to be a smaller issue than clustering at the practice level though, as patients within a practice are likely to be more similar than the patients assigned to a specific GP within a practice, and care is likely to differ more between practices than between GPs within a specific practice. The use of a cross-sectional study design also adds limitations. PR referral is defined as within the last 3 years, but patient characteristics such as smoking status and MRC grade are most recent ever, so it is possible that patient characteristics could reflect those found after, rather than before, completion of PR. This will likely bias predictors towards the null hypothesis. This lack of a clear temporal pattern in the data also prevents any conclusions or assessment of causal associations in the analysis. Finally, several significance tests were performed, increasing the probability of some significant results being chance findings.

4.5.3 Conclusion

Whilst generally, appropriate patients are being prioritised for referral, it is concerning that women, smokers, and more deprived patients are less likely to receive a referral to PR. Ensuring there is easy access to PR programmes in more deprived regions may help to increase referrals among more deprived patients.

Chapter 5. Wales vs. rest of UK National COPD Audit comparison

5.1 Introduction

In the previous chapter I used data from the NACAP primary care audit in Wales to draw conclusions about the patterns of PR referral in the UK. However, it is possible that differences in patterns of COPD care exist between Wales and the rest of the UK. Therefore, in this chapter I first determine if the sample of Welsh practices that contribute to CPRD GOLD are representative of Wales with regard to COPD care, and then determine if Wales is comparable to the other UK nations by using CPRD GOLD to repeat the NACAP primary care audit in each of the four UK countries. Not only does this provide an assessment of the utility of Wales as a sample of the UK, but it also provides information on the suitability of a research database such as CPRD GOLD as an alternative data source for national audit.

Healthcare is a devolved matter in the UK, with each of the four constituent countries being responsible for healthcare within their borders. While per capita healthcare spending is similar in each of the four UK nations (**Figure 8**), healthcare commissioning and incentivisation can differ between them, which may lead to differences in performance(151).

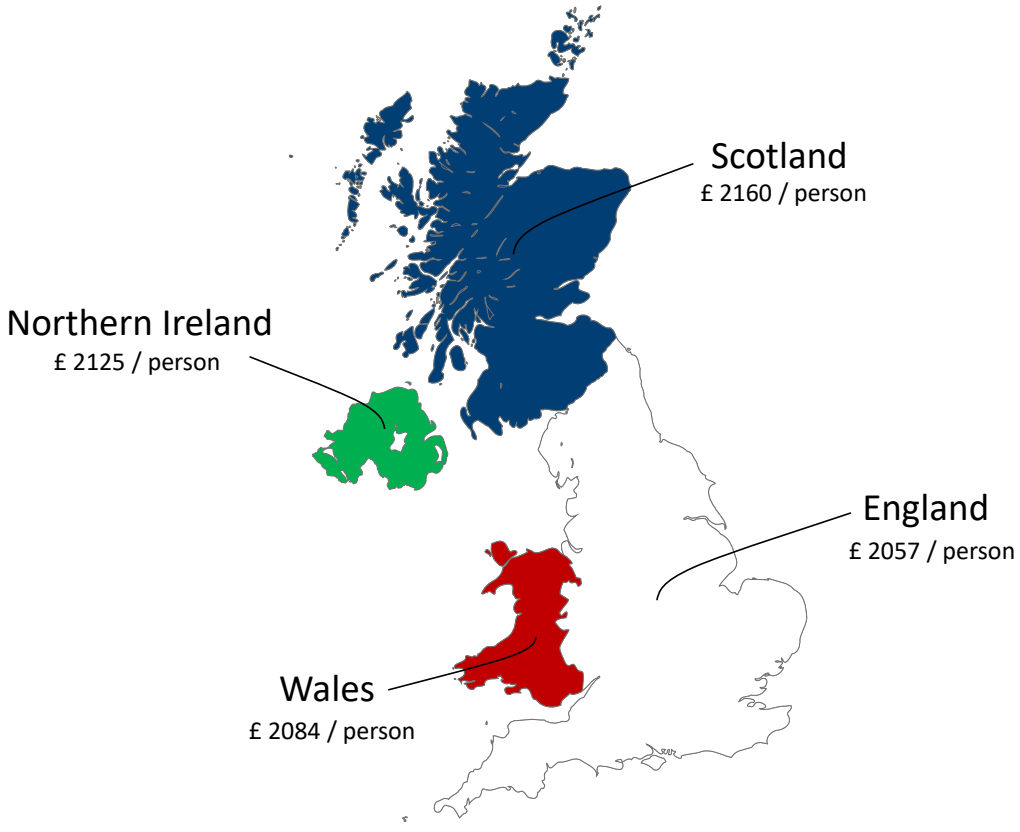

Figure 8. *2014/15 per capita public sector healthcare spend by UK country(152)*

The estimated prevalence of COPD is similar between the UK countries, with England, Northern Ireland, and Wales having estimates of 2.0%, 2.1%, and 2.2%, respectively; however, Scotland does have a slightly higher estimated prevalence of 2.4%(3). COPD mortality is similar between England, Wales, and Northern Ireland, but Scotland has higher than expected mortality for COPD. Scottish women and men with COPD have 32% and 12%, respectively, higher mortality than would be expected based on age-standardised mortality ratios for the UK(3).

In 2017, the National Asthma and COPD Audit Programme conducted an audit of primary care which comprised 94% of all practices in Wales(66). While it had been desired to include all UK countries in the audit, patient confidentiality concerns arising from the 'care.data' project have resulted in a block to the sharing of patient data from English practices, and the proportion of practices from Scotland and Northern Ireland agreeing to participate was too low to ensure generalisability of results. Therefore Wales is the only country to have received national audits of COPD primary care so far(67). As a result of being the only participant in the primary care audits, there may be an increased awareness of best practice COPD care among Welsh GPs that is not present in the rest of the UK. This in turn may have led to improvements in care in Wales that are not occurring in the rest of the UK. For this reason, it is important to investigate that national audit of Wales provides a representative view of COPD care that is generalisable to all the UK. In addition, if CPRD GOLD contains a representative sample of UK general practices, CPRD GOLD or other similar research databases could be used in the future to complete national audits that are easier to conduct and cover the whole country.

5.2 Aim

As NACAP has only been able to audit Wales for COPD primary care so far, the aim of this chapter is to test if there are significant differences between Wales and the other UK countries in COPD care. To do this I complete two sub-objectives:

1. Replicate the 2017 Welsh NACAP primary care audit in Welsh CPRD GOLD practices and calculate proportions of patients receiving best quality COPD care (queries 1-14 (see **3.2.1.2**) from the National COPD Audit primary care audit(113)) and compare results with those in the published audit to assess whether Welsh practices that contribute to the CPRD appear to have similar patterns of COPD care to the national audit.
2. Replicate the primary care audit in all CPRD practices (entire UK) and compare results for key items of care for each of the UK countries to test if there are significant differences in the quality of COPD care between the other three UK countries and Wales.

5.3 Methods

5.3.1 Database/population

Data from CPRD GOLD, as described previously in **3.1.1**, were used in the analysis. The population was a cohort of COPD patients as defined in **3.1.1.1** and **3.2.1.2**, following the same validated(112) definition used in the NACAP primary care audit and **Chapter 4**. Although usage of the Vision GP software package is declining in England with under 2% of English practices (139 of 7372) contributing to CPRD GOLD, it is more commonly used in Wales with 15% of Welsh practices (69 of 453) contributing(111), ensuring a sufficient sample of Welsh practices is available for analysis.

5.3.2 Study design

The study design replicates that of the NACAP primary care audit, detailed in **3.2.1**. Standard data preparation and cleaning procedures were followed as detailed in **3.1.4**. As the study design used for the NACAP primary care audit was not as stringent as design typically used for epidemiological researching using EHRs, I additionally completed a sensitivity analysis repeating the analyses using a more accurate COPD population. This 'improved' COPD population excludes any COPD diagnoses occurring before 35 years of age, requires at least one year of follow-up at the currently registered practice, and one year of follow-up following COPD diagnosis (to allow sufficient time to provide key care items).

Patients were excluded from the analysed cohort if any of the following chronologies were detected:

- First COPD was after the audit date
- First registration was after the audit date
- Current registration was after the audit date
- Transfer out date was before the audit date
- Death date was before the audit date
- Last collection date before the audit date

Patients that were neither male nor female were excluded from the sub-objective 2 country comparison analysis due to the small number of patients in this category.

5.3.3 Variables

5.3.3.1 Sub-objective 1: Audit vs. CPRD

The outcomes in the first sub-objective were the first 14 queries from the NACAP primary care audit (described in **3.2.1.2**). Identical variable definitions were used where possible; however, it should be noted that the primary care audit utilises 5-byte Read V2 codes whereas CPRD GOLD utilises 7-byte

Read V2 codes. The purpose of the additional two bytes is to highlight synonym codes. Therefore, in the production of CPRD GOLD codelists it was ensured that these additional synonym codes were included. One area where it was not possible to exactly replicate the codelists used in the primary care audit was prescriptions. Prescriptions are recorded in CPRD GOLD using gemscript codes instead of Read V2 codes, therefore new codelists were required for all prescribed items. Codelists were generated using the procedure described in **3.1.4.1** to search for all drug and brand names included in the original primary care audit codelists (**Appendix E** and **Appendix F**). The codelists generated for CPRD GOLD are provided in **Appendix J**.

5.3.3.2 Sub-objective 2: Country comparison

In the second sub-objective, the exposure was the country in which the GP practice is located. In this analysis the 14 audit outcomes were limited to 7 key measures (highlighted in bold in **3.2.1.2**) that cover three areas of care: diagnosis, assessment, and high-value care.

Diagnosis:

- Spirometric confirmation of airway obstruction (query 1)
- X-ray completed as part of diagnostic investigation (query 2)

Assessment:

- A record of MRC score in the patient record in the preceding year (query 3)
- A record of smoking status in the patient record in the preceding year (query 5)

High-value care:

- Receipt of the seasonal influenza vaccine (query 9)
- Smoking cessation treatment (query 10)
- Referral to pulmonary rehabilitation (query 11a).

The purpose of limiting the items of care to just 7 key items was to keep the main analysis focused and reduce the possibility of chance findings The covariates included in this sub-objective were age (categorised in 10-year bands), sex, and the 13 comorbidities described in **3.2.1.2**.

5.3.4 Statistical analysis

Data were first summarised with frequencies and proportions, and means and standard deviations, as appropriate.

5.3.4.1 Sub-objective 1: Audit vs. CPRD

The proportions of patients receiving the 14 items of care were compared between the original audit results, the Welsh CPRD population using the original audit methodology, and the Welsh CPRD population using the improved methodology. Differences in proportions were compared visually using bar charts and Bland and Altman's "limits of agreement"(153), a method to assess agreement between two methods of measurement.

5.3.4.2 Sub-objective 2: Country comparison

Mixed-effects logistic regression using a random intercept for practice (to account for clustering of patients within practices) was used to explore the association between country of general practice and each of the seven key elements of COPD care, generating odds ratios and 95% confidence intervals. The logistic regression models were initially adjusted for age and sex, and then further adjusted for the comorbidities described in **3.2.1.2**.

While completing the analyses it became apparent that a substantially larger proportion of Welsh patients were being exempted from referral to pulmonary rehabilitation than patients from other UK countries. Therefore, a sensitivity analysis was undertaken that *included* any patients in the denominator (rather than excluding as in original analyses) if they had a Read code in their health record indicating that they should be exempted from referral to pulmonary rehabilitation.

5.4 Results

5.4.1.1 Sub-objective 1: Audit vs. CPRD

There were 13,588 patients with a diagnosis of COPD in Welsh CPRD GOLD practices. The proportion of patients receiving care items in Welsh CPRD practices was on average 2.35% higher (absolute difference) than in Welsh audit practices. The two populations appeared broadly comparable, however there was greater recording of FEV_1 percent-predicted in audit practices (27.5% in the audit vs. 15.7% in CPRD) and greater referral to pulmonary rehabilitation for patients with an MRC of 3-5 in CPRD practices (70.0% in CPRD vs. 50.2% in the audit) (**Figure 9**).

Sensitivity analysis

There were 12,094 patients with a diagnosis of COPD in Welsh CPRD practices when using the improved methodology to detect COPD patients. The proportion of Welsh patients in CPRD GOLD receiving each item of care were very similar when using either the original audit methodology or the improved methodology, with an average absolute difference in results between the two methodologies of just 0.33% (**Figure 9**).

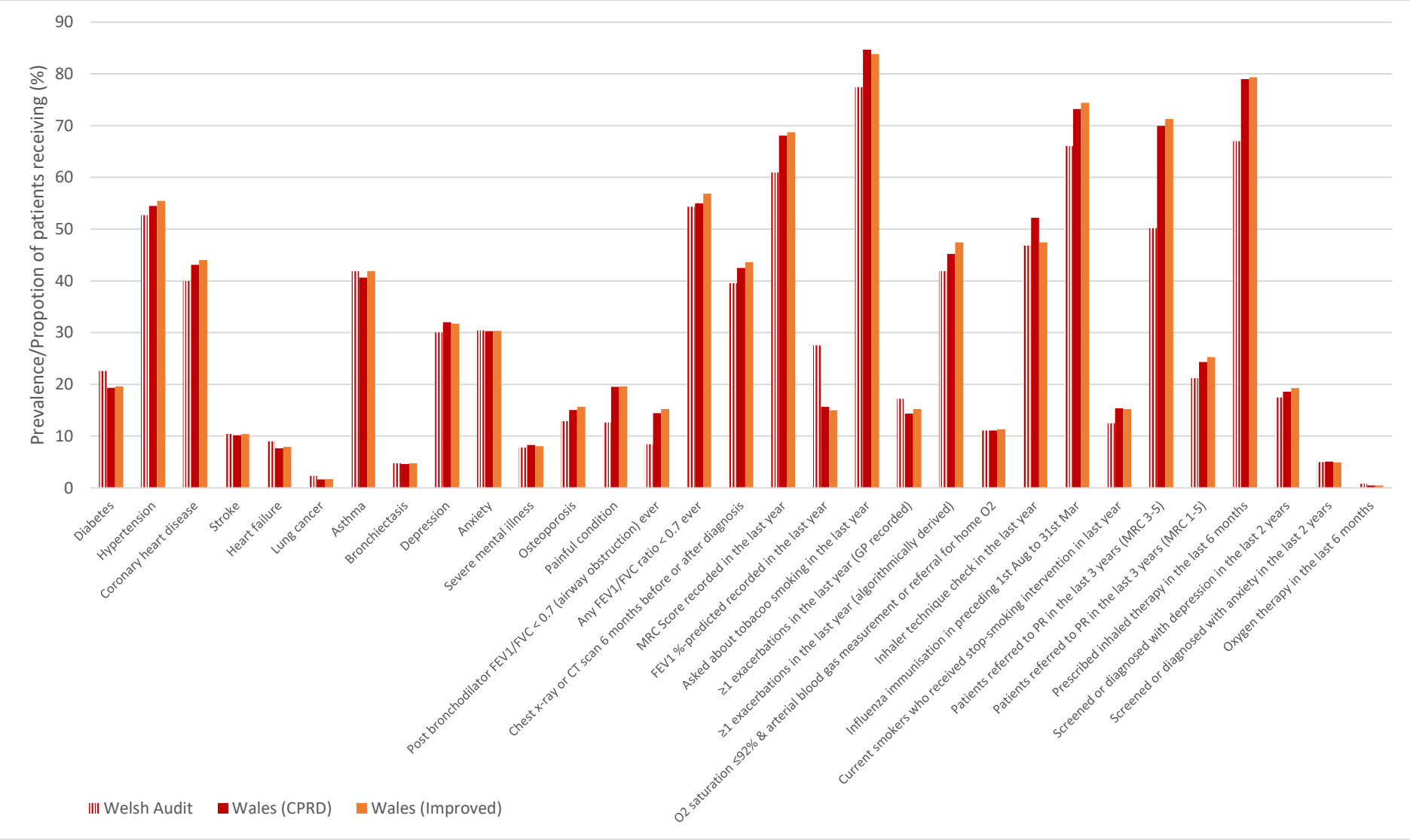

***Figure 9**. Prevalence of comorbidities and receipt of items of COPD care in the Welsh primary care audit, Welsh CPRD practices when using the audit methodology, and Welsh CPRD practices when using an improved methodology*

5.4.1.2 Sub-objective 2: Country comparison

In the 69 Welsh, 141 English, 74 Scottish, and 21 Northern Irish CPRD GOLD practices there were, respectively, 13,587 Welsh, 25,689 English, 13,717 Scottish, and 3,771 Northern Irish male or female patients with a diagnosis of COPD. Compared to Wales, receipt of care was similar in the other three UK countries; however a lower proportion of Scottish patients received a chest X-ray (26.8% in Scotland vs. 42.5% in Wales), and a substantially greater proportion of Welsh patients received a referral to pulmonary rehabilitation (70.0% in Wales vs. 19.0%, 22.3%, and 34.4% in England, Scotland, and Northern Ireland, respectively) (**Figure 10**).

Relative to Welsh patients, English, Scottish, and Northern Irish COPD patients were significantly less likely to have confirmation of airway obstruction (**Figure 11**/**Table 13**). Scottish patients were significantly less likely to have a chest X-ray, but there was no significant difference for English or Northern Irish patients. Scottish patients were significantly less likely to have a record of MRC grade or smoking status in the last year, but English and Northern Irish patients were significantly more likely to have a record of MRC grade and smoking status. English, Scottish, and Northern Irish COPD patients were significantly more likely to have the seasonal influenza vaccine. English and Scottish patients were significantly less likely to receive smoking cessation treatment, whereas Northern Irish patients were significantly more likely to receive it. English, Scottish, and Northern Irish COPD patients were substantially less likely than Welsh patients to receive a referral for pulmonary rehabilitation. The proportion of patients receiving confirmation of airway obstruction was highly correlated within GP practices, with practice random effects composing approximately 77% of the total residual variance (**Table 14**).

In the sensitivity analysis including patients exempted from pulmonary rehabilitation, relative to patients in Welsh practices, patients in English and Scottish practices were still much less likely to receive a pulmonary rehabilitation referral, however the difference for Northern Irish patients was borderline statistically significant (**Figure 12/Table 15**).

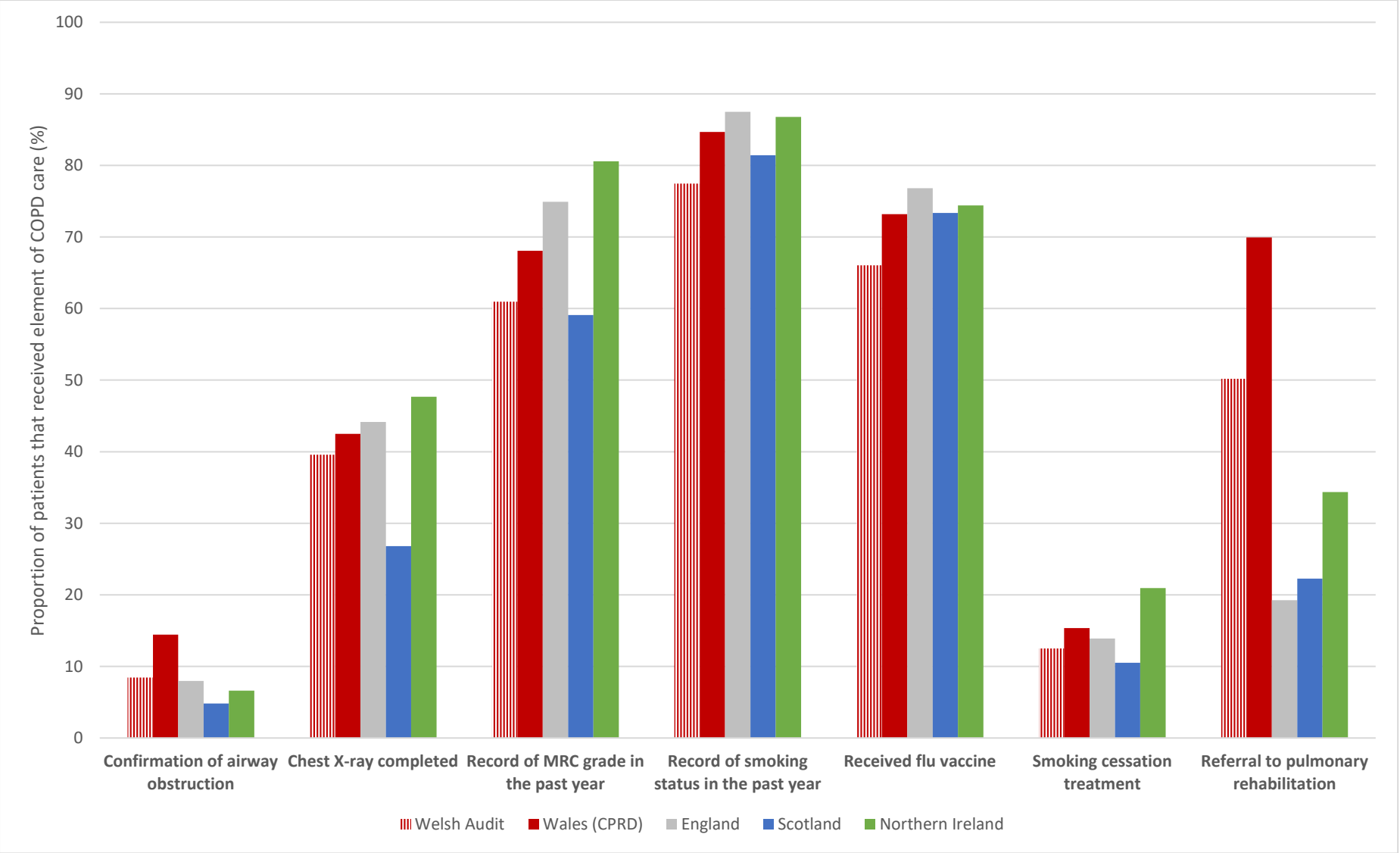

***Figure 10**. Proportion of patients receiving seven key items of COPD care in the Welsh COPD primary care audit and Welsh, English, Scottish, and Northern Irish practices in CPRD GOLD.*

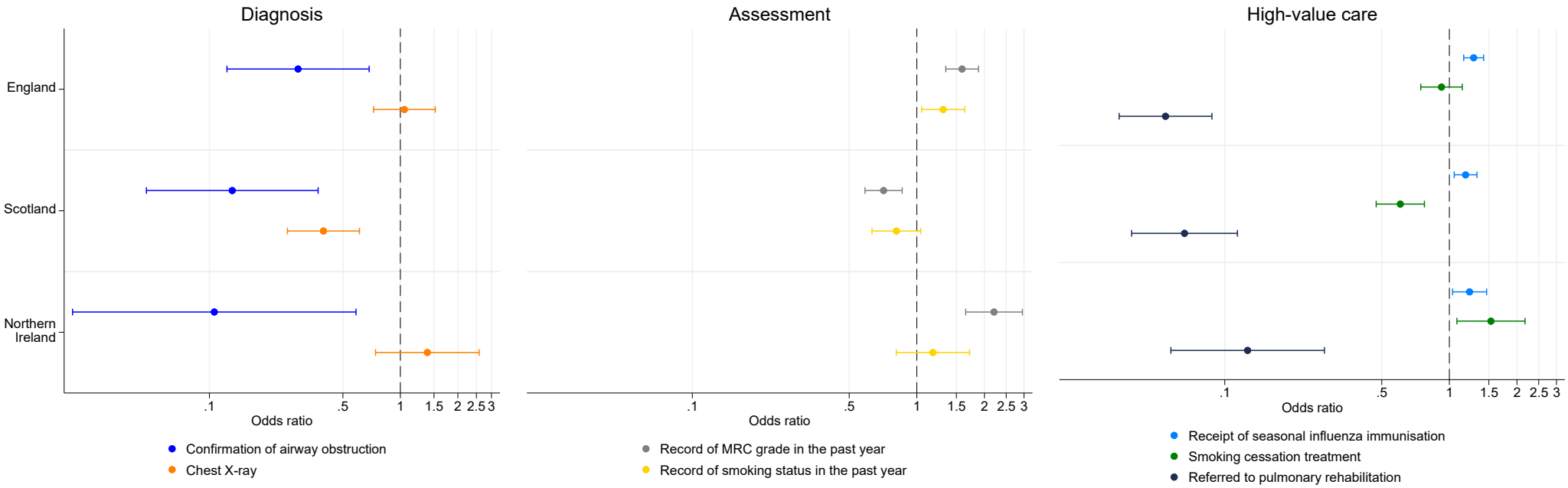

***Figure 11**. Fully adjusted odds ratios and 95% confidence intervals for receipt of item of COPD care (split into care areas of diagnosis, assessment, and high-value care) for each UK country relative to Wales.*

***Table 13**. Odds ratios and 95% confidence intervals for receipt of item of COPD care for each UK country relative to Wales in crude and adjusted models.*

	Odds Ratio (95% confidence interval)					
	Crude		Age and sex adjusted		Age, sex, and comorbidities adjusted	
Confirmation of airway obstruction[1]						
Wales	1		1		1	
England	0.30	(0.13 – 0.71)	0.30	(0.13 – 0.71)	**0.29**	**(0.12 – 0.69)**
Scotland	0.14	(0.05 – 0.38)	0.14	(0.05 – 0.38)	**0.13**	**(0.05 – 0.37)**
Northern Ireland	0.11	(0.02 – 0.59)	0.11	(0.02 – 0.58)	**0.11**	**(0.02 – 0.59)**
Chest X-ray[2]						
Wales	1		1		1	
England	1.04	(0.72 – 1.51)	1.05	(0.72 – 1.52)	1.05	(0.72 – 1.52)
Scotland	0.41	(0.26 – 0.63)	0.41	(0.26 – 0.63)	**0.40**	**(0.26 – 0.61)**
Northern Ireland	1.45	(0.78 – 2.70)	1.45	(0.78 – 2.69)	1.39	(0.74 – 2.59)
Record of MRC grade in the past year						
Wales	1		1		1	
England	1.56	(1.32 – 1.85)	1.59	(1.34 – 1.88)	**1.59**	**(1.34– 1.88)**
Scotland	0.71	(0.59 – 0.86)	0.73	(0.60 – 0.88)	**0.71**	**(0.59 – 0.86)**
Northern Ireland	2.15	(1.61 – 2.88)	2.23	(1.67 – 2.99)	**2.21**	**(1.65 – 2.95)**
Record of smoking status in the past year						
Wales	1		1		1	
England	1.27	(1.02 – 1.58)	1.29	(1.04 – 1.61)	**1.31**	**(1.05 – 1.63)**
Scotland	0.79	(0.62 – 1.01)	0.78	(0.61 – 1.00)	0.81	(0.63 – 1.04)
Northern Ireland	1.18	(0.81 – 1.71)	1.15	(0.79 – 1.67)	1.18	(0.81 – 1.72)
Receipt of the seasonal influenza immunisation in the last year						
Wales	1		1		1	
England	1.23	(1.11 – 1.36)	1.25	(1.13 – 1.39)	**1.28**	**(1.16 – 1.42)**
Scotland	1.04	(0.93 – 1.17)	1.11	(0.99 – 1.25)	**1.18**	**(1.05 – 1.33)**
Northern Ireland	1.11	(0.93 – 1.32)	1.23	(1.03 – 1.46)	**1.23**	**(1.03 – 1.47)**
Smoking cessation treatment						
Wales	1		1		1	
England	0.90	(0.73 – 1.11)	0.91	(0.74 – 1.13)	0.92	(0.75 – 1.14)
Scotland	0.62	(0.49 – 0.79)	0.61	(0.48 – 0.78)	**0.60**	**(0.47 – 0.77)**
Northern Ireland	1.67	(1.18 – 2.35)	1.61	(1.14 – 2.28)	**1.53**	**(1.08 – 2.17)**
Referred to pulmonary rehabilitation[3]						
Wales	1		1		1	
England	0.05	(0.03 – 0.09)	0.05	(0.03 – 0.09)	**0.05**	**(0.03 – 0.09)**
Scotland	0.07	(0.04 – 0.11)	0.07	(0.04 – 0.11)	**0.07**	**(0.04 – 0.11)**
Northern Ireland	0.13	(0.06 – 0.29)	0.13	(0.06 – 0.28)	**0.13**	**(0.06 – 0.28)**

[1]Confirmation of airway obstruction defined as record of post-bronchodilator $FEV_1/FVC < 0.7$

[2]Chest X-ray confirmation of diagnosis defined as record of a chest X-ray 6 months prior to or after COPD diagnosis

[3]"Offered" pulmonary rehabilitation counted as a referral, however any patients that declined the offer were not counted as referred

Table 14. *Variance of random intercepts at GP practice level and intraclass correlation coefficients for the fully adjusted random effects logistic regression models.*

	Variance of random intercepts at GP practice level (95% CI)		Intraclass correlation coefficient (95% CI)	
Confirmation of airway obstruction[1]	10.86	(7.66 - 15.39)	0.77	(0.7 - 0.82)
Chest X-ray[2]	1.44	(1.15 - 1.80)	0.30	(0.26 - 0.35)
Record of MRC grade in the past year	0.30	(0.25 - 0.36)	0.08	(0.07 - 0.1)
Record of smoking status in the past year	0.52	(0.43 - 0.62)	0.14	(0.12 - 0.16)
Receipt of the seasonal influenza immunisation in the last year	0.09	(0.07 - 0.11)	0.03	(0.02 - 0.03)
Smoking cessation treatment	0.41	(0.33 - 0.52)	0.11	(0.09 - 0.14)
Referred to pulmonary rehabilitation[3]	2.39	(1.96 - 2.92)	0.42	(0.37 - 0.47)

[1]Confirmation of airway obstruction defined as record of post-bronchodilator $FEV_1/FVC < 0.7$

[2]Chest X-ray confirmation of diagnosis defined as record of a chest X-ray 6 months prior to or after COPD diagnosis

[3]"Offered" pulmonary rehabilitation counted as a referral, however any patients that declined the offer were not counted as referred

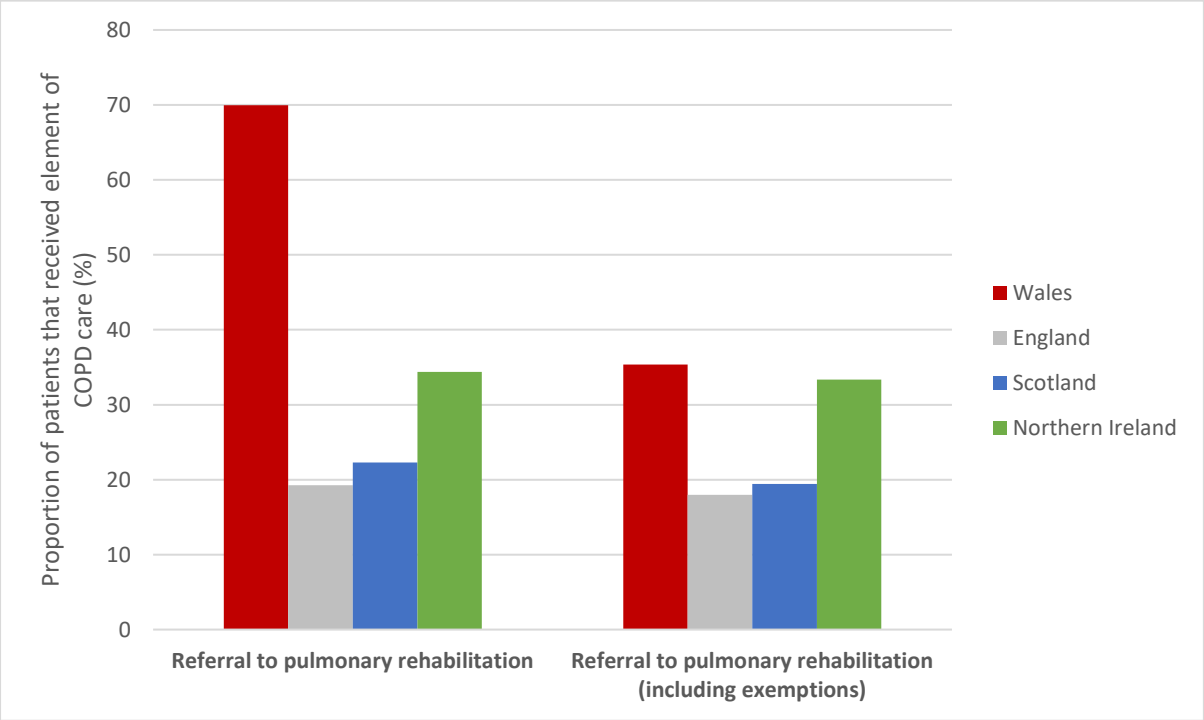

Figure 12*. Proportion of patients in Welsh, English, Scottish, and Northern Irish practices receiving a referral to pulmonary rehabilitation, excluding exempted patients from the denominator, and including exempted patients in the denominator.*

***Table 15**. Odds ratios and 95% confidence intervals for receipt of referral to pulmonary rehabilitation, including patients that were exempted from pulmonary rehabilitation, for each UK country relative to Wales in crude and adjusted models.*

	Odds Ratio (95% confidence interval)					
	Crude		Age and sex adjusted		Age, sex, and comorbidities adjusted	
Referral to pulmonary rehabilitation (including excepted patients)						
Wales	1		1		1	
England	0.21	(0.14 – 0.32)	0.21	(0.14 – 0.32)	**0.21**	**(0.14 – 0.32)**
Scotland	0.24	(0.15 – 0.38)	0.23	(0.15 – 0.37)	**0.23**	**(0.15 – 0.37)**
Northern Ireland	0.58	(0.29 – 1.13)	0.55	(0.28 – 1.09)	**0.55**	**(0.28 – 1.08)**

5.5 Discussion

In this chapter I found that Welsh practices included in CPRD GOLD are comparable to practices included in the Welsh COPD primary care audit, although recording of care items was slightly better on average in CPRD GOLD practices than primary care audit practices. This could be due to CPRD contributing practices being more aware of the importance of accurate data recording, and this slight increase could therefore represent better recording of clinical events rather than any differences in the provision of care.

Reassuringly, it appears that the slightly less precise study design used in the primary care audit has not had a meaningful impact on results, as sensitivity analysis using an improved, more stringent design resulted in very minor changes to outcomes.

While it was already clear from the COPD primary care audit that there is a shortfall in delivering key aspects of COPD, it appears that there is some variability between the UK nations, with Scottish practices often performing less well while English and Northern Irish practices perform similarly to Welsh ones. It is difficult to speculate on reasons for this difference but it could be due to the quality of event recording, quality of care given, or a combination of the two; perhaps driven by participation in the Quality and Outcomes Framework (QOF) pay-for-performance scheme, which Scottish practices no longer participate in. For example, different national priorities, levels of funding/incentivisation, and therefore availability of programmes may explain differences in the proportion of patients being referred to pulmonary rehabilitation.

Welsh primary care practices appeared substantially better at confirming, or at least recording confirmation of airways obstruction via spirometry and referring patients to pulmonary

rehabilitation than the other UK nations; however, it seems that this improvement in referral to pulmonary rehabilitation is largely driven by greater exception reporting, where inappropriate patients are excluded from the denominator. The reason for Wales' greater performance in spirometric confirmation of airway obstruction and referral to pulmonary rehabilitation could perhaps be due to participation in the primary care audit leading to an increased awareness of the importance of these interventions and how to accurately code them in the patient's electronic health record. The greater exception reporting for pulmonary rehabilitation does suggest that there is a greater awareness of how to code certain clinical events in Wales than in the other countries. Interestingly, spirometry recording was highly correlated within practices suggesting that there is substantial variation between practices. In fact, recording of spirometry varies from 0% to 95% at the practice level. This is indicative of substantial variation in the quality of data recording across practices, and results here could perhaps be improved by increasing GP awareness of the best way to record spirometry results in their GP software package. Accurate coding of lung function is easier with the Vision software than other packages and this may explain why recording of spirometry was slightly better in the CPRD GOLD cohort, which comprises practices using Vision, rather than the audit cohort which comprised nearly all practices in Wales. Differences in the locations used for key components of healthcare may also explain some of the differences between the countries. For example, if tests are undertaken in hospital, it is possible that the data are not inputted into the GP computer system. Equally outcomes such as influenza vaccination may be undertaken in a number of settings, and it is possible that although it occurs, it does not get coded in the primary care record. This may also be true for smoking cessation services.

5.5.1 Comparisons with previous studies

CPRD GOLD has previously been shown to be representative of the UK population in terms of age, sex, and ethnicity(108), therefore it is not too surprising that the Welsh population within CPRD GOLD appear to be representative of Wales. Although not used in analysis in this chapter, the population within CPRD Aurum has also been found to be representative of the UK population(154).

Since devolution in 1999 there have been numerous reports into the impact of divergences of health policy on outcomes in the four UK countries. However, one over-arching theme in the reports is that comparisons between the countries is difficult as data are inconsistently recorded in each country(155,156). Analyses of the Quality and Outcomes Framework (QOF) found that patients from all countries generally received best practice care, but Scotland and Northern Ireland performed better at delivering evidence-based care than England and Wales(155,157). Although these studies were from 2008/09(157) and 2010/11(155) so changes in care quality in each nation over the past

10 years could explain the contrasting findings to this chapter, where Scotland generally performed worse than the other UK nations.

5.5.2 Strengths & limitations

The major strength of this study is its size; I was able to include over 13,000 patients from each of Wales and Scotland, over 25,000 from England, and over 3000 from Northern Ireland. However, it would have been desirable to adjust for socioeconomic status or deprivation in the analyses as the UK countries have differing levels of deprivation(158). Unfortunately, each country has its own measure of IMD that is not comparable with the other nations and CPRD does not provide linked data for countries other than England. It should also be noted that when using electronic health records to make assessments of treatment, it is only possible to see what has been recorded, which may not accurately reflect reality. It may be that essential details have been recorded in free text in the patient record or recorded using different codes than would be expected, and therefore levels of care received by patients may be higher than it appears for items of care that are more complex for GPs to code accurately.

5.5.3 Conclusion

CPRD GOLD appears representative of Wales in terms of recording of COPD primary care. England, Scotland, and Northern Ireland appear significantly worse than Wales at confirming airways obstruction in patients with COPD and referring them to pulmonary rehabilitation. It is possible that national audit in Wales is leading to improvements in delivery, or at the very least, improvements in the recording of care that are not being seen in the countries without national audits. This highlights the importance of audits such as the NACAP primary care audit for improving quality of care and the recording of that care for benchmarking and future improvement.

Chapter 6. Does the COPD Best Practice Tariff improve patient outcomes?

6.1 Background

Having investigated quality of COPD care in primary care, in this chapter I move on to the secondary care stream of my thesis and assess whether financial incentivisation in secondary care improves patient outcomes in AECOPD hospital admissions. Results from this chapter have been published in Thorax(159).

In England, optimal care of AECOPD hospital admissions is incentivised through the COPD Best Practice Tariff (BPT), which encourages best practice by paying care providers an additional amount for AECOPD admissions that are:

1. reviewed by a respiratory specialist within 24 hours of admission ***and***
2. receive a discharge care bundle (a group of evidence-based interventions(160)) before the patient leaves hospital.

An example of a discharge care bundle is the British Thoracic Society (BTS) COPD Discharge Care Bundle, which comprises(41):

- a review of medication and check of inhaler technique
- provision of a self-management plan and emergency drug pack, where appropriate
- an offer of support to achieve smoking cessation
- an assessment and referral for pulmonary rehabilitation
- arrangement of follow-up

The specific aim of the BTS COPD discharge bundle is to improve patient self-management and post-discharge care in order to reduce COPD readmissions. Each intervention of the bundle was chosen based on evidence that it improves outcomes for patients with COPD(42): inhalers are often used incorrectly(42,43) and assessing technique provides an opportunity to ensure patients are maximising the benefit from their medication; self-management education is associated with a reduction in admissions(42,44) and allows patients to feel more in control of their condition; smoking cessation is a cost-effective intervention(42,45) associated with reduced decline in lung function(18,42,46,47); pulmonary rehabilitation is associated with improvements in exercise capacity, quality of life(42,48) and hospital admissions(42,49); and follow-up was included to assess

whether patients may require readmission as 50% of readmissions occur during the 38 days following discharge(42,50). Whilst each of the elements of the care bundle have been extensively investigated and shown to improve a number of different outcomes, fewer studies have evaluated the COPD discharge bundle as a whole(51).

Meeting the requirements of the COPD BPT is assessed at NHS trust level, based on admissions recorded in the NACAP secondary care clinical audit. If 60% of audited patients with a primary diagnosis of AECOPD receive the two components of the COPD BPT, the trust will receive the additional payment for all AECOPD admissions. If the 60% target is not met, the trust will not receive the additional payment for any AECOPD admissions(161–164). The COPD BPT is only applied in England and approximately 40% of English trusts have negotiated an alternative payment system of block contracting meaning that the COPT BPT does not apply to them.

Review by a multi-disciplinary respiratory specialist improves the quality of care received by patients(165) and may lead to a reduction in mortality and length of hospital stay(164,166). There is also weak evidence that discharge bundles reduce readmissions(167). However, data suggest that discharge bundles are not always effectively implemented(51). Data from the 2014 COPD audit revealed that only 57% of AECOPD admissions were reviewed by a respiratory specialist(165) and only 69% of healthcare providers used discharge bundles(168). The COPD BPT aims to increase receipt of these two items of care in AECOPD admissions(163). However, to date there has been no investigation of whether implementing the two COPD BPT criteria together improves AECOPD admission outcomes. Therefore, in this chapter I use NACAP secondary care national clinical audit data to determine if people admitted for AECOPD who receive both COPD BPT criteria, have fewer readmissions and lower mortality than those who do not receive both COPD BPT criteria.

6.2 Aim

In this chapter I aim to determine if the combination of specialist review and discharge bundle that the COPD BPT seeks to incentivise improves mortality and readmission. It should be noted that this is not the same as assessing the 60% target used by the COPD BPT to determine delivery of the top-up payment. However, this evaluates whether the incentivised combination of specialist review and discharge bundle improves the key patient outcomes of mortality and readmission. If I were instead to compare trusts that met and did not meet the 60% target in an ecological-type analysis, there would be admissions that both did and did not meet the BPT criteria in both the ≥60% and <60% groups. This would make it harder to determine if it were truly the BPT criteria having an impact on

patient outcomes and therefore this method has not been used in to assess the efficacy of the COPD BPT.

6.3 Methods

6.3.1 Database/population

Data from the NACAP COPD secondary care clinical audit outcomes report (linked 2017 COPD secondary care clinical audit and HES/PEDW admissions data and ONS mortality data) were used in this chapter's analyses (see **3.2.2.2** for detailed description of the dataset).

6.3.2 Variables

The exposure variable was conforming to the COPD Best Practice Tariff (BPT). An admission was considered to have conformed to the BPT if a patient received a respiratory specialist review ≤24 hours after admission *and* a COPD discharge bundle at or before discharge. The nature of that discharge bundle was left to the individual trusts. Admissions where a patient was not reviewed by a respiratory specialist were included in the same category as admissions that received a respiratory specialist review >24 hours after admission. Admissions where 'not clear' was the chosen response to 'Has a BTS, or equivalent, discharge bundle been completed for this admission?' were considered to have not received a discharge bundle. The two components of the COPD BPT (specialist review within 24 hours and discharge bundle) were also considered separately as individual exposures in a secondary analysis.

The outcomes of admissions that were examined were 30-day mortality and 30-day readmissions. The patient was considered to have died within 30 days of admission if there was an ONS death record <30 days after their admission date (as inpatient deaths were excluded this means the definition of 30-day mortality represents a variable period after discharge dependent on the length of stay). The outcomes data only provides 30-day mortality in a binary format (yes/no patient died within 30 days of admission) therefore it is not possible to calculate 30-day post-discharge mortality. The patient was considered to have been readmitted within 30 days of discharge if there was a HES APC or PEDW admission record for any type of emergency hospital admission <30 days after discharge.

Potential confounders used were age, sex, socioeconomic status (SES), oxygen needed during admission, non-invasive ventilation (NIV) administered during admission, length of stay, smoking status, Charlson comorbidity index (CCI)(169), and a history of mental illness. Respiratory specialist review was included as an additional confounder in analyses of the COPD discharge bundle as I hypothesised that individuals that received specialist review were more likely to receive a discharge

bundle. SES was defined using quintile of IMD or WIMD. Length of stay was split into quintile of number of days between admission and discharge. Smoking status was coded as current, ex, never, or not recorded. CCI was calculated using ICD-10 codes defined by Quan et al.(169,170) (**Appendix K**). All patients were assumed to have a CCI of at least 1 as they were admitted for AECOPD. Age was excluded from the CCI as it was used individually as a covariate. Mental health diagnoses were categorised as no mental illness, mild/moderate mental illness, or severe mental illness. Mild/moderate mental illness was classified as a secondary admission diagnosis of either depression or anxiety. Severe mental illness was classified as a secondary admission diagnosis of any schizophrenia, bipolar or other psychotic disorders (see **Appendix L** for mental illness ICD-10 codes).

Patients that died during their admission or self-discharged were excluded from analyses as these patients would not have been able to receive a discharge bundle and the admission therefore could not possibly have conformed to the BPT. Patients with 'other' as the response to whether they received a discharge bundle or not were also excluded from analyses.

6.3.3 Statistical analysis

All data management and statistical analyses were performed using Stata 15 (StataCorp, College Station, TX, USA). Data were first summarised using means and proportions where appropriate. Pearson's X^2 test was used to test for differences in categorical patient demographics and outcomes between exposure groups. The independent samples t-test was used to test for differences in age between the exposure groups.

To account for clustering of patients within hospitals, mixed-effects logistic regression (*xtlogit* command, *re* option) was used to investigate association between an admission conforming to the BPT and 30-day mortality and readmission, with a random intercept for hospital. Odds ratios with 95% confidence intervals were generated for each outcome. After univariate analysis, regression models were adjusted by including the potential confounders described above as covariates in the model.

A secondary analysis was performed using specialist review within 24 hours and receipt of a discharge bundle as the independent variable in place of conformation to the BPT to test the specific components of the BPT. Additionally, the components of the specialist review within 24 hours variable were tested:

- patients who received a specialist review relative to those who did not
- patients who received a specialist review in ≤24 hours relative to those who received a review in >24 hours (for patients who received a review)

Missing data were minimal (<5%) for variables included in regression models and where data were missing, complete case analysis was used. Odds ratio graphs were generated using *coefplot*(141).

6.3.3.1 Sensitivity analyses

The discharge bundle analysis was repeated excluding 'not clear' responses to the 'Has a BTS, or equivalent, discharge bundle been completed for this admission?' audit question to determine if there was a strengthening of the effect of a discharge bundle on outcomes if it was known for certain whether a patient received a bundle or not. The specialist review analyses were also repeated using the full audit cohort (including patients who died as an inpatient or self-discharged) to determine if specialist review was associated with inpatient mortality. Additionally, the analysis was repeated using 90-day mortality and 90-day readmissions as the outcomes to determine if the benefits of the COPD BPT were not detectable until sufficient time had passed for all elements of the discharge bundle to be completed (such as smoking cessation and pulmonary rehabilitation). Finally, the primary analysis was also run excluding Welsh hospitals, as these are not eligible to participate in the BPT, to see if there was any change in patient outcomes.

6.4 Results

After exclusion of patients who self-discharged (n=465 [0.5%]), died during admission (n=1213 [4.0%]), or had 'other' as the response for whether they received a discharge bundle (n=571 [1.9%]), the final analysed cohort in this study comprised 28,345 patients (only first admissions in the audit period were included) from 181 hospitals.

6.4.1 COPD BPT conforming admissions

37% of admissions conformed to the BPT (**Table 16**). BPT conforming admissions, compared with admissions not meeting the BPT, were more frequently prescribed oxygen (60.9% vs. 51.3%), had more NIV administered (11.4% vs. 7.6%; p<0.001), had fewer hospital stays of 0-1 days (24.5% vs. 27.4%), more patients with smoking status recorded (95.6% vs. 87.7%), more patients with a Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) score recorded (26.5% vs. 6.4%), and more patients with spirometry results available (46.0% vs. 32.9%).

In mixed-effects logistic regression analysis, no significant difference in 30-day mortality (OR: 1.09 [95% CI: 0.92 – 1.29]) and 30-day readmission (OR: 0.96 [95% CI: 0.90 – 1.02]) was found between admissions that conformed to the BPT and admissions that did not conform (**Figure 13**/**Table 17**).

Table 16. *Demographics and outcomes for AECOPD admissions that did and did not conform to the COPD Best Practice Tariff (BPT) (receipt of a respiratory specialist review within 24 hours of admission and a discharge bundle). N=28,345*

	Admission conformed to BPT ***N = 10,530***		**Admission did *not* conform to BPT** ***N = 17,815***		***p*-value***
	n	**(%)**	**n**	**(%)**	
Age (years)					
Mean (SD)	71.5	(10.3)	72.5	(11.0)	<0.001
Gender					0.574
Male	4,895	(46.5%)	8,343	(46.8%)	
Female	5,635	(53.5%)	9,472	(53.2%)	
Quintile of IMD/WIMD					0.631
1 (most deprived)	3,485	(33.1%)	5,768	(32.4%)	
2	2,509	(23.8%)	4,254	(23.9%)	
3	1,894	(18.0%)	3,337	(18.7%)	
4	1,492	(14.2%)	2,510	(14.1%)	
5 (least deprived)	1,058	(10.1%)	1,778	(10.0%)	
No data	92	(0.9%)	168	(0.9%)	
Oxygen prescription					<0.001
Not needed	1,773	(16.8%)	3,579	(20.1%)	
Not prescribed	2,341	(22.2%)	5,098	(28.6%)	
Prescribed	6,416	(60.9%)	9,138	(51.3%)	
NIV administered	1,201	(11.4%)	1,354	(7.6%)	<0.001
Length of stay quintile					<0.001
0-1 days	2,581	(24.5%)	4,875	(27.4%)	
2-3 days	2,581	(24.5%)	4,290	(24.1%)	
4-5 days	1,770	(16.8%)	2,878	(16.2%)	
6-8 days	1,685	(16.0%)	2,471	(13.9%)	
9+ days	1,913	(18.2%)	3,301	(18.5%)	
Smoking status					<0.001
Never smoked	256	(2.4%)	732	(4.1%)	
Ex-smoker	6,236	(59.2%)	9,559	(53.7%)	
Current smoker	3,586	(34.1%)	5,335	(30.0%)	
Not recorded	452	(4.3%)	2,189	(12.3%)	

Charlson Comorbidity Index					<0.001
1	5,330	(50.6%)	8,305	(46.6%)	
2	2,598	(24.7%)	4,510	(25.3%)	
3	1,383	(13.1%)	2,457	(13.8%)	
4	662	(6.3%)	1,267	(7.1%)	
5	313	(3.0%)	670	(3.8%)	
6	107	(1.0%)	273	(1.5%)	
7+	137	(1.3%)	333	(1.9%)	
Mental health diagnoses					0.002
No mental illness	8,309	(78.9%)	14,347	(80.5%)	
Mild/moderate mental illness	1,547	(14.7%)	2,366	(13.3%)	
Severe mental illness	674	(6.4%)	1,102	(6.2%)	
DECAF score					<0.001
Low risk (0-1)	1,650	(15.7%)	568	(3.2%)	
Intermediate risk (2)	677	(6.4%)	330	(1.9%)	
High risk (3-6)	468	(4.4%)	237	(1.3%)	
No data	7,735	(73.5%)	16,680	(93.6%)	
Spirometry: FEV_1/FVC ratio					<0.001
≥ 0.7	507	(4.8%)	866	(4.9%)	
< 0.7	4,253	(40.4%)	4,884	(27.4%)	
Invalid (< 0.2 or > 1.0)	83	(0.8%)	115	(0.7%)	
No data	5,687	(54.0%)	11,950	(67.1%)	
Patient died within 30 days of admission	285	(2.7%)	461	(2.6%)	0.546
Patient was readmitted within 30 days of discharge	2,659	(25.3%)	4,577	(25.7%)	0.411

*X^2 test for categorical variables, independent samples t-test for age.

Abbreviations: AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; BPT: best practice tariff; SD: standard deviation; IMD: English Index of Multiple Deprivation; WIMD: Welsh Index of Multiple Deprivation; DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; NIV: non-invasive ventilation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

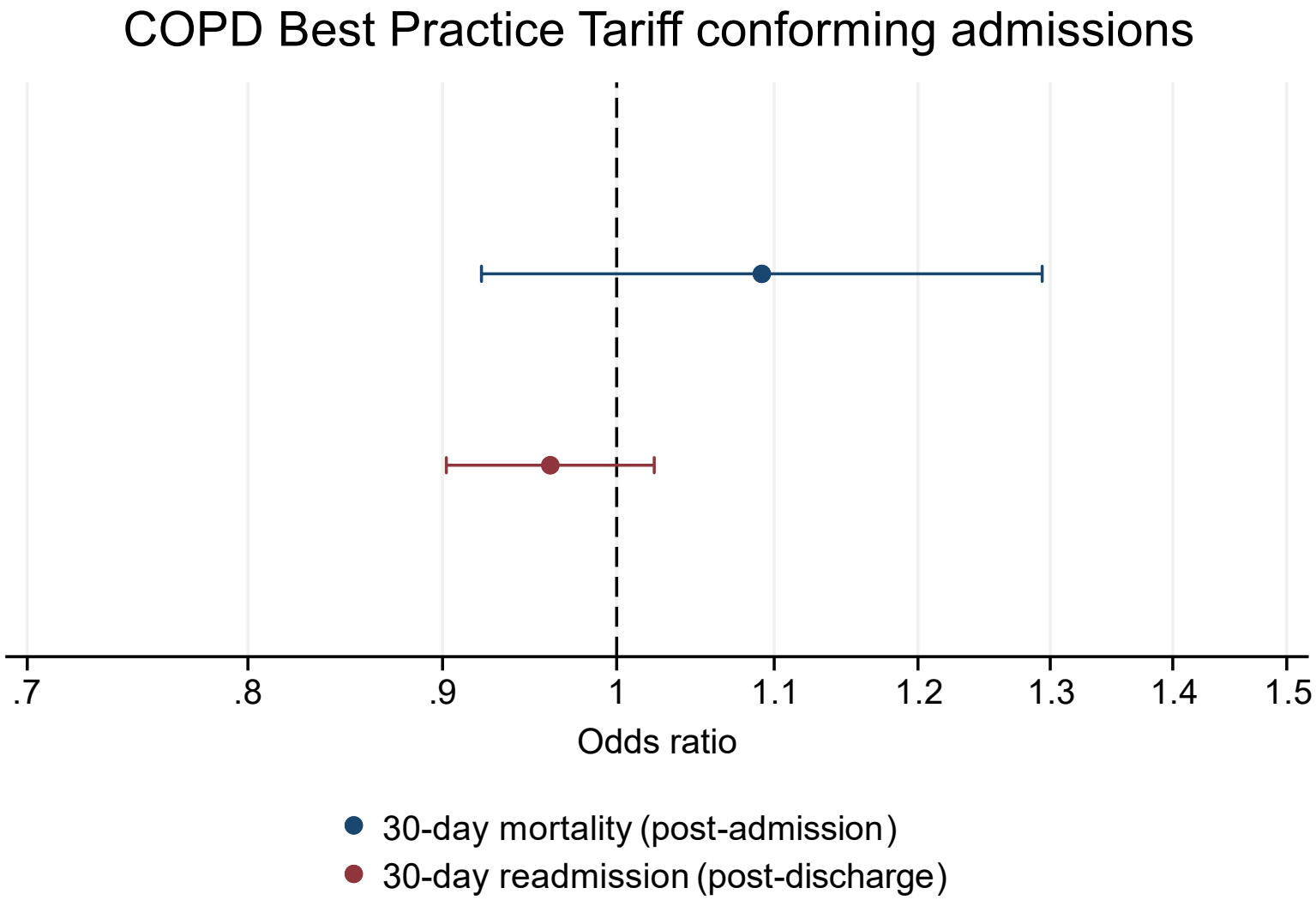

Figure 13. *Forest plot of adjusted odds ratios and 95% confidence intervals for 30-day mortality and 30-day readmission in admissions that conformed to the Best Practice Tariff (BPT) relative to those that did not. Values less than 1 favour conforming the BPT; values greater than 1 favour not conforming to the BPT.*

Table 17. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that conformed to the COPD Best Practice Tariff (BPT) relative to those that did not*

BPT admission outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	1.00 (0.85 – 1.18)	1.09 (0.92 – 1.29)
Death within 90 days of admission	1.02 (0.92 – 1.12)	1.10 (0.99 – 1.22)
Readmission within 30 days of discharge	0.96 (0.90 – 1.02)	0.96 (0.90 – 1.02)
Readmission within 90 days of discharge	1.01 (0.96 – 1.07)	1.04 (0.98 – 1.10)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; BPT: Best Practice Tariff; CI: confidence interval.

6.4.2 The COPD BPT components

6.4.2.1 Respiratory specialist review

53% of admissions were reviewed by a respiratory specialist within 24 hours (**Table 18**). Patients that received a respiratory specialist review within 24 hours, compared with patients who did not receive a respiratory specialist review or received a review in >24 hours, were slightly younger on average (71.3 vs 73.0 years; p<0.001), had more prescribed oxygen (59.5% vs. 49.6%), more NIV administered (11.7% vs. 6.0%; p<0.001), more smoking status recorded (93.9% vs 87.0%), more records of DECAF score (19.7% vs. 7.3%), and more spirometry results available (43.5% vs. 31.3%) (**Table 18**).

Table 18. *Demographics and outcomes for AECOPD admissions that received a respiratory specialist review within 24 hours and those that did not. N=28,345*

	Patient reviewed within 24 hours of admission ***N = 14,991***		**Patient *not* reviewed or reviewed in >24 hours** ***N = 13,354***		***p*-value***
	n	**(%)**	**n**	**(%)**	
Age (years)					
Mean (SD)	71.3	(10.5)	73.0	(11.0)	<0.001
Gender					0.138
Male	6,939	(46.3%)	6,299	(47.2%)	
Female	8,052	(53.7%)	7,055	(52.8%)	
Quintile of IMD/WIMD					0.003
1 (most deprived)	5,049	(33.7%)	4,204	(31.5%)	
2	3,573	(23.8%)	3,190	(23.9%)	
3	2,688	(17.9%)	2,543	(19.0%)	
4	2,074	(13.8%)	1,928	(14.4%)	
5 (least deprived)	1,473	(9.8%)	1,363	(10.2%)	
No data	134	(0.9%)	126	(0.9%)	
Oxygen prescription					<0.001
Not needed	2,642	(17.6%)	2,710	(20.3%)	
Not prescribed	3,424	(22.8%)	4,015	(30.1%)	
Prescribed	8,925	(59.5%)	6,629	(49.6%)	
NIV administered	1,754	(11.7%)	801	(6.0%)	<0.001
Length of stay quintile					<0.001
0-1 days	3,877	(25.9%)	3,579	(26.8%)	
2-3 days	3,699	(24.7%)	3,172	(23.8%)	
4-5 days	2,475	(16.5%)	2,173	(16.3%)	
6-8 days	2,301	(15.4%)	1,855	(13.9%)	
9+ days	2,639	(17.6%)	2,575	(19.3%)	
Smoking status					<0.001
Never smoked	430	(2.9%)	558	(4.2%)	
Ex-smoker	8,596	(57.3%)	7,199	(53.9%)	
Current smoker	5,058	(33.7%)	3,863	(28.9%)	
Not recorded	907	(6.1%)	1,734	(13.0%)	

Charlson Comorbidity Index					<0.001
1	7,630	(50.9%)	6,005	(45.0%)	
2	3,677	(24.5%)	3,431	(25.7%)	
3	1,936	(12.9%)	1,904	(14.3%)	
4	929	(6.2%)	1,000	(7.5%)	
5	462	(3.1%)	521	(3.9%)	
6	159	(1.1%)	221	(1.7%)	
7+	198	(1.3%)	272	(2.0%)	
Mental health diagnoses					0.001
No mental illness	11,859	(79.1%)	10,797	(80.9%)	
Mild/moderate mental illness	2,176	(14.5%)	1,737	(13.0%)	
Severe mental illness	956	(6.4%)	820	(6.1%)	
DECAF score					<0.001
Low risk (0-1)	1,729	(11.5%)	489	(3.7%)	
Intermediate risk (2)	733	(4.9%)	274	(2.1%)	
High risk (3-6)	494	(3.3%)	211	(1.6%)	
No data	12,035	(80.3%)	12,380	(92.7%)	
Spirometry: FEV_1/FVC ratio					<0.001
≥ 0.7	751	(5.0%)	622	(4.7%)	
< 0.7	5,666	(37.8%)	3,471	(26.0%)	
Invalid (< 0.2 or > 1.0)	111	(0.7%)	87	(0.7%)	
No data	8,463	(56.5%)	9,174	(68.7%)	
Patient died within 30 days of admission	401	(2.7%)	345	(2.6%)	0.631
Patient was readmitted within 30 days of discharge	3,763	(25.1%)	3,473	(26.0%)	0.081

*X^2 test for categorical variables, independent samples t-test for age.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; SD: standard deviation; IMD: English Index of Multiple Deprivation; WIMD: Welsh Index of Multiple Deprivation; DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; NIV: non-invasive ventilation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

24% of patients did not receive a respiratory specialist review at all (**Table 19**). Of the 76% of patients who did receive a review, 69% were within 24 hours of admission, meaning that 31% of reviewed patients had to wait more than 24 hours for a review (**Table 20**). Patients who received a respiratory specialist review, compared with patients who did not receive a specialist review at all, had more prescribed oxygen (59.7% vs. 39.2%), more NIV administered (11.3% vs.1.7%; $p<0.001$), fewer hospital stays of 0-1 days (19.5% vs. 48.4%), more hospital stays of 9 or more days (20.9% vs. 10.4%), more smoking status recorded (93.5% vs. 81.4%), more DECAF score recorded (17.7% vs. 1.5%), and more spirometry results recorded (41.7% vs. 24.9%) (**Table 19**). Patients who received a respiratory specialist review within 24 hours of admission, compared with patients who received a specialist review in >24 hours of admission, had more hospital stays of 0-1 days (25.9% vs. 5.2%) and fewer hospital stays of 9 or more days (17.6% vs. 28.2%) (**Table 20**).

In mixed-effects logistic regression analysis, there was no significant difference in 30-day mortality or 30-day readmission between admissions that were reviewed by a respiratory specialist within 24 hours and those that were not reviewed or reviewed in >24 hours (**Figure 14a**/**Table 21**). There was also no significant difference in 30-day mortality or 30-day readmission between patients who did and did not receive a specialist review (**Figure 14b**/**Table 22**) and no significant difference in either outcome between patients who received a review within 24 hours and those who received a review in >24 hours (**Figure 14c**/**Table 23**).

Table 19. *Demographics and outcomes for AECOPD admissions that received a respiratory specialist review and those that did not. N=28,345*

	Patient received a respiratory specialist review ***N = 21,666***		**Patient did *not* receive a respiratory specialist review** ***N = 6,679***		**p-value***
	n	**(%)**	**n**	**(%)**	
Age (years)					
Mean (SD)	71.8	(10.5)	73.2	(11.3)	<0.0001
Gender					<0.001
Male	9,962	(46.0%)	3,276	(49.1%)	
Female	11,704	(54.0%)	3,403	(51.0%)	
Quintile of IMD/WIMD					0.832
1 (most deprived)	7,087	(32.7%)	2,166	(32.4%)	
2	5,187	(23.9%)	1,576	(23.6%)	
3	3,979	(18.4%)	1,252	(18.8%)	
4	3,033	(14.0%)	969	(14.5%)	
5 (least deprived)	2,182	(10.1%)	654	(9.8%)	
No data	198	(0.9%)	62	(0.9%)	
Oxygen prescription					<0.001
Not needed	3,664	(16.9%)	1,688	(25.3%)	
Not prescribed	5,069	(23.4%)	2,370	(35.5%)	
Prescribed	12,933	(59.7%)	2,621	(39.2%)	
NIV administered	2,443	(11.3%)	112	(1.7%)	<0.001
Length of stay quintile					<0.001
0-1 days	4,225	(19.5%)	3,231	(48.4%)	
2-3 days	5,359	(24.7%)	1,512	(22.6%)	
4-5 days	3,961	(18.3%)	687	(10.3%)	
6-8 days	3,601	(16.6%)	555	(8.3%)	
9+ days	4,520	(20.9%)	694	(10.4%)	
Smoking status					<0.001
Never smoked	643	(3.0%)	345	(5.2%)	
Ex-smoker	12,540	(57.9%)	3,255	(48.7%)	
Current smoker	7,084	(32.7%)	1,837	(27.5%)	
Not recorded	1,399	(6.5%)	1,242	(18.6%)	

Charlson Comorbidity Index					<0.001
1	10,660	(49.2%)	2,975	(44.5%)	
2	5,431	(25.1%)	1,677	(25.1%)	
3	2,894	(13.4%)	946	(14.2%)	
4	1,382	(6.4%)	547	(8.2%)	
5	707	(3.3%)	276	(4.1%)	
6	272	(1.3%)	108	(1.6%)	
7+	320	(1.5%)	150	(2.3%)	
Mental health diagnoses					<0.001
No mental illness	17,185	(79.3%)	5,471	(81.9%)	
Mild/moderate mental illness	3,100	(14.3%)	813	(12.2%)	
Severe mental illness	1,381	(6.4%)	395	(5.9%)	
DECAF score					<0.001
Low risk (0-1)	2,167	(10.0%)	51	(0.8%)	
Intermediate risk (2)	980	(4.5%)	27	(0.4%)	
High risk (3-6)	683	(3.2%)	22	(0.3%)	
No data	17,836	(82.3%)	6,579	(98.5%)	
Spirometry: FEV_1/FVC ratio					<0.001
≥ 0.7	1,093	(5.0%)	280	(4.2%)	
< 0.7	7,787	(35.9%)	1,350	(20.2%)	
Invalid (< 0.2 or > 1.0)	166	(0.8%)	32	(0.5%)	
No data	12,620	(58.3%)	5,017	(75.1%)	
Patient died within 30 days of admission	583	(2.7%)	163	(2.4%)	0.264
Patient was readmitted within 30 days of discharge	5,609	(25.9%)	1,627	(24.4%)	0.012

*X^2 test for categorical variables, independent samples t-test for age.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; SD: standard deviation; IMD: English Index of Multiple Deprivation; WIMD: Welsh Index of Multiple Deprivation; DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; NIV: non-invasive ventilation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

Table 20. *Demographics and outcomes for AECOPD admissions that received a respiratory specialist review within 24 hours and those that received a respiratory specialist >24 hours after admission. N=21,666*

	Patient reviewed in ≤24 hours of admission ***N = 14,991***		**Patient reviewed in >24 hours of admission** ***N = 6,675***		**p-value***
	n	**(%)**	**n**	**(%)**	
Age (years)					
Mean (SD)	71.3	(10.5)	72.8	(10.6)	<0.001
Gender					0.173
Male	6,939	(46.3%)	3,023	(45.3%)	
Female	8,052	(53.7%)	3,652	(54.7%)	
Quintile of IMD/WIMD					0.005
1 (most deprived)	5,049	(33.7%)	2,038	(30.8%)	
2	3,573	(23.8%)	1,614	(24.4%)	
3	2,688	(17.9%)	1,291	(19.5%)	
4	2,074	(13.8%)	959	(14.5%)	
5 (least deprived)	1,473	(9.8%)	709	(10.7%)	
No data	134	(0.9%)	64	(1.0%)	
Oxygen prescription					<0.001
Not needed	2,642	(17.6%)	1,022	(15.3%)	
Not prescribed	3,424	(22.8%)	1,645	(24.6%)	
Prescribed	8,925	(59.5%)	4,008	(60.0%)	
NIV administered	1,754	(11.7%)	689	(10.3%)	0.003
Length of stay quintile					<0.001
0-1 days	3,877	(25.9%)	348	(5.2%)	
2-3 days	3,699	(24.7%)	1,660	(24.9%)	
4-5 days	2,475	(16.5%)	1,486	(22.3%)	
6-8 days	2,301	(15.4%)	1,300	(19.5%)	
9+ days	2,639	(17.6%)	1,881	(28.2%)	
Smoking status					<0.001
Never smoked	430	(2.9%)	213	(3.2%)	
Ex-smoker	8,596	(57.3%)	3,944	(59.1%)	
Current smoker	5,058	(33.7%)	2,026	(30.4%)	
Not recorded	907	(6.1%)	492	(7.4%)	

Charlson Comorbidity Index					<0.001
1	7,630	(50.9%)	3,030	(45.4%)	
2	3,677	(24.5%)	1,754	(26.3%)	
3	1,936	(12.9%)	958	(14.4%)	
4	929	(6.2%)	453	(6.8%)	
5	462	(3.1%)	245	(3.7%)	
6	159	(1.1%)	113	(1.7%)	
7+	198	(1.3%)	122	(1.8%)	
Mental health diagnoses					0.42
No mental illness	11,859	(79.1%)	5,326	(79.8%)	
Mild/moderate mental illness	2,176	(14.5%)	924	(13.8%)	
Severe mental illness	956	(6.4%)	425	(6.4%)	
DECAF score					<0.001
Low risk (0-1)	1,729	(11.5%)	438	(6.6%)	
Intermediate risk (2)	733	(4.9%)	247	(3.7%)	
High risk (3-6)	494	(3.3%)	189	(2.8%)	
No data	12,035	(80.3%)	5,801	(86.9%)	
Spirometry: FEV_1/FVC ratio					<0.001
≥ 0.7	751	(5.0%)	342	(5.1%)	
< 0.7	5,666	(37.8%)	2,121	(31.8%)	
Invalid (< 0.2 or > 1.0)	111	(0.7%)	55	(0.8%)	
No data	8,463	(56.5%)	4,157	(62.3%)	
Patient died within 30 days of admission	401	(2.7%)	182	(2.7%)	0.828
Patient was readmitted within 30 days of discharge	3,763	(25.1%)	1,846	(27.7%)	<0.001

*X^2 test for categorical variables, independent samples t-test for age.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; SD: standard deviation; IMD: English Index of Multiple Deprivation; WIMD: Welsh Index of Multiple Deprivation; DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; NIV: non-invasive ventilation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

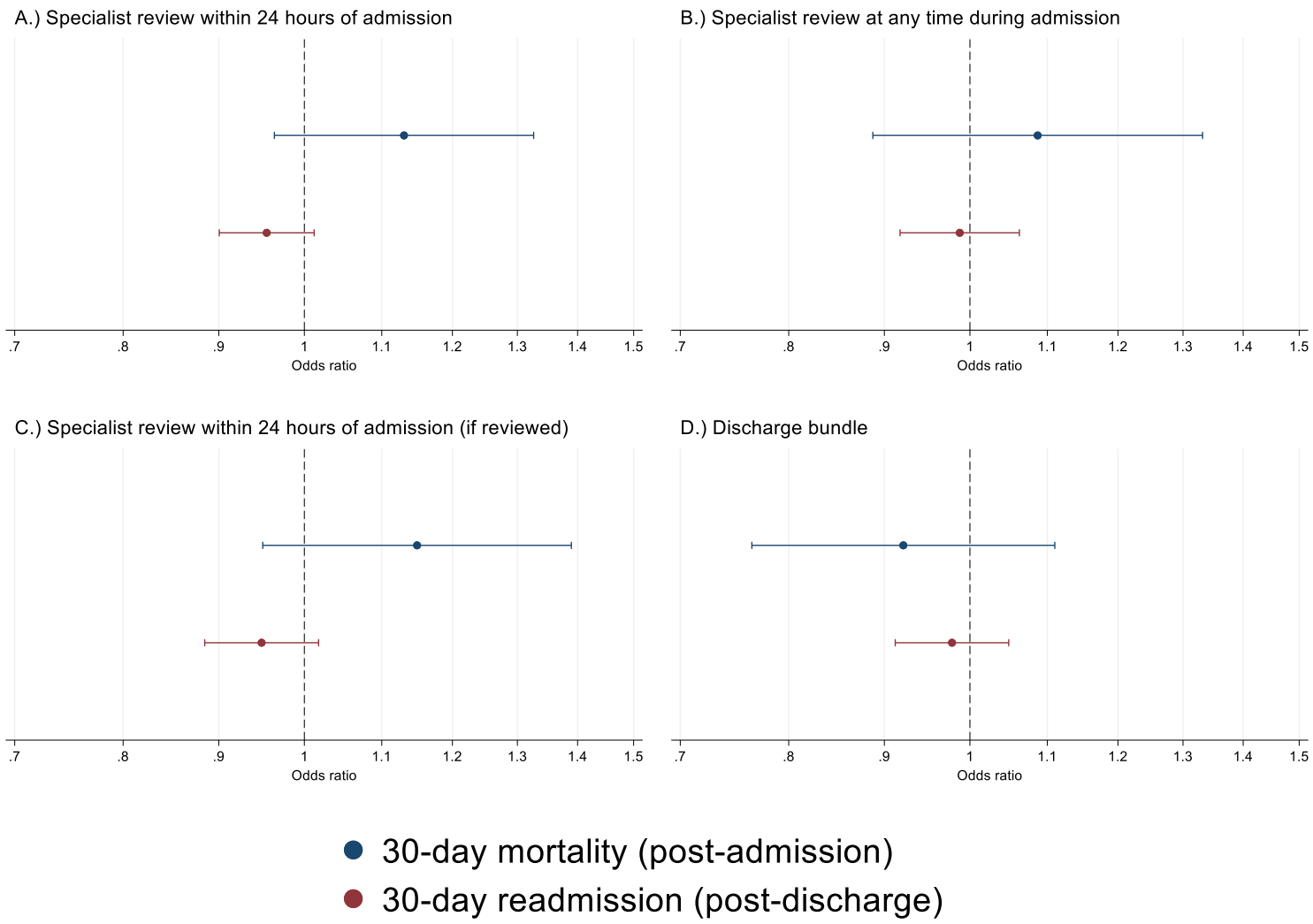

Figure 14. *Forest plot of adjusted odds ratios and 95% confidence intervals for 30-day mortality and 30-day readmission in:* ***A.)*** *admissions that received a respiratory specialist review within 24 hours relative to those that did not receive a review or received a review in >24 hours;* ***B.)*** *admissions that received a respiratory specialist review relative to those that did not;* ***C.)*** *admissions that received a respiratory specialist review in ≤24 hours relative to those that received a respiratory specialist review in >24 hours;* ***D.)*** *admissions that received a discharge bundle relative to those that did not. Values less than 1 favour the intervention; values greater than 1 favour not receiving the intervention.*

Table 21. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that received a respiratory specialist review within 24 hours relative to those that did not receive a review or received a review in >24 hours*

Review in 24 hours outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	1.02 (0.87 – 1.19)	1.13 (0.96 – 1.33)
Death within 90 days of admission	1.05 (0.95 – 1.15)	**1.16 (1.05 – 1.28)**
Readmission within 30 days of discharge	**0.94 (0.89 – 1.00)**	0.95 (0.90 – 1.01)
Readmission within 90 days of discharge	0.99 (0.94 – 1.04)	1.02 (0.97 – 1.08)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval.

Table 22. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that received a respiratory specialist review relative to those that did not receive a review*

Received specialist review outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	1.11 (0.92 – 1.33)	1.09 (0.89 – 1.33)
Death within 90 days of admission	**1.30 (1.16 – 1.46)**	**1.20 (1.06 – 1.36)**
Readmission within 30 days of discharge	**1.10 (1.03 – 1.17)**	0.99 (0.92 – 1.06)
Readmission within 90 days of discharge	**1.10 (1.04 – 1.17)**	1.04 (0.98 – 1.11)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval.

Table 23. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that received a respiratory specialist review within 24 hours relative to those that received a respiratory specialist review in >24 hours*

Time to specialist review outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	0.96 (0.80 – 1.15)	1.14 (0.95 – 1.39)
Death within 90 days of admission	0.91 (0.82 – 1.01)	**1.13 (1.01 – 1.26)**
Readmission within 30 days of discharge	**0.87 (0.82 – 0.93)**	0.95 (0.88 – 1.02)
Readmission within 90 days of discharge	**0.93 (0.88 – 0.99)**	1.00 (0.94 – 1.07)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval.

6.4.2.2 COPD discharge care bundle

54% of admissions received a discharge bundle (**Table 24**). Patients who received a discharge bundle, compared with patients who did not receive a discharge bundle, had more prescribed oxygen (60.1% vs. 48.8%), more NIV administered (10.5% vs. 7.3%; p<0.001), fewer hospital stays of 0-1 days (20.2% vs. 33.5%), more hospital stays of 9 or more days (20.6% vs. 15.8%), more smoking status recorded (95.2% vs. 85.4%), more DECAF score recorded (24.1% vs. 1.9%), and more spirometry results available (44.1% vs. 30.4%) (**Table 24**).

In mixed-effects logistic regression analysis, there was no significant difference in 30-day mortality or 30-day readmission between admissions that received a discharge bundle and those that did not receive a discharge bundle (**Figure 14d/Table 25**).

Table 24. *Demographics and outcomes for AECOPD admissions that received a discharge bundle and those that did not. N=28,345*

	Patient received a discharge bundle at or before discharge ***N = 15,261***		**Patient did *not* receive a discharge bundle** ***N = 13,084***		***p*-value***
	n	**(%)**	**n**	**(%)**	
Age (years)					
Mean (SD)	71.9	(10.3)	72.4	(11.2)	0.001
Gender					0.061
Male	7,049	(46.2%)	6,189	(47.3%)	
Female	8,212	(53.8%)	6,895	(52.7%)	
Quintile of IMD/WIMD					0.064
1 (most deprived)	4,946	(32.4%)	4,307	(32.9%)	
2	3,637	(23.8%)	3,126	(23.9%)	
3	2,755	(18.1%)	2,476	(18.9%)	
4	2,208	(14.5%)	1,794	(13.7%)	
5 (least deprived)	1,579	(10.4%)	1,257	(9.6%)	
No data	136	(0.9%)	124	(1.0%)	
Oxygen prescription					<0.001
Not needed	2,557	(16.8%)	2,795	(21.4%)	
Not prescribed	3,540	(23.2%)	3,899	(29.8%)	
Prescribed	9,164	(60.1%)	6,390	(48.8%)	
NIV administered	1,598	(10.5%)	957	(7.3%)	<0.001
Length of stay quintile					<0.001
0-1 days	3,078	(20.2%)	4,378	(33.5%)	
2-3 days	3,756	(24.6%)	3,115	(23.8%)	
4-5 days	2,761	(18.1%)	1,887	(14.4%)	
6-8 days	2,520	(16.5%)	1,636	(12.5%)	
9+ days	3,146	(20.6%)	2,068	(15.8%)	
Smoking status					<0.001
Never smoked	396	(2.6%)	592	(4.5%)	
Ex-smoker	9,079	(59.5%)	6,716	(51.3%)	
Current smoker	5,061	(33.2%)	3,860	(29.5%)	
Not recorded	725	(4.8%)	1,916	(14.6%)	

Charlson Comorbidity Index					<0.001
1	7,472	(49.0%)	6,163	(47.1%)	
2	3,843	(25.2%)	3,265	(25.0%)	
3	2,061	(13.5%)	1,779	(13.6%)	
4	1,005	(6.6%)	924	(7.1%)	
5	479	(3.1%)	504	(3.9%)	
6	188	(1.2%)	192	(1.5%)	
7+	213	(1.4%)	257	(2.0%)	
Mental health diagnoses					0.001
No mental illness	12,079	(79.2%)	10,577	(80.8%)	
Mild/moderate mental illness	2,216	(14.5%)	1,697	(13.0%)	
Severe mental illness	966	(6.3%)	810	(6.2%)	
DECAF score					<0.001
Low risk (0-1)	2,090	(13.7%)	128	(1.0%)	
Intermediate risk (2)	932	(6.1%)	75	(0.6%)	
High risk (3-6)	660	(4.3%)	45	(0.3%)	
No data	11,579	(75.9%)	12,836	(98.1%)	
Spirometry: FEV_1/FVC ratio					<0.001
≥ 0.7	742	(4.9%)	631	(4.8%)	
< 0.7	5,854	(38.4%)	3,283	(25.1%)	
Invalid (< 0.2 or > 1.0)	130	(0.9%)	68	(0.5%)	
No data	8,535	(55.9%)	9,102	(69.6%)	
Patient died within 30 days of admission	398	(2.6%)	348	(2.7%)	0.786
Patient was readmitted within 30 days of discharge	3,936	(25.8%)	3,300	(25.2%)	0.273

*X^2 test for categorical variables, independent samples t-test for age.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; SD: standard deviation; IMD: English Index of Multiple Deprivation; WIMD: Welsh Index of Multiple Deprivation; DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; NIV: non-invasive ventilation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

Table 25. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that received a discharge bundle relative to those that did not receive a discharge bundle*

Discharge bundle outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	0.93 (0.78 – 1.09)	0.92 (0.76 – 1.11)
Death within 90 days of admission	1.03 (0.93 – 1.13)	0.95 (0.84 – 1.06)
Readmission within 30 days of discharge	1.02 (0.96 – 1.09)	0.98 (0.91 – 1.05)
Readmission within 90 days of discharge	**1.07 (1.01 – 1.12)**	1.04 (0.97 – 1.11)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, mental health diagnoses, and respiratory specialist review.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval.

6.4.3 Sensitivity analysis

Repeating the discharge bundle analysis without 'not clear' responses made no material difference to the odds of 30-day mortality and readmission (**Table 26**).

Table 26. *Odds ratios and 95% confidence intervals for mortality and readmission in AECOPD admissions that received a discharge bundle relative to those that did not receive a discharge bundle (excluding 'not clear' responses)*

Discharge bundle outcomes	**Odds ratio (95% CI)**	**Adjusted* odds ratio (95% CI)**
Death within 30 days of admission	0.96 (0.81 – 1.14)	0.95 (0.79 – 1.16)
Death within 90 days of admission	1.07 (0.97 – 1.19)	0.99 (0.88 – 1.12)
Readmission within 30 days of discharge	1.02 (0.96 – 1.09)	0.98 (0.91 – 1.06)
Readmission within 90 days of discharge	**1.07 (1.01 – 1.13)**	1.05 (0.99 – 1.12)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, mental health diagnoses, and respiratory specialist review.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval.

Repeating the specialist review analyses including patients that died during their admission (summary statistics for the three specialist review exposure definitions are shown in **Table 27**, **Table 28**, and **Table 29**) did result in changes to the odds of 30-day mortality, however the only statistically significant result was found for patients who received a specialist review, who had 18% lower odds (OR: 0.82 [95% CI: 0.72 – 0.94]) of 30-day death than patients who did not receive a specialist review (**Table 30**). Limiting mortality to inpatient mortality only, the effect of specialist review was even stronger with patients who received a specialist review at any time during admission having 31% lower odds (OR: 0.69 [95% CI: 0.58 – 0.81]) of inpatient death (**Table 30**).

Table 27. *Demographics of and outcomes for people admitted to hospital with acute exacerbation of COPD (the full audit cohort, including patients who died as an inpatient or self-discharged) who received a respiratory specialist review within 24 hours of admission and those who did not receive a review or received a review >24 hours after admission. N=30,294*

	Patient reviewed within 24 hours of admission ***N = 15,956***		**Patient *not* reviewed or reviewed in >24 hours** ***N = 14,338***	
	n	**(%)**	**n**	**(%)**
Age (years)				
Mean (SD)	71.5	(10.5)	73.1	(11.0)
Gender				
Male	7,401	(46.4%)	6,789	(47.4%)
Female	8,555	(53.6%)	7,549	(52.7%)
Quintile of IMD/WIMD				
1 (most deprived)	5,348	(33.5%)	4,482	(31.3%)
2	3,750	(23.5%)	3,385	(23.6%)
3	2,893	(18.1%)	2,759	(19.2%)
4	2,221	(13.9%)	2,082	(14.5%)
5 (least deprived)	1,598	(10.0%)	1,493	(10.4%)
No data	146	(0.9%)	137	(1.0%)
Oxygen prescription				
Not needed	2,757	(17.3%)	2,864	(20.0%)
Not prescribed	3,588	(22.5%)	4,261	(29.7%)
Prescribed	9,611	(60.2%)	7,213	(50.3%)
NIV administered	2,028	(12.7%)	1,017	(7.1%)
Length of stay quintile				
0-1 days	4,083	(25.6%)	3,798	(26.5%)
2-3 days	3,924	(24.6%)	3,342	(23.3%)
4-5 days	2,591	(16.2%)	2,319	(16.2%)
6-8 days	2,447	(15.3%)	1,980	(13.8%)
9+ days	2,911	(18.2%)	2,899	(20.2%)
Smoking status				
Never smoked	468	(2.9%)	615	(4.3%)
Ex-smoker	9,155	(57.4%)	7,673	(53.5%)
Current smoker	5,327	(33.4%)	4,136	(28.9%)
Not recorded	1,006	(6.3%)	1,914	(13.4%)

Charlson Comorbidity Index				
1	8,039	(50.4%)	6,344	(44.3%)
2	3,915	(24.5%)	3,698	(25.8%)
3	2,076	(13.0%)	2,064	(14.4%)
4	1,012	(6.3%)	1,101	(7.7%)
5	506	(3.2%)	572	(4.0%)
6	178	(1.1%)	242	(1.7%)
7+	230	(1.4%)	317	(2.2%)
Mental health diagnoses				
No mental illness	12,614	(79.1%)	11,597	(80.9%)
Mild/moderate mental illness	2,328	(14.6%)	1,851	(12.9%)
Severe mental illness	1,014	(6.4%)	890	(6.2%)
DECAF score				
Low risk (0-1)	1,763	(11.1%)	505	(3.5%)
Intermediate risk (2)	764	(4.8%)	286	(2.0%)
High risk (3-6)	540	(3.4%)	237	(1.7%)
No data	12,889	(80.8%)	13,310	(92.8%)
Spirometry: FEV_1/FVC ratio				
≥ 0.7	797	(5.0%)	659	(4.6%)
< 0.7	6,002	(37.6%)	3,714	(25.9%)
Invalid (< 0.2 or > 1.0)	122	(0.8%)	93	(0.7%)
No data	9,035	(56.6%)	9,872	(68.9%)
Outcomes				
Patient died within 30 days of admission	923	(5.8%)	909	(6.3%)
Patient died as an inpatient	585	(3.7%)	628	(4.4%)

Abbreviations: DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IMD: English Index of Multiple Deprivation; NIV: non-invasive ventilation; SD: standard deviation; WIMD: Welsh Index of Multiple Deprivation.

Table 28. *Demographics of and outcomes for people admitted to hospital with acute exacerbation of COPD (the full audit cohort, including patients who died as an inpatient or self-discharged) who received a respiratory specialist review at any time during admission and those who did not receive a review at any point during admission. N=30,294*

	Patient received a respiratory specialist review ***N = 23,113***		**Patient did *not* receive a respiratory specialist review** ***N = 7,181***	
	n	**(%)**	**n**	**(%)**
Age (years)				
Mean (SD)	71.9	(10.5)	73.3	(11.4)
Gender				
Male	10,663	(46.1%)	3,527	(49.1%)
Female	12,450	(53.9%)	3,654	(50.9%)
Quintile of IMD/WIMD				
1 (most deprived)	7,516	(32.5%)	2,314	(32.2%)
2	5,458	(23.6%)	1,677	(23.4%)
3	4,297	(18.6%)	1,355	(18.9%)
4	3,252	(14.1%)	1,051	(14.6%)
5 (least deprived)	2,375	(10.3%)	716	(10.0%)
No data	215	(0.9%)	68	(1.0%)
Oxygen prescription				
Not needed	3,832	(16.6%)	1,789	(24.9%)
Not prescribed	5,330	(23.1%)	2,519	(35.1%)
Prescribed	13,951	(60.4%)	2,873	(40.0%)
NIV administered	2,846	(12.3%)	199	(2.8%)
Length of stay quintile				
0-1 days	4,440	(19.2%)	3,441	(47.9%)
2-3 days	5,648	(24.4%)	1,618	(22.5%)
4-5 days	4,168	(18.0%)	742	(10.3%)
6-8 days	3,835	(16.6%)	592	(8.2%)
9+ days	5,022	(21.7%)	788	(11.0%)
Smoking status				
Never smoked	707	(3.1%)	376	(5.2%)
Ex-smoker	13,361	(57.8%)	3,467	(48.3%)
Current smoker	7,489	(32.4%)	1,974	(27.5%)
Not recorded	1,556	(6.7%)	1,364	(19.0%)

Charlson Comorbidity Index				
1	11,219	(48.5%)	3,164	(44.1%)
2	5,807	(25.1%)	1,806	(25.2%)
3	3,108	(13.5%)	1,032	(14.4%)
4	1,525	(6.6%)	588	(8.2%)
5	777	(3.4%)	301	(4.2%)
6	301	(1.3%)	119	(1.7%)
7+	376	(1.6%)	171	(2.4%)
Mental health diagnoses				
No mental illness	18,331	(79.3%)	5,880	(81.9%)
Mild/moderate mental illness	3,315	(14.3%)	864	(12.0%)
Severe mental illness	1,467	(6.4%)	437	(6.1%)
DECAF score				
Low risk (0-1)	2,216	(9.6%)	52	(0.7%)
Intermediate risk (2)	1,022	(4.4%)	28	(0.4%)
High risk (3-6)	751	(3.3%)	26	(0.4%)
No data	19,124	(82.7%)	7,075	(98.5%)
Spirometry: FEV_1/FVC ratio				
≥ 0.7	1,154	(5.0%)	302	(4.2%)
< 0.7	8,245	(35.7%)	1,471	(20.5%)
Invalid (< 0.2 or > 1.0)	182	(0.8%)	33	(0.5%)
No data	13,532	(58.6%)	5,375	(74.9%)
Outcomes				
Patient died within 30 days of admission	1,390	(6.0%)	442	(6.2%)
Patient died as an inpatient	908	(3.9%)	305	(4.3%)

Abbreviations: DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IMD: English Index of Multiple Deprivation; NIV: non-invasive ventilation; SD: standard deviation; WIMD: Welsh Index of Multiple Deprivation.

Table 29. *Demographics of and outcomes for people admitted to hospital with acute exacerbation of COPD (the full audit cohort, including patients who died as an inpatient or self-discharged) who received a respiratory specialist review within 24 hours of admission and those who received a respiratory specialist >24 hours after admission. N=23,113*

	Patient reviewed in ≤24 hours of admission ***N = 15,956***		**Patient reviewed in >24 hours of admission** ***N = 7,157***	
	n	**(%)**	**n**	**(%)**
Age (years)				
Mean (SD)	71.5	(10.5)	72.9	(10.6)
Gender				
Male	7,401	(46.4%)	3,262	(45.6%)
Female	8,555	(53.6%)	3,895	(54.4%)
Quintile of IMD/WIMD				
1 (most deprived)	5,348	(33.5%)	2,168	(30.3%)
2	3,750	(23.5%)	1,708	(23.9%)
3	2,893	(18.1%)	1,404	(19.6%)
4	2,221	(13.9%)	1,031	(14.4%)
5 (least deprived)	1,598	(10.0%)	777	(10.9%)
No data	146	(0.9%)	69	(1.0%)
Oxygen prescription				
Not needed	2,757	(17.3%)	1,075	(15.0%)
Not prescribed	3,588	(22.5%)	1,742	(24.3%)
Prescribed	9,611	(60.2%)	4,340	(60.6%)
NIV administered	2,028	(12.7%)	818	(11.4%)
Length of stay quintile				
0-1 days	4,083	(25.6%)	357	(5.0%)
2-3 days	3,924	(24.6%)	1,724	(24.1%)
4-5 days	2,591	(16.2%)	1,577	(22.0%)
6-8 days	2,447	(15.3%)	1,388	(19.4%)
9+ days	2,911	(18.2%)	2,111	(29.5%)
Smoking status				
Never smoked	468	(2.9%)	239	(3.3%)
Ex-smoker	9,155	(57.4%)	4,206	(58.8%)
Current smoker	5,327	(33.4%)	2,162	(30.2%)
Not recorded	1,006	(6.3%)	550	(7.7%)

Charlson Comorbidity Index				
1	8,039	(50.4%)	3,180	(44.4%)
2	3,915	(24.5%)	1,892	(26.4%)
3	2,076	(13.0%)	1,032	(14.4%)
4	1,012	(6.3%)	513	(7.2%)
5	506	(3.2%)	271	(3.8%)
6	178	(1.1%)	123	(1.7%)
7+	230	(1.4%)	146	(2.0%)
Mental health diagnoses				
No mental illness	12,614	(79.1%)	5,717	(79.9%)
Mild/moderate mental illness	2,328	(14.6%)	987	(13.8%)
Severe mental illness	1,014	(6.4%)	453	(6.3%)
DECAF score				
Low risk (0-1)	1,763	(11.1%)	453	(6.3%)
Intermediate risk (2)	764	(4.8%)	258	(3.6%)
High risk (3-6)	540	(3.4%)	211	(3.0%)
No data	12,889	(80.8%)	6,235	(87.1%)
Spirometry: FEV_1/FVC ratio				
≥ 0.7	797	(5.0%)	357	(5.0%)
< 0.7	6,002	(37.6%)	2,243	(37.6%)
Invalid (< 0.2 or > 1.0)	122	(0.8%)	60	(0.8%)
No data	9,035	(56.6%)	4,497	(62.8%)
Outcomes				
Died within 30 days of admission	923	(5.8%)	467	(6.5%)
Died as an inpatient	585	(3.7%)	323	(4.5%)

Abbreviations: DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IMD: English Index of Multiple Deprivation; NIV: non-invasive ventilation; SD: standard deviation; WIMD: Welsh Index of Multiple Deprivation.

Table 30. *Odds ratios and 95% confidence intervals for 30-day mortality and inpatient mortality for each respiratory specialist review exposure in the full audit cohort of acute exacerbation of COPD admissions (including patients who died as an inpatient or self-discharged)*

Exposure (intervention/control) / Outcome	**Odds ratio (95% CI)**		**Adjusted* odds ratio (95% CI)**	
Specialist review in 24 hours (yes/no)				
Death within 30 days of admission	0.94	(0.85 – 1.04)	0.93	(0.83 – 1.03)
Death while an inpatient	0.90	(0.80 – 1.02)	**0.82**	**(0.72 – 0.93)**
Received specialist review (yes/no)				
Death within 30 days of admission	1.01	(0.90 – 1.14)	**0.82**	**(0.72 – 0.94)**
Death while an inpatient	0.99	(0.86 – 1.14)	**0.69**	**(0.58 – 0.81)**
Time to specialist review (≤24hrs/>24hrs)				
Death within 30 days of admission	0.91	(0.81 – 1.03)	1.03	(0.90 – 1.17)
Death while an inpatient	0.88	(0.76 – 1.02)	0.96	(0.82 – 1.12)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

Notes: Statistically significant results in bold.

Abbreviations: CI: confidence interval.

When using 90-day mortality and 90-day readmission as study outcomes, review within 24 hours of admission was significantly associated with 90-day mortality, with patients reviewed within 24 hours having 16% greater odds of dying within 90 days (OR: 1.16 [95% CI: 1.05 – 1.28]) (**Table 21**). Patients who were reviewed by a respiratory specialist at any time also had 20% higher odds (OR: 1.20 [95% CI: 1.06 – 1.36]) of dying within 90 days than patients who weren't reviewed by a respiratory specialist (**Table 22**) and patients who were reviewed within 24 hours had 13% higher odds (OR: 1.13 [95% CI: 1.01 – 1.26]) of dying within 90 days than patients who were reviewed in >24 hours (**Table 23**). There was no material difference in mortality or readmissions at 90-days compared to 30-days for patients who received a discharge bundle (**Table 25**).

In analysis using only English hospitals, there was no material difference in 30-day outcome results, however there were some changes in significance for 90-day outcome results. Patients had 12% lower odds (OR: 0.88 [95% CI: 0.79 – 0.98]) of death within 90 days if they received a discharge bundle and patients who received a specialist review within 24 hours (relative to those who received a review in >24hours) were no longer significantly likely (OR: 1.11 [95% CI: 0.99 – 1.24]) to die within 90 days of admission (**Table 31**).

Table 31. *Odds ratios and 95% confidence intervals for mortality and readmission for all COPD Best Practice Tariff (BPT) exposures in AECOPD admissions to English hospitals only*

English Hospitals Outcome	Odds ratio (95% CI)		Adjusted* odds ratio (95% CI)	
BPT conforming admission (yes/no)				
Death within 30 days of admission	0.95	(0.81 – 1.12)	1.04	(0.88 – 1.23)
Death within 90 days of admission	0.97	(0.88 – 1.07)	1.04	(0.94 – 1.15)
Readmission within 30 days of discharge	0.95	(0.90 – 1.01)	0.96	(0.90 – 1.02)
Readmission within 90 days of discharge	1.00	(0.95 – 1.06)	1.03	(0.97 – 1.08)
Specialist review in 24 hours (yes/no)				
Death within 30 days of admission	0.99	(0.85 – 1.16)	1.10	(0.94 – 1.29)
Death within 90 days of admission	1.02	(0.93 – 1.11)	**1.13**	**(1.03 – 1.24)**
Readmission within 30 days of discharge	**0.94**	**(0.89 – 0.99)**	0.95	(0.90 – 1.01)
Readmission within 90 days of discharge	0.98	(0.93 – 1.03)	1.01	(0.96 – 1.07)
Received specialist review (yes/no)				
Death within 30 days of admission	1.08	(0.90 – 1.30)	1.06	(0.86 – 1.30)
Death within 90 days of admission	**1.26**	**(1.13 – 1.41)**	**1.17**	**(1.03 – 1.32)**
Readmission within 30 days of discharge	**1.08**	**(1.01 – 1.16)**	0.98	(0.91 – 1.05)
Readmission within 90 days of discharge	**1.08**	**(1.02 – 1.15)**	1.03	(0.96 – 1.10)
Time to specialist review (≤24hrs/>24hrs)				
Death within 30 days of admission	0.94	(0.78 – 1.12)	1.12	(0.93 – 1.36)
Death within 90 days of admission	**0.89**	**(0.80 – 0.99)**	1.11	(0.99 – 1.24)
Readmission within 30 days of discharge	**0.87**	**(0.82 – 0.94)**	0.95	(0.88 – 1.02)
Readmission within 90 days of discharge	**0.93**	**(0.87 – 0.98)**	1.00	(0.94 – 1.06)
Discharge bundle (yes/no)**				
Death within 30 days of admission	0.87	(0.74 – 1.02)	0.86	(0.71 – 1.03)
Death within 90 days of admission	0.96	(0.88 – 1.06)	**0.88**	**(0.79 – 0.98)**
Readmission within 30 days of discharge	1.01	(0.95 – 1.07)	0.97	(0.90 – 1.04)
Readmission within 90 days of discharge	1.05	(0.99 – 1.10)	1.02	(0.96 – 1.09)

*Adjusted for age, sex, socioeconomic status, oxygen requirement, non-invasive ventilation requirement, length of stay, smoking status, Charlson comorbidity index, and mental health diagnoses.

**Additionally adjusted for receipt of respiratory specialist review.

Notes: Statistically significant results in bold.

Abbreviations: AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; BPT: Best Practice Tariff; CI: confidence interval.

6.5 Discussion

In this chapter I did not find an association between the criteria of the COPD BPT pay-for-performance scheme and a reduction in 30-day mortality or readmissions among people admitted to hospital with AECOPD. Whilst the COPD BPT was not specifically designed to reduce mortality or readmission rates, the intention was to promote better quality patient care, and it might therefore be anticipated that better patient care would translate into better outcomes for readmission and mortality.

In further analyses individually examining the two COPD BPT components, I found no association between being reviewed by a respiratory specialist within 24 hours or receiving a discharge bundle and 30-day mortality or readmissions. However, when including patients who died as an inpatient, I found that receiving a specialist review at any time during the admission was associated with 18% lower odds of 30-day mortality and 31% lower odds of inpatient mortality. This suggests that specialist review at any point during an admission is beneficial for inpatient mortality but does not improve mortality after discharge. When repeating the analyses using 90-day outcomes, patients who were reviewed by a specialist within 24 hours of admission had greater odds of dying within 90 days than those who were not reviewed or were reviewed after 24 hours. The most likely explanation for this is that there is important confounding from admission severity that I have not been able to adjust for and that, appropriately, sicker patients are being reviewed in priority to those who are less unwell. In fact, given that patients seen by a respiratory specialist were more frequently prescribed oxygen and required NIV, respiratory specialist review may simply be a proxy for admission severity.

Whilst it is difficult to argue that discharge bundles do not increase best practice care, these analyses do call into question the current pay-for-performance model and raise concern that while the right boxes are being ticked in the audit, there is not always effective intervention. It is possible to measure conformance to the BPT, but the quality of the delivery of its components cannot be measured. For example, the bundle component of inhaler technique check will not provide any benefit if the inhaler is used poorly by the patient and optimal use is not then demonstrated and confirmed by the medical team, with a switch to an alternative device as appropriate. It is possible that some hospitals or members of the multi-professional team may consider a bundle complete if just a few of the items have been completed, while others may complete all bundle items without realising and state that a bundle has not been completed. For example, results from the most recent COPD audit(32) show that 74% of admissions were described as having received a discharge bundle, yet the patient was assessed for suitability for pulmonary rehabilitation in only 56% of admissions.

In sensitivity analysis, limiting analyses to just English hospitals to exclude hospitals ineligible to participate in the BPT (in case recording of data was better in those participating in the BPT) did not demonstrate a material change in outcomes other than a possible suggestion that a discharge bundle was beneficial for 90-day mortality. One possible reason for not seeing a benefit from the COPD BPT could be that benefits from some of the bundle items, such as smoking cessation and pulmonary rehabilitation are not seen until after a longer period than 30 days (although no benefit was observed in the 90 days following discharge either), or the benefits are manifest in other ways (such as improved quality of life) that are not captured by readmission or mortality outcomes. Though it seems reasonable to believe that improvements in inhaler use and self-management could help prevent future exacerbations from becoming severe enough to require hospitalisation, therefore reducing readmissions in the 30- and 90-day windows assessed. Alternatively, it may be that those with frequent exacerbations and/or admissions are more knowledgeable of inhaler use/self-management and therefore these interventions are of less benefit to them, and this could perhaps affect the observed benefit of the discharge bundle, as only recently diagnosed and milder cases benefit. It could also be that the follow-up component of the discharge bundle serves to increase readmissions rather than reduce them, as a necessary readmission may be discovered sooner. This could perhaps mask any reduction in readmission caused by the other components of the discharge bundle. These are important aspects that this analysis cannot address and deserve further study.

6.5.1 Comparisons with previous studies

While there have not been any previous studies of the COPD BPT, there are prior studies of the individual components included within it. A systematic review(167) of COPD discharge bundles found that they did not significantly improve mortality or quality of life, and only weak evidence for a reduction in readmissions. A more recent literature review(171) concluded that it was inconclusive whether COPD admission or discharge care bundles reduced readmissions, and that further study was required. A recent UK study(51) found no evidence that COPD care bundles reduced 28-day readmission, although emergency department attendances did reduce after care bundles were implemented in hospitals. It was also found that not all items of the admission and discharge bundles were reliably completed. A recent French study(172) also concluded that a COPD discharge care bundle had no impact on 28-day AECOPD readmission or mortality. However, one recent US study(173) found that all-cause readmissions reduced after implementing a COPD care bundle. It is worth noting that all mentioned bundle studies have comparatively small numbers of included patients and generally compare outcomes at a population level rather than the patient level as I have done. No formal assessment of publication bias was completed in the literature

reviews(167,171) due to the limited number of published randomised controlled trials (RCTs) so there may be resultant publication bias. In the context of results presented here and in previous studies, there does appear to be growing evidence that COPD discharge bundles are not producing improvements in mortality or readmission. However, given that bundles do not appear reliably implemented, any potential benefits may not be being realised. This does not mean that the individual components of the bundle are not of importance to COPD patients.

Timely receipt of respiratory specialist input in AECOPD admissions has not been as extensively studied as COPD discharge bundles, however a study in North East England(174) found that after implementing a model that ensured respiratory specialists were available 24 hours a day, 7 days a week, 30-day mortality decreased. An increase in 90-day (but not 30-day) readmissions was also observed. Again, this study compared population-level figures at two time points, which could explain differences from the results I have presented.

While there are not any prior studies of the COPD BPT, there are studies examining the impact of the hip fracture BPT on patient outcomes. Oakley et al.(175) compared admissions before and after the introduction of the hip fracture BPT, and BPT compliant and BPT non-compliant admissions. They found that the hip fracture BPT did not lead to any improvements at the organisational level (pre- vs. post- BPT) however at the patient level mortality was significantly reduced (BPT vs. non-BPT admissions). Survival analysis also found a significant long-term survival benefit for BPT conforming admissions. Whitaker et al.(176) similarly found 1-year survival was significantly better for BPT conforming admissions. Metcalfe et al.(177) compared admissions in England and Scotland following the introduction of the BPT (which only applies to England) and found that there was a greater reduction in mortality, readmissions, and length of hospital stay during the BPT period in England than in Scotland. It should be noted that the hip fracture BPT has the definitive intervention of surgery that is not present in the COPD BPT, so the two may not necessarily be comparable.

6.5.2 Strengths & limitations

The primary strength of these analyses comes from the number of patients included. However, this study does have limitations. I have used adjustment to attempt to control for differences between BPT admissions and non-BPT admissions. However, the results suggest that there is unmeasured confounding. Another possible limitation is that all-cause readmissions have been used as the outcome rather than just AECOPD admissions. It is not clear whether the BPT or discharge bundle aims to reduce just AECOPD readmissions or any readmissions. However, over 50% of the readmissions in the study cohort were for either AECOPD or pneumonia and some of the other studies discussed used all-cause readmission as an outcome too(51,173). A limitation of the dataset

used is that it is not clear which specific elements of the discharge bundle have been completed; there is no further detail in the dataset than a 'yes' response to the 'discharge bundle completed?' question. As Morton et al.(51) noted, certain elements of the discharge bundle are not always well completed.

6.5.3 Conclusion

Mere documentation of conforming to the COPD BPT and its individual components is not associated with a reduction in mortality or readmission. However, receiving a respiratory specialist review at any point during an admission is associated with lower inpatient mortality. Further thought and work is needed to better understand the benefits of pay-for-performance models. The COPD BPT and other financial incentive schemes should be specific in the outcomes they seek to improve so that interventions with the strongest evidence base can be financially incentivised. If the COPD BPT is failing to have the desired improvement to patient outcomes because the components of the COPD discharge bundle are not being adequately completed, it may be sensible to add each bundle item to the COPD BPT separately rather than including them under the single requirement of 'COPD discharge bundle'.

6.5.4 Future work

It may be that COPD discharge care bundles are not leading to desired improvements in patient outcomes because discharge bundles are not implemented fully or given that they are a composite measure with elements that provide different benefits, evaluating them as a whole may not be appropriate. Therefore, useful future work would be to evaluate the effectiveness of the COPD BPT criteria when all bundle items are fully implemented or the individual components as separate interventions. While the cut of audit data used in analyses in this current chapter did not have this detail, future COPD clinical audit datasets will contain detailed information on the specific bundle items completed, and therefore analysis of the effectiveness of the individual and combined bundle items can be assessed.

Chapter 7. Utility of NEWS2 as a severity store for hospitalised COPD exacerbations

7.1 Introduction

With care quality in both primary and secondary care investigated in previous chapters, in this chapter I move on to investigate the suitability of the revised National Early Warning Score (NEWS2)(178) as a possible risk categorisation score for AECOPD admissions. If NEWS2 can accurately risk stratify AECOPD admissions it will serve as a useful covariate to adjust for in the analyses of my next chapter using linked primary and secondary care data, as admission outcomes are likely to correlate with the severity of the exacerbation. Accurate risk categorisation may also enable clinicians to rapidly detect patients at highest risk and place them under greater observation, ensuring they can provide necessary care as rapidly as possible, which may in turn lead to better outcomes.

GOLD classifies COPD exacerbations as mild when needing only a change in inhaled bronchodilators, moderate when requiring oral antibiotics and/or corticosteroids, and severe when resulting in hospitalisation or a visit to A&E(12). Unfortunately, there is no widely accepted way to further risk-stratify hospitalised AECOPD, despite there being a need from a clinical and research perspective. To further complicate any assessment of exacerbation severity, severity will represent a combination of the underlying severity of COPD, the severity of the exacerbation itself, and the presence and severity of any comorbidities.

A recent systematic review(179) examining risk scoring in COPD found no studies at low risk of bias that had been designed to risk-stratify AECOPD. Whilst the DECAF score(131) offers good prediction of outcomes, it requires blood count, blood gas, chest radiograph and clinical assessment of heart rhythm to score, meaning that it cannot be calculated quickly and simply. Additionally, DECAF has only been validated in patients with prior spirometric diagnosis of COPD(180) (whereas many patients presenting at hospital will not have a prior diagnosis), and some clinicians consider the presence of radiographic consolidation – the ‘C’ component of DECAF - to represent a diagnosis of pneumonia in COPD, rather than a COPD exacerbation(181).

In hospital fast and efficient response of the clinical team to deterioration in a patient’s condition is essential for best possible outcomes for the patient. Early warning scores (EWSs) are used in hospitals as part of clinical monitoring of a patient and are a way to identify patients that are at risk of clinical deterioration. In 2012, the National Early Warning Score (NEWS)(182) was developed to create a standard EWS that could be used across the NHS and replace the current different EWSs

used across different hospitals and departments. NEWS collects information on 6 physiological parameters that are routinely collected during a patient's hospital stay:

- Respiratory rate
- Oxygen saturation
- Systolic blood pressure
- Pulse rate
- Level of consciousness (Alert, responds to Voice, responds to Pain, Unresponsive [AVPU])

A score (0-3) is given to each of these measures based on how much the measure deviates from the norm. The values for each measure are then added together to produce the NEWS, with an additional 2 points being added to the NEWS if the patient is on supplemental oxygen. NEWS is designed to be simple to use and provides a single chart (intended to replace multiple different charts previously used for temperature, pulse, and respiration rate) for the clinical team to fill in with information on the patient's condition. Regular updating of the patient's NEWS on the chart allows the clinical team to track the patient's condition and alert them of any deterioration that requires a timely response. The trigger levels of NEWS are:

- Low (NEWS of 1-4): patient should be promptly assessed by a registered nurse with the appropriate competencies. 4-6 hourly monitoring recommended.
- Medium (NEWS of 5-6) or Red (NEWS of 3 for a single physiological parameter): patient should be urgently reviewed by a clinician with appropriate competencies in acute illness. Minimum hourly monitoring recommended.
- High (NEWS of 7 or more): emergency assessment of patient by clinical team with competencies in critical care. Continuous monitoring and recording of vital signs recommended.

It should be noticed that a healthcare professional's concerns about a patient should always override what is suggested by the NEWS if they consider it necessary to escalate care. All staff using NEWS should be trained in the appropriate use of NEWS and all clinical response to the NEWS should be recorded on the NEWS chart so that a record of the patient's care is available.

In 2017 an update to NEWS, NEWS2(178), was released in response to concerns about safe use of the score in patients with hypercapnic respiratory failure (also known as type 2 respiratory failure), which is often due to COPD. Patients with hypercapnic respiratory failure are at increased risk of rapidly worsening hypercapnia if too much oxygen is delivered, therefore an oxygen saturation target of 88-92% is recommended in these patients(183), rather than the ≥96% target incentivised

by the original NEWS. Therefore, an additional oxygen scale (SpO_2 Scale 2) (see **Figure 15**) was added to be used in patients with confirmed hypercapnic respiratory failure; confirmation of which is by blood gas analysis performed in either the current or a prior hospital admission. The decision to use Scale 2 must be made be a competent clinical decision maker and clearly recorded in the patient's notes. In all other cases, SpO_2 Scale 1 should be used. NEWS2 also introduced "new confusion" to the consciousness physiological measure which receives a NEWS of 3 (a 'Red' alert). This changes the consciousness score from AVPU to ACVPU, the 'C' representing confusion. NEWS2 also introduces some design changes to the chart to make it easier to use and guidance to consider sepsis at a NEWS of 5 or more in patients with suspected infection.

NEWS2 is endorsed(184) and mandated(185) for use by NHS England and NHS Improvement in acute and ambulance settings and is in use in 76% of acute trusts and 100% of ambulance trusts(184). Therefore, given NEWS2's widespread availability, it provides a useful indication of the patient's condition and could potentially also serve as a simple, readily-available alternative to the DECAF score for risk-classification of AECOPD admissions.

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Reproduced from: Royal College of Physicians. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party*. London: RCP, 2017

***Figure 15**. NEWS2 calculation*

7.2 Aim

In this chapter I aim to determine if NEWS2 can be used to predict the short-term outcomes of inpatient mortality, requirement for NIV, and length of stay in AECOPD admissions. If NEWS2 accurately predicts key AECOPD outcomes and indicates severity, then it may serve a useful tool for clinicians to identify cases that require greater observation. It may also provide a useful covariate to adjust for in epidemiological research on AECOPD admissions. Secondary aims are to determine if the addition of patient characteristics (such as age, sex, and smoking status) to NEWS2 models will improve their predictive ability and if these patient characteristics are able to predict admission NEWS2.

7.3 Methods

7.3.1 Database/population

Data from the 2019 cut of the NACAP COPD secondary care clinical audit data, representing AECOPD hospital admissions between 01/10/2018 and 30/09/2019 were used in analyses for this chapter. Further details on the 2018-2019 NACAP COPD clinical audit can be found in the published reports(32,186) and **3.2.2.3.**

7.3.2 Variables

NEWS2 was the independent variable in the primary analysis but used as an outcome variable in secondary analysis. It was recorded on arrival to hospital in A&E and was available in 89% of cases. A NEWS2 score of 0-4 is defined as low risk, 5 or 6 as medium risk, and 7 or more as high risk(178). The individual components of NEWS2 were not used in analyses as these were only available in 17.8% (9,315) of admissions, and the data are likely missing not at random (MNAR) as their values are likely to have influenced whether they were recorded.

The outcome variables were inpatient death, need for acute treatment with NIV at any point during the admission, and length of stay for those surviving to discharge. As length of stay was not normally distributed and could not be successfully transformed, it was analysed as a binary outcome, coded as either ≤4 days or >4 days (4 days was the median length of stay).

The following variables were assessed as potential predictors of the three AECOPD outcomes and NEWS2 (in the secondary analysis): sex, index of multiple deprivation, COPD severity, smoking status, history of cardiovascular disease, and history of mental illness. Transgender and patients without gender data were excluded from analysis due to small numbers. Deprivation was defined as

quintile of 2019 IMD(187) (1 = most deprived quintile). COPD severity (GOLD stage) was determined using the patients most recently recorded lung function (FEV_1 percent-predicted). Smoking status was recorded as current-, ex-, or never smoker. Current vapers were included with current smokers. History of cardiovascular disease and history of mental illness included any relevant diagnosis from the current admission or previous admissions.

Where more than 5% of values for a variable were missing, an additional 'Not recorded' category was added to categorical variables, otherwise complete case analysis was used.

7.3.3 Statistical analysis

Data management and analyses were performed using Stata 16. English hospitals were randomly split 50:50 to provide separate development and internal validation cohorts for the prediction models. Patients admitted to Welsh hospitals were used as an external validation cohort (where quintile of 2019 Welsh Index of Multiple Deprivation (WIMD)(188) was used in place of IMD). Baseline characteristics of the cohorts were summarised using proportions or means and standard deviation, as appropriate. Differences between the development, validation, and external validation cohorts were assessed using Pearson's X^2 test for categorical variables and linear regression for the continuous variable, age.

7.3.3.1 Univariable association between NEWS2 and exacerbation outcomes

Logistic regression was used to model the relationship between NEWS2 and the three AECOPD outcomes. The Akaike information criterion (AIC) was used to determine whether NEWS2 should be analysed as a categorical (low, medium, or high risk) or continuous variable. All models provided a better fit when using NEWS2 as a continuous variable (lower AIC). Therefore, NEWS2 was included in the models as a continuous variable. Discrimination of NEWS2 in predicting inpatient mortality, requirement for NIV, and length of stay was assessed using area under the receiver operating characteristic (ROC) curves (AUC). The optimal NEWS2 value for outcome prediction was chosen based on Youden's index(189). Calibration of NEWS2 models was assessed using calibration plots with deciles of predicted risk plotted against observed risk.

7.3.3.2 Multivariable analysis of all potential predictors of exacerbation outcomes

NEWS2 and other potential predictors were included in logistic regression models for each of the three AECOPD outcomes to form adjusted models. Age was included in the models as a categorical variable (in quintiles). As above, discrimination was assessed using AUC and calibration was assessed using calibration plots.

7.3.3.3 Predictors of NEWS2

Predictors of NEWS2 were assessed by including all potential predictors in a multiple linear regression model. As with the previous models, calibration was assessed using calibration plots.

7.4 Results

The development cohort consisted of 26,776 patients from 83 hospitals and the internal validation cohort consisted of 29,244 patients from 84 hospitals. 2,537 patients admitted to 16 Welsh hospitals were used as an external validation cohort. However, as 2,595 (9.69%), 3,656 (12.50%), and 22 (0.87%) admissions did not have an available NEWS2 score in the development, validation, and external validation cohorts, respectively, the final numbers of patients available for use in the cohorts were 24,181 (model development), 25,588 (internal validation), and 2,515 (external validation) (**Figure 16**). Admissions without a NEWS2 recorded did not differ substantially in outcome measures from admissions with NEWS2 in the combined English and Welsh cohort (**Table 32**), the English cohort (**Table 33**), or the Welsh cohort (**Table 34**).

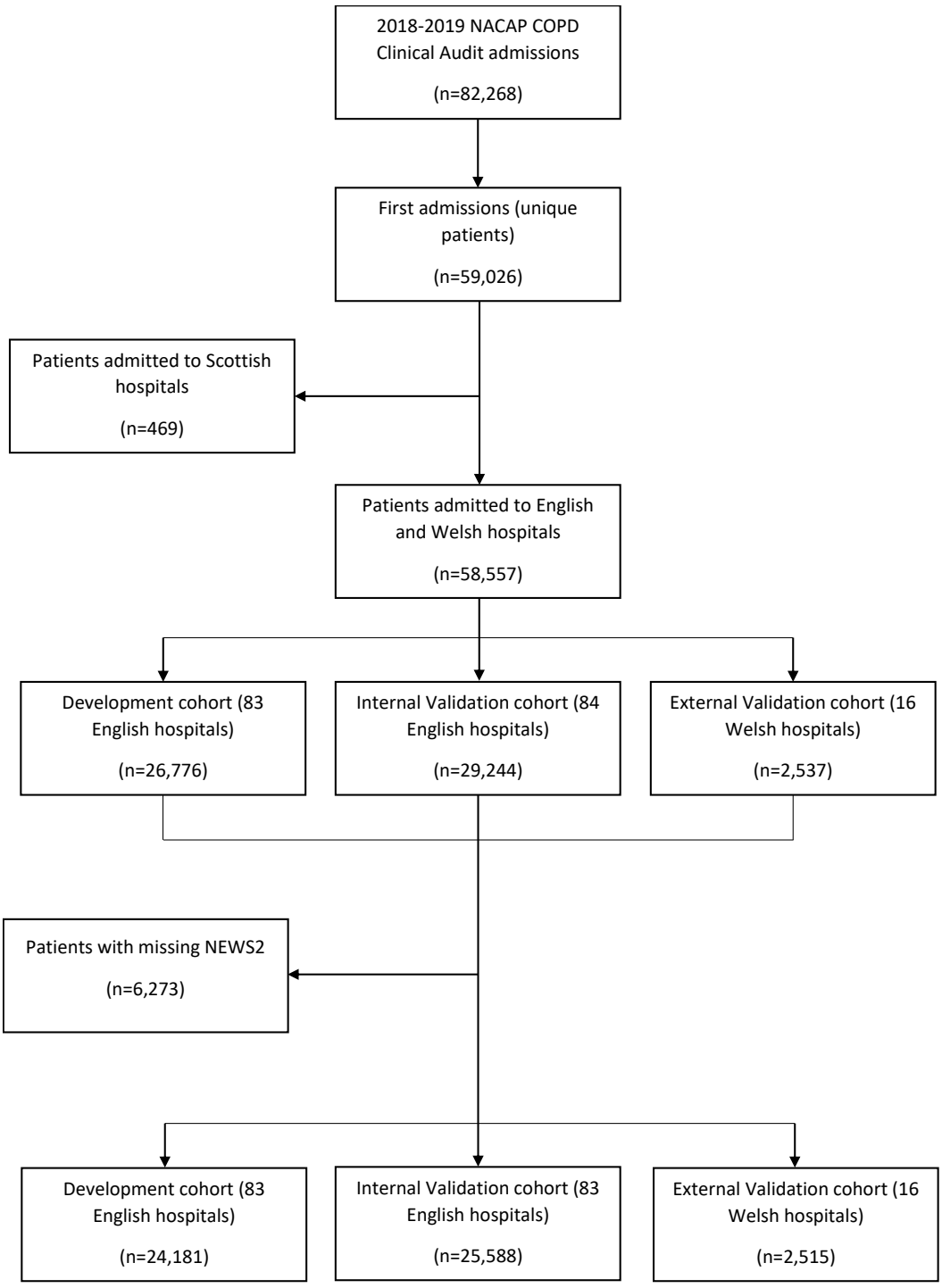

Figure 16. *Flowchart of patients included in analysis to assess predictive ability of NEWS2 for AECOPD outcomes*

Table 32. *Characteristics of patients admitted to English and Welsh hospitals included in the National Asthma and COPD Audit Programme (first admission in audit period), with and without a NEWS2 assessment. Data are n (%) or mean (SD) as appropriate*

Criteria	First admissions with NEWS2 (N=52,284)	First admissions without NEWS2 (N=6,273)	p-value*
Age (years)	72.1 (10.8)	72.4 (10.5)	0.1005
Quintiles of age (years)			0.262
35–63	10,852 (20.76%)	1,233 (19.66%)	
64–70	10,264 (19.63%)	1,266 (20.18%)	
71–75	10,179 (19.47%)	1,246 (19.86%)	
76–81	10,727 (20.52%)	1,313 (20.93%)	
≥82	10,262 (19.63%)	1,215 (19.37%)	
Sex			0.001
Female	28,181 (53.90%)	3,419 (54.50%)	
Male	24,068 (46.03%)	2,841 (45.29%)	
Transgender/other/not recorded	35 (0.07%)	13 (0.21%)	
ADMISSION NEWS2**			
Low Risk (0-4)	27,380 (52.37%)		
Medium Risk (5-6)	12,555 (24.01%)		
High Risk (7+)	12,349 (23.62%)		
Not Available		6,273 (100.00%)	
Quintile of English 2019 Index of Multiple Deprivation			<0.001
1 (most deprived)	17,599 (33.66%)	2,128 (33.92%)	
2	11,967 (22.89%)	1,338 (21.33%)	
3	9,394 (17.97%)	1,003 (15.99%)	
4	7,456 (14.26%)	917 (14.62%)	
5 (least deprived)	5,101 (9.76%)	787 (12.55%)	
Not recorded	767 (1.47%)	100 (1.59%)	
GOLD Stage (COPD Severity)			<0.001
1 – mild	1,926 (3.68%)	206 (3.28%)	
2 – moderate	7,956 (15.22%)	828 (13.20%)	
3 – severe	8,504 (16.27%)	854 (13.61%)	
4 – very severe	3,881 (7.42%)	442 (7.05%)	
Not recorded	30,017 (57.41%)	3,943 (62.86%)	

Smoking status* **			<0.001
Never smoked	1,793 (3.43%)	190 (3.03%)	
Ex-smoker	28,843 (55.17%)	3,617 (57.66%)	
Current smoker	18,665 (35.70%)	2,158 (34.40%)	
Not recorded	2,983 (5.71%)	308 (4.91%)	
Comorbidities			
History of cardiovascular disease	19,825 (37.92%)	1,961 (31.26%)	<0.001
History of mental illness	7,812 (14.94%)	706 (11.25%)	<0.001
OUTCOMES			
Died as an in patient	1,852 (3.54%)	239 (3.81%)	0.280
Need for acute treatment with NIV	4,786 (9.15%)	593 (9.45%)	0.438
Length of stay >4 days (for those surviving to discharge)	20,865/50,432 (41.37%)	2,570/6,034 (42.59%)	0.069

*: Pearson's X^2 test for categorical variables, independent samples t-test for continuous variables

**: of those with a NEWS2 available on admission, 82% entered the total score and 18% entered individual variables allowing calculation of NEWS2. Of those with variables provided, 53% were using oxygen scale 1 and 47% were using oxygen scale 2.

***: Current vapers included with current smokers irrespective of cigarette smoking status

Table 33. *Characteristics of patients admitted to English hospitals included in the National Asthma and COPD Audit programme clinical audit (first admission in audit period) with and without a NEWS2 score. Data are n (%) or mean (SD) as appropriate*

Criteria	English first admissions with NEWS2 (N=49,769)	English first admissions without NEWS2 (N=6,251)	p-value*
Age (years)	72.2 (10.8)	72.4 (10.5)	0.1394
Quintiles of age (years)			0.239
35–63	10,295 (20.69%)	1,226 (19.61%)	
64–70	9,751 (19.59%)	1,263 (20.20%)	
71–75	9,645 (19.38%)	1,238 (19.80%)	
76–81	10,236 (20.57%)	1,311 (20.97%)	
≥82	9,842 (19.78%)	1,213 (19.40%)	
Sex			0.001
Female	26,708 (53.66%)	3,409 (54.54%)	
Male	23,027 (46.27%)	2,829 (45.26%)	
Transgender/other/not recorded	34 (0.07%)	13 (0.21%)	
ADMISSION NEWS2**			
Low Risk (0-4)	26,182 (52.61%)		
Medium Risk (5-6)	11,894 (23.90%)		
High Risk (7+)	11,693 (23.49%)		
Not Available		6,251 (100.00%)	
Quintile of English 2019 Index of Multiple Deprivation (IMD)			<0.001
1 (most deprived)	16,704 (33.56%)	2,117 (33.87%)	
2	11,348 (22.80%)	1,334 (21.34%)	
3	8,963 (18.01%)	997 (15.95%)	
4	7,153 (14.37%)	916 (14.65%)	
5 (least deprived)	4,862 (9.77%)	787 (12.59%)	
Not recorded	739 (1.48%)	100 (1.60%)	
GOLD Stage			<0.001
1 – mild	1,846 (3.71%)	205 (3.28%)	
2 – moderate	7,610 (15.29%)	828 (13.25%)	
3 – severe	8,158 (16.39%)	853 (13.65%)	
4 – very severe	3,732 (7.50%)	440 (7.04%)	
Not recorded	28,423 (57.11%)	3,925 (62.79%)	

Smoking status* **			<0.001
Never smoked	1,683 (3.38%)	190 (3.04%)	
Ex-smoker	27,484 (55.22%)	3,606 (57.69%)	
Current smoker	17,700 (35.56%)	2,147 (34.35%)	
Not recorded	2,902 (5.83%)	308 (4.93%)	
Comorbidities			
History of cardiovascular disease	18,672 (37.52%)	1,951 (31.21%)	<0.001
History of mental illness	7,275 (14.62%)	700 (11.20%)	<0.001
OUTCOMES			
Died as an in patient	1,730 (3.48%)	238 (3.81%)	0.180
Need for acute treatment with NIV	4,453 (8.95%)	590 (9.44%)	0.201
Length of stay >4 days (for those surviving to discharge)	19,753/48,039 (41.12%)	2,565/6,013 (42.66%)	0.022

*: Pearson's X^2 test for categorical variables, independent samples t-test for continuous variables

**: of those with a NEWS2 available on admission, 81.5% entered the total score and 18.5% entered individual variables allowing calculation of NEWS2. Of those with variables provided, 52.9% were using oxygen scale 1 and 47.1% were using oxygen scale 2.

***: Current vapers included with current smokers irrespective of cigarette smoking status

Table 34. *Characteristics of patients admitted to Welsh hospitals included in the National Asthma and COPD Audit Programme (first admission in audit period), with and without a NEWS2 assessment. Data are n (%) or mean (SD) as appropriate*

Criteria	Welsh first admissions with NEWS2 (N=2,515)	Welsh first admissions without NEWS2 (N=22)	p-value*
Age (years)	71.4 (10.5)	68.2 (12.7)	0.1610
Quintiles of age (years)			0.221
35–63	557 (22.15%)	7 (31.82%)	
64–70	513 (20.40%)	3 (13.64%)	
71–75	534 (21.23%)	8 (36.36%)	
76–81	491 (19.52%)	2 (9.09%)	
≥82	420 (16.70%)	2 (9.09%)	
Sex			0.459
Female	1,473 (58.57%)	10 (45.45%)	
Male	1,041 (41.39%)	12 (54.55%)	
Transgender/other/not recorded	1 (0.04%)	0 (0.00%)	
ADMISSION NEWS2**			
Low Risk (0-4)	1,198 (47.63%)		
Medium Risk (5-6)	661 (26.28%)		
High Risk (7+)	656 (26.08%)		
Not Available		22 (100.00%)	
Quintile of Welsh 2019 Index of Multiple Deprivation (WIMD)			0.278
1 (most deprived)	895 (35.59%)	11 (50.00%)	
2	619 (24.61%)	4 (18.18%)	
3	431 (17.14%)	6 (27.27%)	
4	303 (12.05%)	1 (4.55%)	
5 (least deprived)	239 (9.50%)	0 (0.00%)	
Not recorded	28 (1.11%)	0 (0.00%)	
GOLD Stage (COPD Severity)			0.196
1 – mild	80 (3.18%)	1 (4.55%)	
2 – moderate	346 (13.76%)	0 (0.00%)	
3 – severe	346 (13.76%)	1 (4.55%)	
4 – very severe	149 (5.92%)	2 (9.09%)	
Not recorded	1,594 (63.38%)	18 (81.82%)	

Smoking status* **			0.475
Never smoked	110 (4.37%)	0 (0.00%)	
Ex-smoker	1,359 (54.04%)	11 (50.00%)	
Current smoker	965 (38.37%)	11 (50.00%)	
Not recorded	81 (3.22%)	0 (0.00%)	
Comorbidities			
History of cardiovascular disease	1,153 (45.84%)	10 (45.45%)	0.971
History of mental illness	537 (21.35%)	6 (27.27%)	0.500
OUTCOMES			
Died as an in patient	122 (4.85%)	1 (4.55%)	0.947
Need for acute treatment with NIV	333 (13.24%)	3 (13.64%)	0.957
Length of stay >4 days (for those surviving to discharge)	1,112/2,393 (46.47%)	5/21 (23.81%)	0.038

*: Pearson's X^2 test for categorical variables, independent samples t-test for continuous variables

**: of those with a NEWS2 available on admission, 95.8% entered the total score and 4.3% entered individual variables allowing calculation of NEWS2. Of those with variables provided, 72.0% were using oxygen scale 1 and 28.0% were using oxygen scale 2.

***: Current vapers included with current smokers irrespective of cigarette smoking status

The patient characteristics and three outcome measures in the three cohorts are reported in **Table 35**. In the development cohort, the inpatient mortality was 3.5%, 8.7% required treatment with NIV and 41.6% had a length of stay greater than the median of four days. Regarding admission NEWS2, 52.7%, 24.0% and 23.3% were in the low, medium, and high risk NEWS2 groups, respectively. Outcomes were similar in the internal validation cohort, but inpatient mortality, need for NIV and length of stay appeared higher in the external validation cohort compared with the development cohort (**Table 35**).

Table 35. *Characteristics of patients included in the development, internal validation, and external validation cohorts. Data are n (%) or mean (SD) as appropriate*

	Development (N=24,181)	**Internal validation (N=25,588)**	**External validation (N=2,515)**
Age (years)	72.2 (10.8)	72.1 (10.8)	71.4 (10.5)
Quintiles of age (years)			
35–63	4,923 (20.36%)	5,372 (20.99%)	557 (22.15%)
64–70	4,752 (19.65%)	4,999 (19.54%)	513 (20.40%)
71–75	4,763 (19.70%)	4,882 (19.08%)	534 (21.23%)
76–81	4,897 (20.25%)	5,339 (20.87%)	491 (19.52%)
≥82	4,846 (20.04%)	4,996 (19.52%)	420 (16.70%)
Sex			
Male	12,800 (52.93%)	13,908 (54.35%)	1,473 (58.57%)
Female	11,373 (47.03%)	11,654 (45.54%)	1,041 (41.39%)
Transgender/other/not recorded	8 (0.03%)	26 (0.10%)	1 (0.04%)
ADMISSION NEWS2			
Low Risk (0-4)	12,738 (52.68%)	13,444 (52.54%)	1,198 (47.63%)
Medium Risk (5-6)	5,809 (24.02%)	6,085 (23.78%)	661 (26.28%)
High Risk (7+)	5,634 (23.30%)	6,059 (23.68%)	656 (26.08%)
Quintile of 2019 Index of Multiple Deprivation			
1 (most deprived)	7,466 (30.88%)	9,238 (36.10%)	895 (35.59%)
2	5,397 (22.32%)	5,951 (23.26%)	619 (24.61%)
3	4,684 (19.37%)	4,279 (16.72%)	431 (17.14%)
4	3,754 (15.52%)	3,399 (13.28%)	303 (12.05%)
5 (least deprived)	2,529 (10.46%)	2,333 (9.12%)	239 (9.50%)
Not recorded	351 (1.45%)	388 (1.52%)	28 (1.11%)
GOLD (COPD Severity) Stage			
1 – mild	935 (3.87%)	911 (3.56%)	80 (3.18%)
2 – moderate	3,655 (15.12%)	3,955 (15.46%)	346 (13.76%)
3 – severe	3,975 (16.44%)	4,183 (16.35%)	346 (13.76%)
4 – very severe	1,787 (7.39%)	1,945 (7.60%)	149 (5.92%)
Not recorded	13,829 (57.19%)	14,594 (57.03%)	1,594 (63.38%)

Smoking status			
Never smoked	836 (3.46%)	847 (3.31%)	110 (4.37%)
Ex-smoker	13,343 (55.18%)	14,141 (55.26%)	1,359 (54.04%)
Current smoker	8,403 (34.75%)	9,297 (36.33%)	965 (38.37%)
Not recorded	1,599 (6.61%)	1,303 (5.09%)	81 (3.22%)
Comorbidities			
History of cardiovascular disease	8,849 (36.59%)	9,823 (38.39%)	1,153 (45.84%)
History of mental illness	3,343 (13.82%)	3,932 (15.37%)	537 (21.35%)
OUTCOMES			
Died as an in patient	847 (3.50%)	883 (3.45%)	122 (4.85%)
Need for acute treatment with NIV	2,107 (8.71%)	2,346 (9.17%)	333 (13.24%)
Length of stay >4 days (for those surviving to discharge)	9,695/23,334 (41.55%)	10,058/24,705 (40.71%)	1,112/2,393 (46.47%)

7.4.1 NEWS2 as a univariable predictor of exacerbation outcomes

In the development cohort, inpatient mortality was 2.2%, 3.6% and 6.5% respectively for low, medium, and high risk NEWS2. The proportion needing NIV were, respectively, 4.4%, 9.2%, and 18.0%. The discriminatory ability of NEWS2 to predict inpatient mortality, need for acute NIV, and hospital stay longer than the median is summarised in **Table 36**, with the ROC curves illustrated in **Figure 17**. The external validation cohort shows acceptable discrimination of NEWS2 in predicting inpatient mortality and need for NIV, but not length of stay.

Table 36. *Area under the ROC curve (and 95% CI) for the univariable NEWS2 and multivariable predictive models for inpatient mortality, requirement for non-invasive ventilation, and a length of stay greater than the median of 4 days in the development and validation cohorts*

Prediction model	Area under the ROC curve (95% CI)		
	Development	Validation	External validation
Inpatient mortality			
NEWS2	0.64 (0.62 – 0.66)	0.65 (0.63 – 0.67)	0.72 (0.68 – 0.77)
Multivariable	0.74 (0.72 – 0.75)	0.71 (0.69 – 0.72)	0.77 (0.74 – 0.81)
Non-invasive ventilation			
NEWS2	0.70 (0.69 – 0.71)	0.70 (0.69 – 0.71)	0.70 (0.67 – 0.73)
Multivariable	0.73 (0.72 – 0.74)	0.73 (0.72 – 0.74)	0.72 (0.69 – 0.75)
Length of stay >4 days			
NEWS2	0.57 (0.56 – 0.58)	0.58 (0.57 – 0.59)	0.59 (0.57 – 0.61)
Multivariable	0.61 (0.61 – 0.62)	0.61 (0.61 – 0.62)	0.61 (0.59 – 0.63)

The performance of individual NEWS2 cut points are provided for inpatient mortality, requirement for NIV, and length of stay in **Table 37**, **Table 38**, and **Table 39**, respectively, and summarised in **Table 40** for medium and high risk cut points (in the internal validation cohort). Youden's index indicated that a NEWS2 of 6 would provide optimal prediction of the three admission outcomes (**Table 41**).

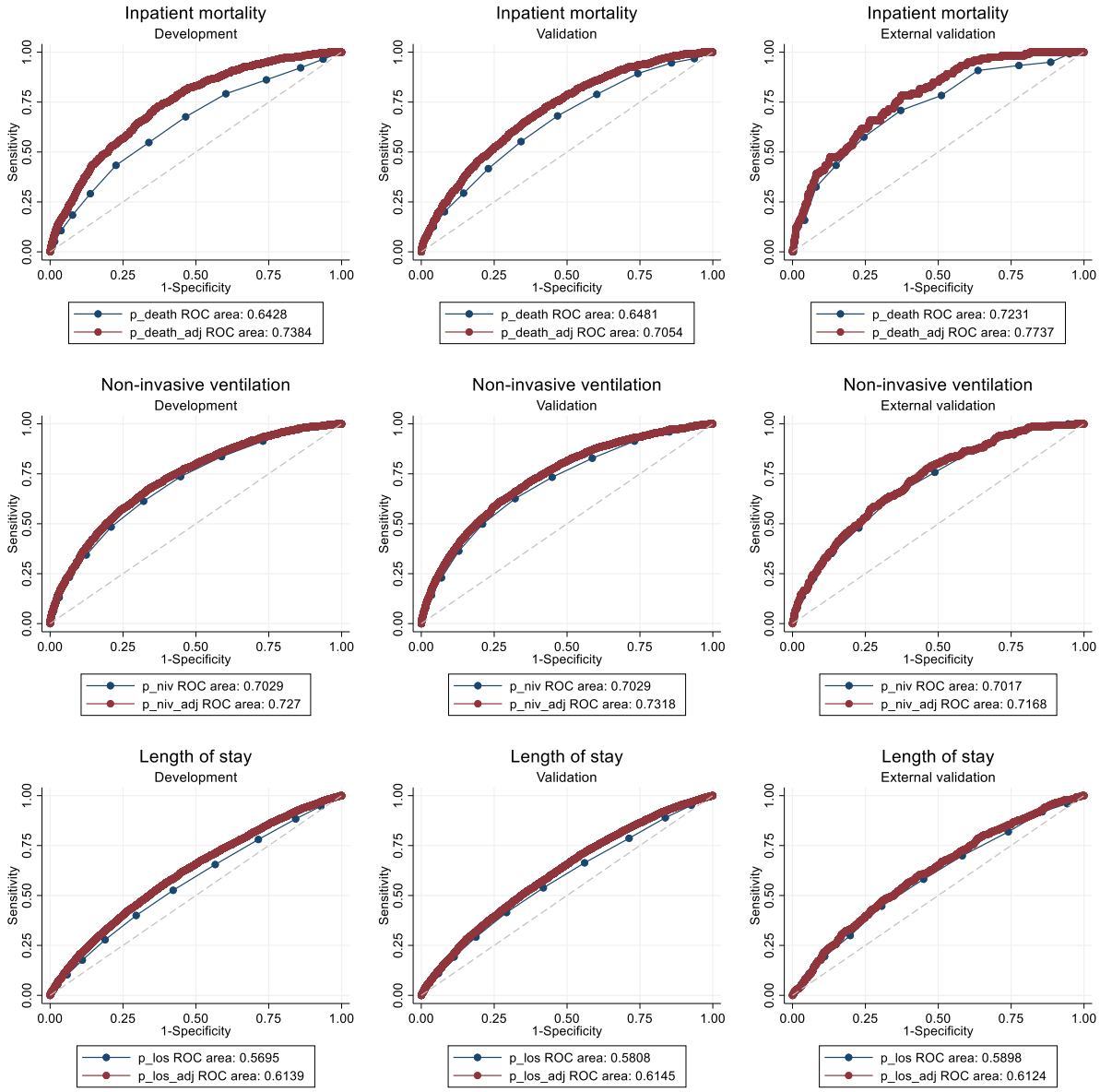

Figure 17. *Receiver Operating Characteristic (ROC) curves representing the discriminatory capacity of NEWS2 (blue) and the multivariable final model (red) to predict inpatient mortality, requirement for non-invasive ventilation, and a length of stay greater than the median of 4 days in the development, validation, and external validation cohorts*

Table 37. *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for NEWS2 prediction of inpatient mortality in the development and validation cohorts*

NEWS2 cut point	Development				Validation				External validation			
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
≥ 1	96.58%	6.33%	3.61%	98.08%	96.83%	6.31%	3.56%	98.24%	99.18%	4.89%	5.05%	99.15%
≥ 2	92.21%	14.03%	3.75%	98.02%	94.68%	14.19%	3.79%	98.68%	95.08%	11.37%	5.19%	97.84%
≥ 3	86.30%	25.76%	4.05%	98.11%	89.47%	25.75%	4.13%	98.56%	92.62%	22.15%	5.72%	98.33%
≥ 4	79.22%	39.59%	4.54%	98.13%	79.16%	39.81%	4.49%	98.16%	90.16%	36.27%	6.73%	98.64%
≥ 5	67.53%	53.41%	5.00%	97.84%	68.52%	53.29%	4.98%	97.93%	77.87%	48.93%	7.21%	97.75%
≥ 6	54.55%	66.09%	5.52%	97.56%	55.49%	65.77%	5.48%	97.64%	70.49%	62.89%	8.83%	97.66%
≥ 7	43.09%	77.42%	6.48%	97.40%	42.02%	76.98%	6.12%	97.38%	57.38%	75.51%	10.67%	97.20%
≥ 8	28.81%	86.25%	7.07%	97.09%	29.56%	85.49%	6.79%	97.14%	43.44%	85.04%	12.89%	96.72%
≥ 9	18.30%	92.34%	7.98%	96.89%	20.27%	92.03%	8.33%	97.00%	32.79%	91.85%	17.02%	96.40%
≥ 10	10.63%	96.26%	9.35%	96.74%	12.68%	95.80%	9.74%	96.84%	15.57%	95.82%	15.96%	95.70%
≥ 11	5.19%	98.44%	10.78%	96.62%	7.47%	98.15%	12.61%	96.74%	12.30%	98.16%	25.42%	95.64%
≥ 12	2.48%	99.32%	11.69%	96.56%	4.53%	99.30%	18.79%	96.68%	4.92%	99.16%	22.99%	95.34%
≥ 13	1.30%	99.69%	13.21%	96.53%	2.38%	99.73%	23.96%	96.62%	0.00%	99.67%	0.00%	95.13%
≥ 14	0.71%	99.85%	14.66%	96.52%	1.13%	99.87%	23.70%	96.58%	0.00%	99.83%	0.00%	95.14%
≥ 15	0.35%	99.92%	13.70%	96.51%	0.45%	99.95%	24.34%	96.56%	0.00%	99.87%	0.00%	95.14%
≥ 16	0.35%	99.96%	24.11%	96.51%	0.23%	99.99%	45.12%	96.56%	-	-	-	-
≥ 17	0.12%	99.97%	12.68%	96.50%	-	-	-	-	0.00%	99.96%	0.00%	95.15%
≥ 18	-	-	-	-	-	-	-	-	-	-	-	-
≥ 19	0.12%	99.99%	30.34%	96.50%	0.00%	99.99%	0.00%	96.55%	-	-	-	-

Table 38. *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for NEWS2 prediction of requiring non-invasive ventilation (NIV) during admission in the development and validation cohorts*

NEWS 2 cut point	Development				Validation				External validation			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
≥ 1	99.10%	6.73%	9.21%	98.74%	98.59%	6.69%	9.64%	97.92%	100.00%	5.41%	13.89%	100.00%
≥ 2	97.01%	14.84%	9.81%	98.11%	96.08%	14.89%	10.23%	97.41%	99.10%	12.60%	14.75%	98.92%
≥ 3	91.27%	26.92%	10.65%	97.00%	91.43%	26.90%	11.21%	96.88%	94.59%	23.88%	15.94%	96.66%
≥ 4	83.53%	41.08%	11.92%	96.31%	82.91%	41.39%	12.49%	96.00%	86.19%	38.22%	17.55%	94.77%
≥ 5	73.56%	55.18%	13.54%	95.63%	73.36%	55.15%	14.17%	95.35%	75.38%	51.15%	19.06%	93.16%
≥ 6	61.03%	67.89%	15.36%	94.81%	62.49%	67.81%	16.38%	94.71%	63.96%	65.12%	21.87%	92.21%
≥ 7	48.17%	79.07%	18.01%	94.11%	49.70%	78.95%	19.25%	93.96%	47.75%	77.22%	24.24%	90.64%
≥ 8	34.08%	87.61%	20.80%	93.30%	36.32%	87.12%	22.16%	93.13%	35.14%	86.53%	28.48%	89.73%
≥ 9	22.92%	93.39%	24.87%	92.70%	22.98%	93.08%	25.10%	92.29%	22.82%	92.71%	32.33%	88.73%
≥ 10	12.91%	96.87%	28.25%	92.10%	14.32%	96.50%	29.23%	91.78%	13.81%	96.65%	38.62%	88.02%
≥ 11	6.26%	98.75%	32.34%	91.69%	7.80%	98.54%	35.03%	91.37%	8.41%	98.58%	47.47%	87.58%
≥ 12	3.18%	99.49%	37.31%	91.50%	3.37%	99.43%	37.37%	91.07%	3.90%	99.40%	49.80%	87.14%
≥ 13	1.80%	99.80%	46.21%	91.41%	1.66%	99.79%	44.38%	90.95%	0.90%	99.77%	37.39%	86.84%
≥ 14	0.90%	99.90%	46.21%	91.35%	0.72%	99.90%	42.09%	90.88%	0.60%	99.91%	50.43%	86.82%
≥ 15	0.43%	99.95%	45.08%	91.32%	0.26%	99.96%	39.62%	90.85%	0.30%	99.91%	33.72%	86.78%
≥ 16	0.24%	99.96%	36.42%	91.30%	0.04%	99.98%	16.80%	90.83%	-	-	-	-
≥ 17	0.14%	99.98%	40.05%	91.30%	-	-	-	-	0.30%	100.00%	100.00%	86.79%
≥ 18	-	-	-	-	-	-	-	-	-	-	-	-
≥ 19	0.05%	99.99%	32.31%	91.29%	0.00%	99.99%	0.00%	90.83%	-	-	-	-

Table 39. *Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for NEWS2 prediction of a length of stay greater than the median 4 days in the development and validation cohorts*

NEWS2 cut point	Development				Validation				External validation			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
≥ 1	94.74%	7.08%	42.02%	65.44%	95.23%	7.37%	41.38%	69.23%	96.04%	5.70%	46.92%	62.38%
≥ 2	88.38%	15.73%	42.71%	65.57%	89.00%	16.39%	42.23%	68.45%	92.00%	14.29%	48.23%	67.30%
≥ 3	78.13%	28.53%	43.73%	64.73%	78.72%	28.82%	43.16%	66.36%	82.10%	25.84%	49.01%	62.45%
≥ 4	65.59%	43.28%	45.11%	63.89%	66.39%	44.08%	44.91%	65.63%	69.87%	41.61%	50.95%	61.40%
≥ 5	52.66%	57.72%	46.96%	63.17%	53.94%	58.26%	47.02%	64.81%	58.09%	55.04%	52.87%	60.21%
≥ 6	40.01%	70.43%	49.03%	62.29%	41.54%	70.79%	49.41%	63.81%	44.69%	69.48%	55.97%	59.14%
≥ 7	27.81%	81.13%	51.16%	61.26%	29.27%	81.27%	51.76%	62.59%	30.04%	80.33%	57.00%	56.95%
≥ 8	17.62%	89.00%	53.24%	60.32%	19.24%	88.74%	53.99%	61.54%	19.60%	89.07%	60.89%	56.07%
≥ 9	10.28%	94.20%	55.75%	59.63%	10.97%	94.09%	56.04%	60.61%	11.06%	94.38%	63.08%	55.00%
≥ 10	5.36%	97.42%	59.62%	59.15%	6.10%	97.11%	59.17%	60.10%	5.58%	97.03%	61.99%	54.21%
≥ 11	2.36%	99.00%	62.65%	58.79%	2.98%	98.93%	65.66%	59.76%	2.61%	98.83%	65.95%	53.90%
≥ 12	1.16%	99.66%	70.80%	58.65%	1.17%	99.63%	68.47%	59.48%	1.35%	99.61%	75.03%	53.77%
≥ 13	0.54%	99.85%	71.90%	58.55%	0.47%	99.87%	71.29%	59.37%	0.45%	99.77%	62.94%	53.59%
≥ 14	0.26%	99.92%	69.79%	58.49%	0.24%	99.95%	76.72%	59.33%	0.27%	99.92%	74.55%	53.58%
≥ 15	0.12%	99.96%	68.08%	58.47%	0.09%	99.98%	75.55%	59.30%	0.18%	99.92%	66.14%	53.56%
≥ 16	0.08%	99.99%	85.04%	58.47%	0.03%	100.00%	100.00%	59.29%	-	-	-	-
≥ 17	0.05%	99.99%	78.04%	58.46%	-	-	-	-	0.00%	99.92%	0.00%	53.51%
≥ 18	-	-	-	-	-	-	-	-	-	-	-	-
≥ 19	0.01%	99.99%	41.55%	58.45%	0.02%	100.00%	100.00%	59.29%	-	-	-	-

Table 40. *NEWS2 category and prediction of inpatient mortality, requirement for non-invasive ventilation, and length of stay greater than the median of 4 days in the internal validation cohort*

	Sensitivity	Specificity	PPV	NPV
Inpatient Mortality				
Medium and High Risk (≥5)	68.52%	53.29%	4.98%	97.93%
High Risk (≥7)	42.02%	76.98%	6.12%	97.38%
Need for acute NIV				
Medium and High Risk (≥5)	73.36%	55.15%	14.17%	95.35%
High Risk (≥7)	49.70%	78.95%	19.24%	93.96%
Length of Stay >4 days				
Medium and High Risk (≥5)	53.94%	58.26%	47.01%	64.81%
High Risk (≥7)	29.27%	81.27%	51.76%	62.59%

Table 41. *Prediction of inpatient mortality, requirement for non-invasive ventilation, and length of stay greater than the median of 4 days in the internal validation cohort for the optimal threshold of NEWS2 (NEWS2 ≥6)*

	Sensitivity	Specificity	PPV	NPV
Inpatient Mortality	55.49%	65.77%	5.48%	97.64%
Need for acute NIV	62.49%	67.81%	16.38%	94.71%
Length of Stay >4 days	41.54%	70.79%	49.41%	63.81%

The coefficients for NEWS2 to predict inpatient mortality, need for acute NIV, and a length of stay greater than four days are reported in **Table 42**. For each one-point increase in NEWS2, the odds of inpatient death increased by 20% (OR: 1.20 [95% CI: 1.17 – 1.23]), odds of needing acute NIV during admission increased by 30% (OR: 1.30 [95%CI: 1.28 – 1.33]), and the odds of having a hospital stay of more than 4 days increased by 10% (OR: 1.10 [95% CI: 1.09 – 1.11]). **Figure 18** shows good calibration in the internal validation cohort, however calibration is poorer in the external validation cohort where there is under-estimation of risk at the highest NEWS2.

Table 42. *NEWS2 coefficients and odds ratios for inpatient mortality, requirement for non-invasive ventilation, and length of stay greater than the median of 4 days in the univariable prediction models*

Prediction model	Coefficient (95% CI)	Odds ratio (95% CI)	p-value*
Inpatient mortality			
NEWS2	0.180 (0.157 – 0.204)	1.20 (1.17 – 1.23)	<0.001
Constant	-4.244 (-4.398 – -4.090)	0.01(0.01 – 0.02)	<0.001
Non-invasive ventilation			
NEWS2	0.266 (0.249 – 0.282)	1.30 (1.28 – 1.33)	<0.001
Constant	-3.761 (-3.871 – -3.651)	0.02 (0.02 – 0.03)	<0.001
Length of stay >4 days			
NEWS2	0.095 (0.085 – 0.105)	1.10 (1.09 – 1.11)	<0.001
Constant	-0.770 (-0.821 – -0.718)	0.46 (0.44 – 0.49)	<0.001

*: Wald test

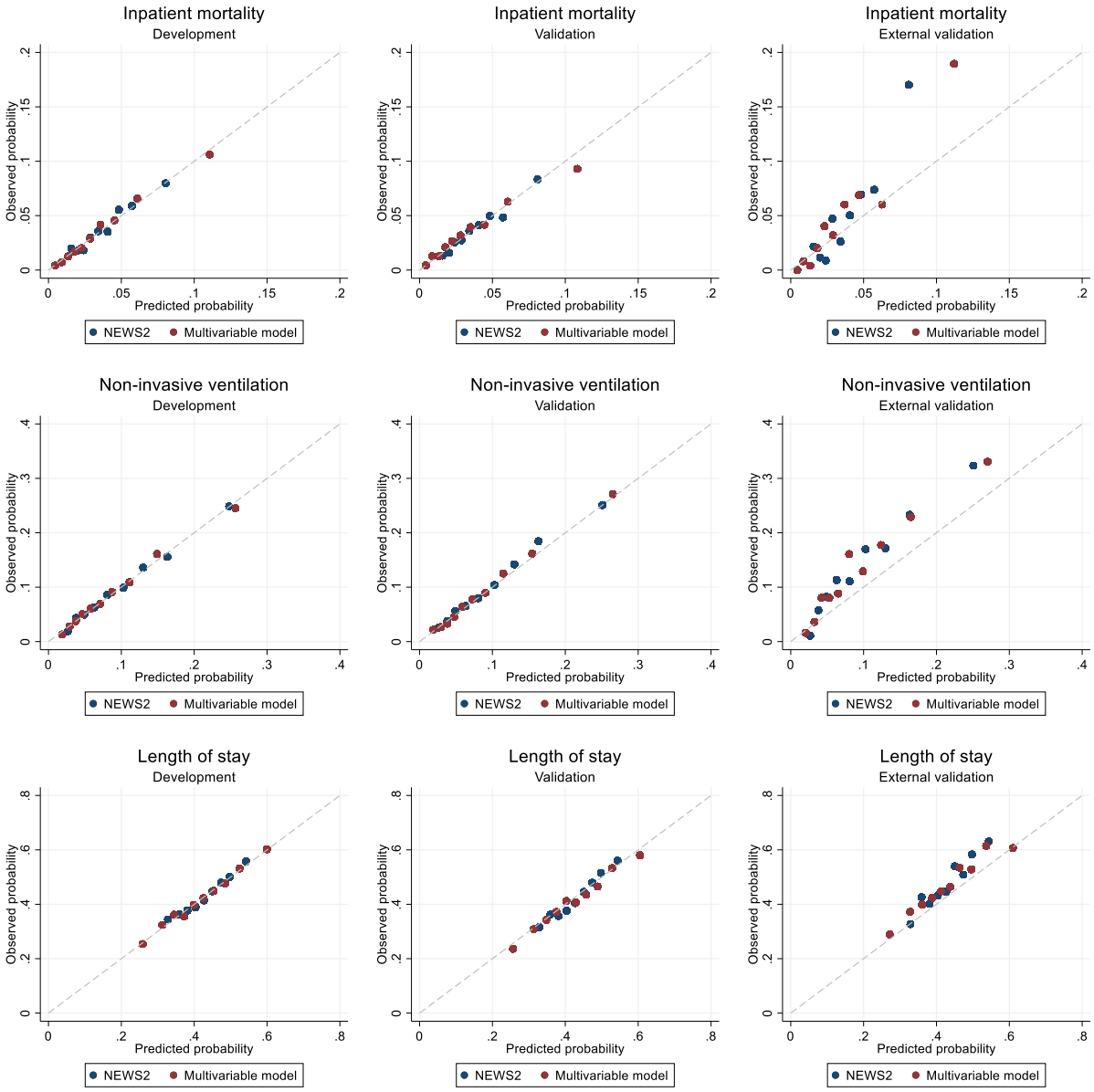

Figure 18. *Calibration plots for NEWS2 and multivariable prediction models for inpatient mortality, requirement for NIV, and a length of stay greater than the median of 4 days in the development, validation, and external validation cohorts*

7.4.2 Multivariable predictors of exacerbation outcomes

Results from the multivariable analysis for the association of all potential predictors with inpatient mortality, need for acute NIV, and length of stay in the development cohort are reported in **Table 43**, with model discrimination in comparison to NEWS2 reported in **Table 36**. Lung function, which was used to calculate GOLD stage (COPD severity), was poorly recorded with 57% of admissions missing this information in the development cohort (**Table 35**). ROC curves for NEWS2 and multivariable prediction models for each of the three outcomes in each cohort are presented in **Figure 17**.

Including all potential predictors in the mortality prediction model increased the AUC to 0.71 (95% CI: 0.69 – 0.72) in the internal validation cohort, compared to 0.65 (95%CI 0.63 – 0.67) for NEWS2 alone (**Table 36**). Including all potential predictors in the need for NIV prediction model increased the AUC to 0.73 (95% CI: 0.72 – 0.74) in the internal validation cohort, compared to 0.70 (95%CI 0.69 – 0.71) for NEWS2 alone (**Table 36**). Including all potential predictors in the length of stay prediction model increased the AUC to 0.61 (95% CI: 0.61 – 0.62) in the internal validation cohort, compared to 0.58 (95%CI 0.57 – 0.59) for NEWS2 alone (**Table 36**).

Calibration of the multivariable models for each outcome appeared good in the internal validation cohort (**Figure 18**).

Table 43. *Results from multivariable analysis of the association of all potential predictors with inpatient mortality, requirement for non-invasive ventilation, and a length of stay greater than the median of 4 days in the development cohort*

	Inpatient mortality		Requirement for NIV		Length of stay > 4 days	
Predictor	**Odds ratio (95% CI)**	**p-value***	**Odds ratio (95% CI)**	**p-value***	**Odds ratio (95% CI)**	**p-value***
NEWS2	1.21 (1.18 – 1.24)	<0.001	1.30 (1.28 – 1.32)	<0.001	1.10 (1.09 – 1.11)	<0.001
Quintiles of age (years)						
35–63	1		1		1	
64–70	2.96 (2.10 – 4.18)	<0.001	0.99 (0.86 – 1.13)	0.844	1.22 (1.12 – 1.33)	<0.001
71–75	3.11 (2.20 – 4.39)	<0.001	0.83 (0.72 – 0.97)	0.017	1.37 (1.26 – 1.50)	<0.001
76–81	3.91 (2.79 – 5.50)	<0.001	0.83 (0.71 – 0.97)	0.016	1.57 (1.43 – 1.71)	<0.001
≥82	5.80 (4.15 – 8.11)	<0.001	0.69 (0.59 – 0.82)	<0.001	1.88 (1.72 – 2.07)	<0.001
Gender						
Male	1		1		1	
Female	0.87 (0.76 – 1.00)	0.059	1.10 (1.00 – 1.21)	0.041	1.24 (1.17 – 1.31)	<0.001
Quintiles of IMD						
1 (most deprived)	1		1		1	
2	1.06 (0.86 – 1.30)	0.592	0.93 (0.82 – 1.06)	0.261	1.10 (1.02 – 1.18)	0.012
3	1.17 (0.95 – 1.44)	0.144	0.89 (0.78 – 1.02)	0.104	1.06 (0.98 – 1.15)	0.139
4	1.36 (1.10 – 1.68)	0.005	0.94 (0.82 – 1.09)	0.441	1.11 (1.02 – 1.21)	0.014
5 (least deprived)	1.04 (0.81 – 1.34)	0.757	0.95 (0.80 – 1.12)	0.532	1.03 (0.94 – 1.13)	0.545
GOLD COPD Severity						
1 – mild	1		1		1	
2 – moderate	1.03 (0.64 – 1.65)	0.902	1.35 (0.93 – 1.97)	0.120	1.03 (0.89 – 1.20)	0.664
3 – severe	1.40 (0.89 – 2.20)	0.150	2.34 (1.63 – 3.37)	<0.001	1.25 (1.08 – 1.46)	0.004
4 – very severe	1.93 (1.19 – 3.14)	0.008	4.64 (3.20 – 6.73)	<0.001	1.87 (1.58 – 2.21)	<0.001
Not recorded	1.54 (1.01 – 2.37)	0.047	2.19 (1.54 – 3.12)	<0.001	1.11 (0.97 – 1.28)	0.136
Smoking status						
Never smoked	1		1		1	
Ex-smoker	0.71 (0.51 – 0.98)	0.037	1.04 (0.77 – 1.40)	0.789	0.97 (0.83 – 1.12)	0.648
Current smoker	0.59 (0.41 – 0.83)	0.003	1.31 (0.97 – 1.77)	0.08	0.88 (0.75 – 1.02)	0.095
Not recorded	1.45 (1.01 – 2.09)	0.047	1.10 (0.78 – 1.55)	0.595	0.72 (0.61 – 0.87)	<0.001
History of CVD	1.61 (1.39 – 1.85)	<0.001	1.24 (1.12 – 1.37)	<0.001	1.27 (1.20 – 1.35)	<0.001
History of mental illness	0.95 (0.76 – 1.18)	0.623	0.96 (0.84 – 1.10)	0.537	1.24 (1.15 – 1.34)	<0.001
Constant	0.00 (0.00 – 0.01)	<0.001	0.01 (0.02 – 0.02)	<0.001	0.24 (0.19 – 0.29)	<0.001

*: Wald test

7.4.3 Multivariable predictors of NEWS2

Coefficients of the predictors in the NEWS2 prediction model are shown in **Table 44**. Only 1.3% of the variation in admission NEWS2 was explained by age, gender, deprivation, GOLD stage, smoking status, history of cardiovascular disease, and history of mental illness. Calibration of the model to predict NEWS2 was reasonable in the internal validation cohort but poorer in the external validation cohort (**Figure 19**).

Table 44. *Coefficients of NEWS2 predictors*

Predictor	Coefficient (95% CI)	p-value*
Quintiles of age (years)		
35–63	0	
64–70	0.086 (-0.023 – 0.196)	0.122
71–75	0.078 (-0.034 – 0.190)	0.173
76–81	-0.059 (-0.172 – 0.054)	0.306
≥82	-0.207 (-0.325 – -0.090)	0.001
Gender		
Male	0	
Female	0.246 (0.177 – 0.315)	<0.001
Quintile of 2019 Index of Multiple Deprivation		
1 (most deprived)	0	
2	-0.005 (-0.099 – 0.090)	0.923
3	-0.016 (-0.115 – 0.083)	0.753
4	-0.054 (-0.161 – 0.053)	0.322
5 (least deprived)	-0.096 (-0.219 – 0.027)	0.125
GOLD COPD Severity		
1 – mild	0	
2 – moderate	0.162 (-0.033 – 0.356)	0.103
3 – severe	0.656 (0.463 – 0.850)	<0.001
4 – very severe	1.031 (0.815 – 1.246)	<0.001
Not recorded	0.368 (0.189 – 0.548)	<0.001
Smoking status		
Never smoked	0	
Ex-smoker	0.467 (0.276 – 0.657)	<0.001
Current smoker	0.383 (0.187 – 0.580)	<0.001
Not recorded	0.162 (-0.065 – 0.389)	0.162
History of CVD	-0.096 (-0.169 – -0.024)	0.009
History of mental illness	-0.079 (-0.179 – 0.021)	0.123
Constant	3.642 (3.369 – 3.915)	<0.001

*: Wald test

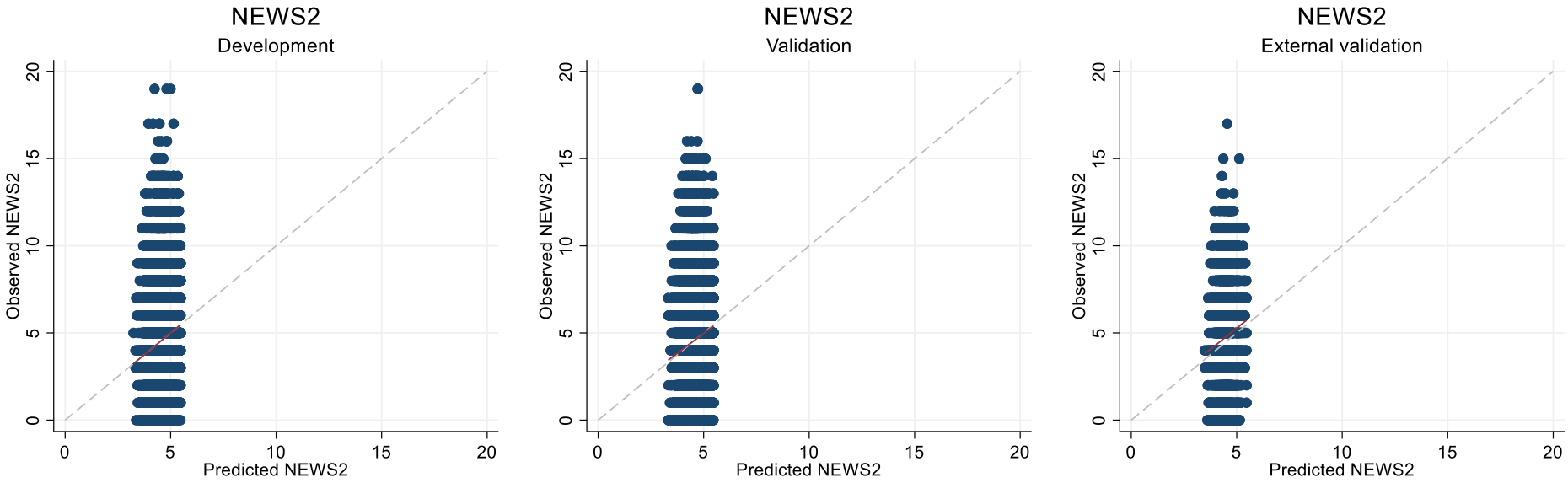

Figure 19. *Calibration plots for NEWS2 prediction in the development, validation, and external validation cohorts*

7.5 Discussion

In this chapter I have found that NEWS2 does not reasonably predict length of stay and provides limited prediction of inpatient mortality and requirement for NIV. However, if the patient characteristics of age, gender, deprivation, GOLD stage, smoking status, history of cardiovascular disease, and history of mental illness are additionally included in prediction models, those models have acceptable discrimination for inpatient mortality and requirement for NIV. Additionally, patient characteristics did not provide good prediction of admission NEWS2.

While NEWS2 did not offer good prediction of AECOPD outcomes, it is worth noting that each one-point increase in NEWS2 was significantly associated with a 20% increase in the odds of inpatient death and a 30% increase in odds of requirement for NIV. NEWS2 may therefore have some utility in identifying higher risk admissions where no alternative risk prediction tool is available.

A recent systematic review reported on 155 risk prediction models for patients with COPD(179) and found all to be at risk of bias. There is thus no standardised clinical risk prediction tool for AECOPD hospital admissions. There are, in addition, clear advantages of using a generic risk prediction tool for emergency admissions rather than multiple disease-specific scores, which had been the goal with the original NEWS. NEWS2 may provide better risk prediction than the original iteration of NEWS in patients with COPD(190), although this has been controversial(191) and may be dependent on how use of the separate oxygen scale for patients at risk of type 2 respiratory failure has been interpreted(192). NEWS2 has also been compared against the disease-specific DECAF score(190) and the authors found similar AUCs to those found in this study. DECAF was designed to predict mortality and inform decisions on need for hospital admission at exacerbation of COPD(131,180). However, DECAF has not been widely implemented, being disease specific and requiring assessment of blood eosinophils, radiographic consolidation, arterial blood pH and cardiac rhythm. Moreover, the DECAF derivation and validation cohorts(131,180,190) all consisted of patients with documented pre-existing airflow obstruction (spirometry was not available in more than half of the real-life admissions included in the present analysis). The DECAF studies also included patients with radiographic consolidation which is a controversial area in COPD and may be considered as pneumonia in a patient with underlying COPD(181). Patients with COPD and a primary diagnosis of pneumonia should not have data entered into the national COPD audit.

7.5.1 Strengths & limitations

The strength of this analysis is the very large sample size enabling examination of risk prediction in development and two separate validation datasets. However, there are some limitations to the study. Assessment of ‘requirement for NIV’ is whether a patient ‘received NIV’, which is not quite

the same, as it is possible that a patient may require NIV but not be willing to receive it. It seems plausible that individuals under greater observation would be more likely to receive NIV when they require it than those that are not being observed as intensely. Therefore, this may lead to some misclassification bias that would mean the null hypothesis (NEWS2 does not predict) for NIV prediction is more likely to be rejected. In this study, admissions were limited to the first admission for each patient within the audit period. While this simplifies the analysis, it may limit generalisability as real-world admissions will include readmissions. There were some issues with missing data too. FEV_1 percent-predicted, used to determine GOLD stage, had 57% of data missing meaning that prediction from this variable may be more likely to derive from its presence or absence rather than its value. There was also a fairly large proportion of missing NEWS2 data. It may be that presence of NEWS2 data is related to the quality of a hospital or severity of an admission and therefore it is possible that AECOPD admissions that may have been more likely to have worse outcomes have been excluded from the study due to the absence of NEWS2 data. Limited information was available on the value of the specific physiological parameters that make up the NEWS2, and therefore examination of these separately from the calculated NEWS2 was not possible in this study. It could be possible that a subset of the parameters used to calculate NEWS2 offer better predictive ability of AECOPD outcomes than the NEWS2, and these could be easily extracted from the patient's NEWS2 chart to predict outcomes. This may be worth investigating on a dataset with more complete information on the value of the individual NEWS2 parameters.

7.5.2 Conclusion

NEWS2, readily calculated from routine physiological variables at presentation to hospital with AECOPD, may provide acceptable prediction of inpatient mortality and the need for acute NIV in situations where rapid assessment of disease severity is required, and more complex physiological measures are unavailable. NEWS2 may also provide a method to classify AECOPD severity in epidemiological research where more detailed information on a patient's condition is unavailable. Useful further work would be to examine the predictive ability of the individual physiological parameters that comprise the NEWS2.

Chapter 8. Linked primary and secondary care data: how management of COPD patients and their pathways through healthcare affect admissions for AECOPD

8.1 Background

In previous chapters I have examined the quality of care received by COPD patients in primary and secondary care individually. In this chapter I expand on this by linking primary and secondary care data to examine the quality of care received by patients across the patient pathway.

The UK has one of highest COPD mortality rates in Europe, with a rate 50% higher than the EU average(3,71), and within England there is substantial variation between clinical commissioning groups (CCGs) in terms of the quality of COPD care received(71). There is 5-fold variation in rates of emergency hospital admissions for COPD between CCGs and over 3.7-fold variation in the proportion of admissions readmitted within 30 days of discharge(71).

COPD is part of a group of conditions known as ambulatory care sensitive conditions (ACSC), which are conditions where primary care interventions have the potential to prevent hospital admissions(193). Patients often have multiple attendances at primary care before an AECOPD hospital admission(194), meaning that each of these attendances is an opportunity to intervene and prevent admission. In addition, patients can often be admitted to hospital due to social isolation rather than clinical necessity(195,196). No data are available on the proportion of admissions due to social rather than clinical factors(196), but linkage of primary and secondary care data provides an opportunity to assess whether admissions are reduced where there is greater contact between primary and secondary care.

8.2 Aim

In this chapter I link primary care data from CPRD with secondary care AECOPD data from the NACAP COPD clinical audit to better understand the patient journey through primary and secondary care and the overarching quality of care received through the entire pathway. Specifically, I examine:

1. How many AECOPD admissions are potentially avoidable?
2. How many AECOPD admissions appear clinically inappropriate?
3. Does contact with primary care in the two weeks prior to an admission reduce the likelihood of an admission appearing inappropriate?
4. Does a COPD discharge care bundle increase the likelihood of receiving best practice care after discharge?
5. Do patients that receive best practice care after discharge have a lower risk of readmission?

8.3 Methods

8.3.1 Datasets

In this chapter, primary care data were obtained from the April 2020 snapshots of CPRD GOLD and CPRD Aurum, which have linkage eligible populations (current and historic patients) of 9,083,558 and 20,104,475, respectively. Additional data provided by CPRD were IMD deprivation and ONS mortality data which derived from the set 18 release (comprising data up to 01/05/2019). Secondary care acute exacerbation of COPD data were obtained from the 2019 cut (admissions between 01/10/2018 and 30/09/2019) of the NACAP COPD secondary care clinical audit. Detailed information on the CPRD GOLD, CPRD Aurum, IMD deprivation, ONS mortality, and NACAP secondary care COPD exacerbation databases can be found in **Chapter 3**.

The linkage of CPRD primary care data and NACAP secondary care AECOPD data was completed by CPRD as a bespoke linkage funded the Health Foundation. Ethical approval for the linkage can be found from CPRD in **Appendix D** and HQIP in **Appendix M**.

8.3.2 Data cleaning and inclusion/exclusion criteria

Stata 16 was used for all data management. Data were initially processed using the general method of dataset building and cleaning described in **3.1.4**. Patients whose data were not up to CPRD's acceptable data quality standards had already been removed before data were transferred to Imperial College London and therefore this stage of data cleaning was not necessary to complete. All clinical events with a missing date were removed to reduce the size of the dataset, as it cannot be known whether these events occurred during the follow-up period.

Malformation of the tab-delimited files provided by NACAP meant that manual editing of the files was required, and 9 patients were removed from the dataset as their entries contained unexpected additional data. All further processing of the NACAP secondary care audit data was identical to the methods used in the published reports(32) and described in **3.2.2.4** and **3.2.2.5**.

To generate the study cohort the dataset was limited to CPRD GOLD and CPRD Aurum patients with a linked record in the NACAP COPD clinical audit. This dataset was then further limited to those patients eligible for linkage to HES secondary care, IMD deprivation, and ONS mortality data. At least 1 year of follow-up since registration at a practice was required before a patient was included in the study period.

Start of follow-up was defined as the latest of:

- Registration start date + 365 days
- Start of HES follow-up
- Start of ONS follow-up
- 01/02/2017

End of follow-up was defined as the earliest of:

- Last collection of practice data date
- Registration end date
- Date of data linkage
- End of HES follow-up
- End of ONS follow-up
- 30/09/2020

Any admissions with follow-up beginning on or after the end of follow-up were excluded. Any admissions before the start of, or any admissions after the end of follow-up were excluded. Admissions were limited to index admissions only (i.e., patient's first in follow-up period). Admissions that were discharged after the end of follow-up were excluded. Patients that survived to discharge were excluded if they had fewer than 30 days of follow-up after discharge (**Figure 20**).

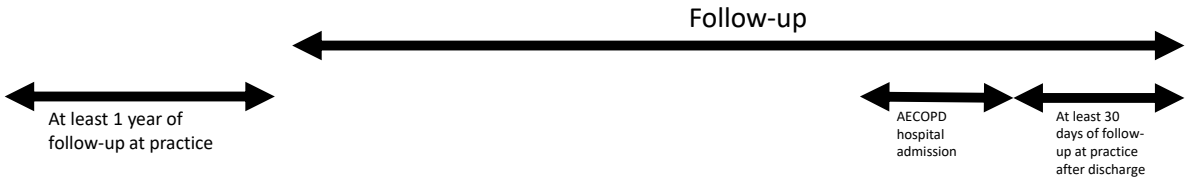

Figure 20. *Diagram of required follow-up for patients included in analysis of linked CPRD primary care data and NACAP COPD secondary care clinical audit data*

During data cleaning the following were excluded when deriving variables required for analysis:

- Any clinical events occurring after the end of follow-up
- First COPD diagnosis dates that occurred before the year in which a patient turned 35
- The top and bottom 1% of BMI values as these values were implausibly extreme
- Height values above 2 metres or below 1.2 metres
- FEV_1 volume readings above 7 litres or below 0.1 litres
- FEV_1 percent-predicted values above 151% or below 8%

8.3.3 Variable definitions

The following variables were used in analyses in this chapter. All variables marked with an asterisk (*) are defined, at least in part, in CPRD primary care data and are therefore defined using Read V2 codes in CPRD GOLD and SNOMED CT codes in CPRD Aurum, which can be found in **Appendix N** and **Appendix O**, respectively. Where possible, codelists replicate those used previously in this thesis.

8.3.3.1 COPD

COPD cases were defined by their presence in the NACAP COPD secondary care clinical audit. Presence of a COPD diagnosis in primary care was defined using new COPD codelists that included all Read V2 or SNOMED CT terms related to COPD, chronic bronchitis, or emphysema. New codelists were used to maximise detection of diagnoses, and to create consistency between the CPRD GOLD and CPRD Aurum definitions of COPD, as there is no current validated definition of COPD using SNOMED CT codes that could be used in the CPRD Aurum data. This new codelist was split into a 'broad' version including all terms, and a 'specific' version excluding terms that are less specific to a diagnosis of COPD. COPD codelist definitions for this chapter can be found for CPRD GOLD in **Appendix N** and for CPRD Aurum in **Appendix O**.

8.3.3.2 Exposures

- **Prior contact with primary care*:** any consultation record in the two weeks prior to admission. The purpose of this variable is to highlight admissions that may have been avoidable. Admissions without prior contact with primary care represent admissions that could potentially have been avoided.

- **Prescription of a rescue pack prior to admission*:** any patient with a prescription for antibiotics and oral corticosteroids at any point in the two weeks prior to admission (prescriptions can be on separate days in the two-week period). This will also serve to highlight potentially avoidable admissions as early treatment of an exacerbation shortens the severity and length of the exacerbation and may therefore prevent admission.

- **Discharge bundle:** binary variable available in the NACAP dataset that indicates whether a patient received a discharge bundle or not.

- **Best practice care*:** any primary care consultation record two weeks after discharge, assessment for referral to pulmonary rehabilitation (in either primary or secondary care), referral for smoking cessation help (from primary or secondary care) or prescription of a stop-smoking drug, inhaler technique check (in primary or secondary care), and prescription of a rescue pack of antibiotics and oral corticosteroids, all in the 30 days after discharge.

8.3.3.3 Outcomes

- **Appropriate admission:** an admission NEWS2 of 1 or more, prescription of oxygen, administration of oxygen, or administration of NIV at any point during admission. The purpose of this variable is to highlight admissions that could perhaps be due to social rather than clinical factors. For the purpose of this analysis, any admission not meeting this definition would not be justified from a clinical perspective but may be justified due to social factors.

- **Best practice care*:** (as described above).

- **30-day readmission:** any second admission recorded for a patient in the NACAP COPD clinical audit in the 30 days following discharge for their index admission.

8.3.3.4 Covariates

- **Age**: only year of birth is available in CPRD data therefore all patients were assumed to be born on 1st July and age was calculated at end of follow-up.

- **Comorbidities (anxiety, asthma, bronchiectasis, coronary heart disease, depression, gastro-oesophageal reflux disease, heart failure, interstitial lung disease, lung cancer, osteoporosis, and stroke)*:** any Read V2 (CPRD GOLD) or SNOMED CT (CPRD Aurum) code for disease at any time before end of follow-up.

- **Body Mass Index (BMI)*:** most recent BMI record in primary care data before admission (from no longer than 10 years before the end of follow-up), categorised as underweight, normal, overweight, or obese, as per the WHO definition(197).

- **Lung function (GOLD stage of airflow obstruction)***: most recent FEV_1 (volume) before end of follow-up (no longer than 5 years before the end of follow-up) used to calculate FEV_1 percent-predicted, or where unavailable, most recent record of FEV_1 percent-predicted

before end of follow-up. FEV_1 percent-predicted values were categorised as Mild, Moderate, Severe, and Very severe as per the GOLD definition(1).

- **Exacerbation frequency*:** number of exacerbations in the year preceding admission were defined using the validated Rothnie et al.(72) method of counting exacerbation records, lower respiratory tract infections, and prescriptions of antibiotics and oral corticosteroids in the primary care record, requiring a 14 day gap between events to count as a separate exacerbation. Exacerbation frequency was coded as 0, 1, or ≥2 exacerbations in the year preceding admission.

8.3.4 Statistical analysis

Analyses were completed using Stata 16. Firstly, summary statistics were computed. Age was normally distributed and summarised using mean and standard deviation. All other variables, as categorical variables, were summarised using frequencies and proportions. A sample size calculation determined that the required sample to be able to detect a significant difference (alpha = 0.05) in readmission between patients that received best practice care after discharge and those who did not at 80% power would be 7,727. The number of patients in the sample received from CPRD was only sufficient to provide power of 54%.

Assessment of association between exposure and outcome variables was done using logistic regression. Odds ratios and 95% confidence intervals were generated for each outcome. All analyses were adjusted for age, sex, deprivation, comorbidities (bronchiectasis, asthma, interstitial lung disease, heart failure, osteoporosis, lung cancer, stroke, coronary heart disease (CHD), gastro-oesophageal reflux disease (GORD), anxiety, and depression), BMI, lung function (GOLD stage), and exacerbation frequency. The specific associations examined were:

1. Contact with primary care and admission appropriateness
2. Receipt of a rescue pack of antibiotics and oral corticosteroids and admission appropriateness
3. Receipt of a discharge bundle and receipt of best practice care after discharge
4. Receipt of best practice care after discharge and readmission within 30 days of discharge

As not all admissions labelled as receiving a discharge bundle received all bundle elements, the association between receiving all bundle items (inhaler technique check, medication review, self-management plan, provision of a rescue pack of antibiotics and oral corticosteroids, smoking cessation treatment (if a current smoker), assessment for referral to pulmonary rehabilitation, and arrangement for follow-up) and receipt of best practice care after discharge was assessed as a further analysis.

Additionally, as a large proportion of best practice post-discharge care was completed in secondary care, the association between receiving a discharge bundle and receipt of each element of best practice care (post-discharge review in primary care, assessment of suitability for pulmonary rehabilitation, referral for smoking cessation services or prescription of a stop-smoking drug, inhaler technique check, and prescription of a rescue pack of antibiotics and oral corticosteroids) was assessed individually in patients who had not received that element of care in secondary care.

BMI data were obtained from the past 10 years rather than the past 5 years, as was originally intended, to minimise missing data. With the exception of spirometry, where 14.8% of data were missing, missing data for other variables were minimal (<5%). Complete case analysis was used where data were missing.

8.4 Results

3,955 patients met the inclusion criteria and were available for analysis. Summary statistics are shown in **Table 45**. The cohort was older with a mean age of 71.8 and deprived with a plurality (30.4%) being in the most deprived quintile. There was a roughly 50:50 distribution of current (49.0%) and ex-smokers (49.3%), and very few were never smokers or had an unknown smoking status (1.7%). 50.8% of the cohort had either severe or very severe lung disease based on GOLD classification of FEV_1 percent predicted. 57.5% were frequent exacerbators with more than 2 exacerbations in the year preceding admission, and roughly 5% did not have a diagnosis of COPD in their primary care record. 44.9% of patients had a diagnosis of asthma ever; the prevalence for each of stroke, CHD, and GORD was more than 20%. Mental health issues were also highly prevalent with anxiety and depression having a prevalence of over 35% in the cohort. Over 50% of the cohort was overweight or obese and 4.2% died as an inpatient. 71.7% were labelled as having received a discharge bundle but only 9% of patients received all bundle items. 79.6% had contact with primary care in the two weeks prior to admission, 20.1% received a prescription for a rescue pack of antibiotics and oral corticosteroids from primary care in the two weeks prior to admission, 85.8% of admissions were appropriate from a clinical perspective, 21% of patients received best practice care after discharge, and 10% of patients surviving to discharge were readmitted within 30 days of discharge.

Table 45. *Summary statistics for the cohort of patients with linked CPRD primary care and NACAP secondary care COPD clinical audit data*

	Frequency (%) (N=3,955)
Age	
Mean (SD)	71.8 (10.7)
Gender	
Male	1,790 (45.26%)
Female	2,165 (54.74%)
Quintile of 2015 Index of Multiple Deprivation	
1 (least deprived)	502 (12.69%)
2	619 (15.65%)
3	723 (18.28%)
4	904 (22.86%)
5 (most deprived)	1,203 (30.42%)
No data	4 (0.10%)
Smoking status	
Never	16 (0.40%)
Ex	1,949 (49.28%)
Current	1,938 (49.00%)
No data	52 (1.31%)
GOLD stage	
Mild	246 (6.22%)
Moderate	1,114 (28.17%)
Severe	1,352 (34.18%)
Very severe	657 (16.61%)
No data	586 (14.82%)
Exacerbations in year preceding admission	
0	870 (22%)
1	813 (20.56%)
≥2	2,272 (57.45%)
COPD diagnosis	
Specific definition	3,754 (94.92%)
Broad definition	3,760 (95.07%)
Comorbidities	
Bronchiectasis	362 (9.15%)
Asthma	1,774 (44.85%)
ILD	89 (2.25%)
Heart failure	604 (15.27%)
Osteoporosis	761 (19.24%)
Lung cancer	167 (4.22%)
Stroke	1,073 (27.13%)
CHD	949 (23.99%)

GORD	886 (22.4%)
Anxiety	1,376 (34.79%)
Depression	1,524 (38.53%)
BMI	
Underweight	467 (11.81%)
Normal	1,379 (34.87%)
Overweight	969 (24.5%)
Obese	1,036 (26.19%)
No data	104 (2.63%)
Inpatient mortality	
Alive	3,788 (95.78%)
Died as inpatient	167 (4.22%)
Discharge bundle completed	
No	926 (23.41%)
Yes	2,837 (71.73%)
Self-discharge	25 (0.63%)
Died	167 (4.22%)
Received discharge bundle items	
No	3,434 (86.83%)
Yes	354 (8.95%)
Died	167 (4.22%)
Primary care events prior to admission	
Contact with primary care in the 2 weeks prior to admission	3,149 (79.62%)
Receipt of a rescue pack of antibiotics and oral corticosteroids in the 2 weeks prior to admission	796 (20.13%)
Clinically appropriate admission	3,395 (85.84%)
Events after admission	
Follow-up in primary care within 2 weeks of discharge	3,422 (86.52%)
Patient assessed for referral to PR	2,083 (52.67%)
Inhaler technique checked	2,750 (69.53%)
Prescribed a rescue pack of antibiotics and oral corticosteroids	1,724 (43.59%)
Smoking cessation treatment provided	
No	1,125 (28.45%)
Yes	813 (20.56%)
Not a current smoker	2,017 (51%)
Patient received best practice care after discharge	832 (21.04%)
Patient readmitted within 30 days of discharge	
No	3,409 (86.19%)
Yes	379 (9.58%)
Died during index admission	167 (4.22%)

8.4.1 Association between prior contact with primary care and admission appropriateness

The proportion of clinically appropriate admissions was near identical for patients who had contact with primary care in the two weeks prior to admission and those who did not have contact (**Table 46**). Likewise, the proportion of clinically appropriate admissions was near identical for patients who did and did not receive a rescue pack of antibiotics and oral corticosteroids from primary care in the two weeks prior to admission (**Table 47**).

Table 46. *Number of clinically appropriate admissions for patients who had contact with primary care in the two weeks prior to their admission and patients who did not have any contact with primary care*

	No contact with primary care in the 2 weeks prior to admission (N=806)	**Contact with primary care in the 2 weeks prior to admission (N=3,149)**
Appropriate admission	689 (85.48%)	2,706 (85.93%)

Table 47. *Number of clinically appropriate admissions for patients who received a rescue pack of antibiotics and oral corticosteroids from primary care in the two weeks prior to their admission and patients who did not receive a prescription for a rescue pack*

	Did not receive a rescue pack of antibiotics and oral corticosteroids in the 2 weeks prior to admission (N=3,159)	**Received a rescue pack of antibiotics and oral corticosteroids in the 2 weeks prior to admission (N=796)**
Appropriate admission	2,716 (85.98%)	679 (85.30%)

8.4.2 Association between receipt of a discharge bundle and receipt of best practice care in the 30 days after discharge

Patients who received a discharge bundle had 20 times the odds (OR: 20.54 [95% CI: 12.22 – 34.54]) of receiving all the components of best practice care (**Table 48**). Patients who received all discharge bundle components had almost 13 times greater odds (OR: 12.85 [95% CI: 9.84 – 16.78]) of receiving all components of best practice care (**Table 49**).

Table 48. *Number of patients who received best practice care following discharge for patients who received a discharge bundle and for patients who did not receive a discharge bundle*

	Did not receive a discharge bundle (N=926)	Received a discharge bundle (N=2,837)
Best practice care	15 (1.62%)	815 (28.73%)

Table 49. *Number of patients who received best practice care following discharge for patients who received all components of the COPD discharge bundle and for patients who did not receive all components of the discharge bundle*

	Did not receive all components of the COPD discharge bundle (N=3,434)	Received all components of the COPD discharge bundle (N=354)
Best practice care	576 (16.77%)	256 (72.32%)

8.4.2.1 Primary care only (excluding patients who received best practice care in secondary care)

Numbers and proportions of patients receiving best practice care and the individual care components by receipt of a discharge bundle is shown in **Table 50**. There was no significant difference (OR: 0.49 [95% CI: 0.14 – 1.73]) in receipt of best practice care (for patients who did not receive that best practice care in secondary care) between patients who received a discharge bundle and those who did not.

Table 50. *Number of patients who received all best practice care components and each care component individually following discharge,* ***excluding patients who received that item of care in secondary care****, for patients who received a COPD discharge bundle and for patients who did not receive a discharge bundle*

	Did not receive a discharge bundle (N=926)	Received a discharge bundle (N=2,837)
Best practice care in primary care (for patients who did not receive it in secondary care)	<5 (<0.54%)	7 (0.25%)
Follow-up in primary care 2 weeks after discharge	801 (86.50%)	2,490 (87.77%)
Assessed for referral to pulmonary rehabilitation (N=1742)	28 (3.28%)	28 (3.15%)
Referred for smoking cessation or prescribed smoking cessation medication (N=1255)	59 (15.00%)	143 (16.71%)
Inhaler technique check (N=1059)	31 (4.05%)	7 (2.39%)
Prescription of a rescue pack (N=2742)	209 (23.46%)	484 (26.00%)

Numbers and proportions of patients receiving best practice care and the individual care components by receipt of all discharge bundle components were similar (**Table 51**). Again, there was no significant difference (OR: 0.99 [95% CI: 0.12 – 7.97]) in receipt of best practice care between patients who received all bundle components and those who did not.

Table 51. *Number of patients who received all best practice care components and each care component individually following discharge,* ***excluding patients who received that item of care in secondary care****, for patients who received all COPD discharge bundle components and for patients who did not receive all discharge bundle components*

	Did *not* receive all components of the COPD discharge bundle (N=3434)	**Received all components of a COPD discharge bundle (N=354)**
Best practice care in primary care (for patients who did not receive it in secondary care)	10 (0.29%)	<5 (<1.41%)
Follow-up in primary care 2 weeks after discharge	2993 (87.16%)	320 (90.4%)
Assessed for referral to pulmonary rehabilitation (N=1761)	56 (3.18%)	*
Referred for smoking cessation or prescribed smoking cessation medication (N=1269)	196 (16.24%)	8 (12.90%)
Inhaler technique check (N=1077)	39 (3.62%)	*
Prescription of a rescue pack (N=2763)	690 (25.24%)	8 (27.59%)

*Item of care was received by all patients in this exposure group in secondary care and therefore no patients were included in the denominator for this item

8.4.3 Association between receipt of best practice care within 30 days of discharge and 30-day readmission

No significant difference (OR: 1.21 [95% 0.93 – 1.58]) was found in 30-day readmission between patients who received all items of best practice care and patients who did not (**Table 52**).

Table 52. *Number of patients who were readmitted within 30 days of discharge for patients who received all items of best practice care and for patients who did not receive all items of best practice care*

	Patient did not receive all items of best practice care (N=2956)	**Patient received all items of best practice care (N=832)**
Readmitted within 30 days of discharge	280 (9.47%)	99 (11.90%)

8.5 Discussion

In this chapter I have found that 80% of patients who were admitted to hospital with an acute exacerbation of COPD had contact with their GP in the two weeks prior to admission, and that 86% of admissions were appropriate from a clinical perspective. Contact with primary care did not appear to be associated with the appropriateness of an admission. 20% of patients received a prescription for a rescue pack of antibiotics and oral corticosteroids in the two weeks prior to their admission but again this did not appear to be associated with admission appropriateness.

I also found that patients who received a COPD discharge bundle had 20 times greater odds of receiving best practice care (follow-up within two weeks, assessment for referral to pulmonary rehabilitation, referral for smoking cessation, inhaler technique check, and prescription of a rescue pack) than those who did not receive a discharge bundle. However, this association is weaker when examining completion of the combination of the required bundle items (rather than the claim that a bundle was completed) with admissions that received all the bundle items having almost 13 times greater odds of receiving best practice care. To determine if the strength of this association was due to the bundle items being part of my definition of best practice care, I repeated the analysis excluding patients who received best practice care in secondary care. In this analysis I found no association between receipt of a discharge bundle or receipt of the discharge bundle items and receiving best practice care. This may suggest that the strength of association between discharge bundles and best practice care is driven by the care received in secondary rather than primary care; but equally it could simply be that the exposure and outcome (when including secondary care) are highly correlated due to their similar definitions including bundle components indirectly in the exposure and directly in the outcome definition. Stata did not highlight any collinearity between the two variables in analyses that would provide evidence for this second possible explanation, but inconsistent recording of discharge bundles could possibly have helped diminish the strength of association enough for collinearity not to be observed. It should be noted however, that this further analysis was substantially underpowered, with a power of just 18%, so it is not possible to draw any conclusion on associations or lack thereof.

Finally, I found no association between receipt of best practice care (irrespective of claimed receipt of a discharge bundle) and 30-day readmission. However, again this analysis was underpowered with a power of only 54% and would require roughly double the sample size in order to detect a significant difference at 80% power.

8.5.1 Previous studies of discharge bundles

Previous studies(51,198) have found that the implementation of discharge bundles does significantly increase receipt of bundle components, however the implementation was not reliable as not all bundle items were fully completed. This appears consistent with results found in this chapter as there was a strong association between receipt of a bundle and receiving best practice care, but not all bundle items were implemented for admissions that claimed to have received a discharge bundle. As mentioned in **Chapter 6** on the COPD BPT, literature reviews(167,171) have not been able to find evidence for discharge bundles leading to an improvement in mortality or quality of life, and only weak evidence for a reduction in readmissions. A recent study in the UK(51) was also unable to find an improvement in readmission, only finding a reduction in A&E attendances following the implementation of bundles.

8.5.2 Strengths & limitations

Unfortunately, being limited to less than one year of audit data has meant that analyses in this chapter were underpowered, and it is therefore not possible to draw conclusions from the analyses. There is also a fair proportion of missing data for lung function; although this may perhaps be explained by the fact that 5% of patients were not diagnosed with COPD and others may have recent diagnoses. While multiple imputation could perhaps be used to fill missing lung function values, it seems plausible that there is an association between lung function and missingness of lung function data, as patients with worse lung function are plausibly more likely to have a record of lung function. Therefore, the data may be missing not at random (MNAR), making imputation problematic. The definition of an 'appropriate' admission will not have taken account of all possible reasons for an admission and therefore it is possible that an admission may be appropriate for other reasons, such as the patient being vulnerable, that my definition does not include.

8.5.3 Conclusion

Receipt of a discharge bundle is associated with receipt of best practice care. While a large proportion of admissions are labelled as receiving a discharge bundle, only a few receive all components of the bundle. Contact with primary care does not appear to affect the appropriateness of an admission. Limited power from the small sample received for this chapter's analyses mean that it is not possible to draw further conclusions on whether discharge bundles improve care in primary care or whether best practice care reduces readmissions.

Chapter 9. Discussion

In this final chapter I summarise the findings of this thesis, discuss what it means, make suggestions for future work that would build upon the findings of this thesis.

In this thesis I aimed to link secondary care AECOPD data from national clinical audit with primary care EHR data to explore how variations in patient pathways through healthcare affect AECOPD hospital admissions in England. To complete this aim, I first examined care quality in primary care, then secondary care, and finally using linked primary and secondary care data to examine the full patient pathway.

In the first objective of this thesis, I aimed to find validated definitions of AECOPD in EHRs to obtain the most accurate definition of AECOPD to use in subsequent chapters and to provide a helpful resource for other researchers. Disappointingly few studies have validated AECOPD definitions in EHRs and it has therefore only been possible to produce a list of the current best AECOPD finding algorithms, rather than produce a quantitative synthesis with pooled estimates of sensitivity and specificity for each algorithm. Although I think a researcher using the best algorithm from any of the few validation studies included would be reasonable given the limited information available to say otherwise. The current best AECOPD detection algorithms are summarised in **Table 8** and the Read code algorithm has been utilised in **Chapter 4**, **Chapter 5**, and **Chapter 8**. I think this piece of work combined with the large collection (including unvalidated) of COPD codes found by the BREATHE team(99–101) should provide a useful resource for anyone wishing to study AECOPD using EHRs.

One area of critique that I would have for the review of AECOPD definitions is the use of the QUADAS-2 risk of bias tool. While the tool itself appeared to be the most appropriate option for the study, QUADAS-2 requires customisation for each study, which feels very subjective. Determining the risk of bias for each category of QUADAS-2 also felt quite subjective, and I would be curious to know if other researchers would obtain similar risk of bias results, even with me having had a second reviewer to discuss any disagreements with.

Given that too few studies have been published to produce pooled estimates of AECOPD detection algorithm validity, further validation studies of the commonly used AECOPD detection algorithms would be useful to improve estimates of validity and generalisability. Specifically, it would be useful to ascertain a PPV for the recommended ICD-10 algorithm as this is missing from currently available data. It would also be desirable to obtain NPV and specificity values for the recommended algorithms, however finding true and false negatives requires substantially more time and effort than finding true and false positives. As AECOPD prevalence data were not provided in many of the

studies, it would be helpful if this information were included in future AECOPD validation studies to make comparisons between studies easier. With event detection there is generally a trade-off between sensitivity and specificity, and further investigation of whether a one-size-fits-all approach has acceptable validity for AECOPD detection in multiple scenarios, or if different algorithms would be required depending on the need for greater sensitivity or greater specificity, would also prove useful.

In the next objective of this thesis, I aimed to determine the predictors of referral to pulmonary rehabilitation from primary care to help identify patient groups that may need greater targeting. Reassuringly it appeared that patients were receiving good care with those with more severe symptoms being appropriately prioritised for referral to PR. There also appeared to be an association between other best practice care and referral to PR, as recent records of an MRC score and influenza immunisation were associated with referral. This could indicate that quality of care in practices is highly variable, and where patients receive good care in one regard, they receive good care in other regards too. However, given that variability between practices was controlled for using a random intercept in regression models, it may simply be that where sicker patients are prioritised for one item of care, they are also prioritised for other key elements of care.

It was concerning to observe that current smokers, older (≥70 years), female, and more deprived patients were less likely to be referred to PR. However, further analysis found that with the exception of women, these groups were no less likely to be *considered* for referral, meaning that the reason for these groups not being is referred is either refusal of the referral or lack of availability of a PR programme. The finding that women were both less likely to be considered for and referred for PR could indicate that an unconscious bias exists against women in the treatment as well as diagnosis of COPD. Therefore, even though the reduction in consideration for referral for women may be small, further investigation of the reasons behind this reduced referral is important given that women make up large portion of the COPD population. Assessment of gender as a potential predictor of PR referral from secondary care, and in other countries, would determine if the issue is more widespread. This analysis may also be limited by its use of a stepwise regression model, which in hindsight, might not have been the most appropriate choice for analysis. Repeating this analysis with careful consideration of the appropriate variables may give a more accurate picture of key predictors of referral to pulmonary rehabilitation.

For the second primary care objective of this thesis, I aimed to determine if Welsh practices in CPRD GOLD showed comparable patterns of care to practices included within the Welsh primary care audit, and therefore if Welsh CPRD practices are representative of Wales. I followed this by

comparing the care received in English, Scottish, and Northern Irish CPRD GOLD practices against Welsh practices to assess whether the four UK nations were comparable for COPD primary care, or if the Welsh primary care audit has led to improvements in care in Wales that are not being observed in the rest of the UK.

Welsh practices in CPRD GOLD appeared comparable to Welsh national audit practices in terms of COPD care, and therefore CPRD GOLD appears representative of Wales for COPD primary care. All four nations were poor at recording spirometry, chest X-rays, and smoking cessation. England, Scotland, and Northern Ireland were all significantly worse than Wales at confirming airways obstruction and referring patients to pulmonary rehabilitation. These findings indicate that completing the primary care audit in Wales only may have led to improvements in the quality of care delivery, or at least, improvements in the quality of recording of healthcare delivery in Wales that are not being seen elsewhere in the UK. The audit could have led to these improvements through increased awareness of the importance of these interventions and/or increased awareness of accurate coding of these events. Increased exception reporting for pulmonary rehabilitation in Wales suggests that Welsh GPs have a greater awareness of how to accurately code events in the patient record. Financial incentivisation may play a role as well; as Scotland no longer participates in the Quality and Outcomes Framework (QOF), this may provide some explanation as to why Scottish results were often poorer than the other nations. High correlation of spirometry results within practices also appears to add further weight to poor outcomes perhaps being more a matter of accurate recording in the patient health record rather than actual completion of the care.

Like all studies using EHRs this study does appear to be limited by the accuracy of the recording of events in the patient health record. Financial incentives for accurate coding of events could perhaps improve this and would have clear benefits for increasing the research quality of the data but may have more limited clinical benefits. Feeding these results back to the developers of the GP EHR software could perhaps help them tweak their software to make it easier for GPs to code these events accurately. Useful further work would be to repeat the audit analyses in each year following 2017 to assess care quality over time. A qualitative study of GPs in each UK country to query why certain key elements of COPD care are poorly recorded may provide helpful insight on how care delivery could be improved.

In the first of the secondary care objectives, I aimed to determine if the combination of respiratory specialist review and COPD discharge care bundle that the COPD BPT seeks to incentivise, improves mortality and readmissions. This is the analysis I'm most happy with in this thesis. I think the analysis is a good as it can possibly be, and it has survived several rounds of peer review.

Respiratory specialist review and COPD discharge care bundles, both combined and individually, were not associated with an improvement in 30-day mortality or readmission. In further analysis including patients who did not survive to discharge, a respiratory specialist review at any point during admission was associated with 31% lower odds of inpatient mortality. This indicates that respiratory specialist review is important during admission but has limited impact after discharge. Interestingly specialist review within 24 hours is part of the COPD admission bundle and this finding seems to validate its role as an important part of an AECOPD admission to improve admission outcomes.

Examination of 90-day outcomes found that patients who were reviewed by a specialist within 24 hours of admission had 16% greater odds of 90-day mortality than those who did not receive a review in 24 hours. The likely explanation for this finding is that there is unmeasured confounding from admission severity that I have not been able to adjust for, and that more severe cases were appropriately prioritised for rapid review and treatment. It may in fact be that rapid review by a respiratory specialist is an indicator of admission severity.

It may be that one reason for not finding a benefit from discharge bundles in this analysis is that the components of a discharge bundle all work in slightly different ways and potentially even counteract one another. For example, while receiving a self-management plan and review of medication may help reduce readmissions, follow-up calls might increase readmissions.

Discharge bundles are not always implemented fully so this could be why COPD discharge care bundles are not leading to desired improvements in patient outcomes. Therefore, useful future work would be to evaluate the effectiveness of the COPD BPT criteria when all bundle items are fully implemented. This analysis will be possible in newer cuts of audit data as future COPD clinical audit datasets will contain detailed information on the specific bundle items completed. It may also be appropriate the redesign the COPD BPT. The COPD BPT includes one item from the COPD admission bundle, but the whole discharge bundle; maybe it would be more appropriate to pick key interventions from the bundles that all target one specific outcome, for example, mortality.

For the second of the secondary care objectives, I aimed to determine whether NEWS2 can be used to predict inpatient mortality, requirement for NIV, and length of stay in AECOPD admissions, and therefore if it is a useful tool for risk/severity categorisation of AECOPD admissions. NEWS2 did not reasonably predict length of stay and only provided limited prediction of inpatient mortality and requirement for NIV. NEWS2 prediction of requirement for NIV was the best; however, the AUC was still only 0.7, and with the cut-point for NEWS2 being a score that would recommend at least hourly

monitoring of the patient, maybe an indication of greater likelihood of need for NIV is of limited benefit when a patient is being closely monitored anyway.

The addition of age, gender, deprivation, GOLD stage, smoking status, history of cardiovascular disease, and history of mental illness to the inpatient mortality and requirement for NIV prediction models increased discriminative ability of the models to acceptable levels. While NEWS2 has disappointing prediction of AECOPD outcomes, each point increase in NEWS2 was associated with a 20% increase in odds of inpatient death and a 30% increase in odds of requirement for NIV. NEWS2 may therefore provide some utility in risk/severity categorisation of AECOPD admissions where no alternative (such as DECAF) is available.

NEWS2 is designed to track risk over time, aiding detection and management of a deteriorating patient; therefore, further research to explore the utility of examining changes in NEWS2 during an AECOPD admission and how these changes may relate to outcome measures could be useful. Additional useful further work would be to compare NEWS2 with other AECOPD risk prediction tools in identical populations; this would give a better picture of its relative performance.

For the final objective, I aimed to link primary care EHR data with secondary care COPD audit data to better understand variation in patient pathways and how the interaction between primary and secondary care affects patient outcomes. Specifically, I examined: (i) how many AECOPD admissions were potentially avoidable, (ii) how many AECOPD admissions were clinically appropriate, (iii) whether contact with primary care prior to admission affects admission appropriateness, (iv) whether a COPD discharge care bundle increases the odds of receiving best practice care after discharge, (v) whether patients that receive best practice care after discharge have lower odds of readmission.

This objective turned out to be a huge disappointment. I was only provided with the most recent year of audit data, rather than all data ever, and this year of data only had a roughly 9 month overlap with the most recent CPRD data, further limiting data that could be used for analysis. Consequently, the dataset did not have sufficient power to be able to test the hypotheses, and no conclusions can be drawn from the work.

Results of analyses found that 80% of patients who were admitted to hospital with AECOPD had contact with their GP in the two weeks prior to admission, suggesting that admission was unlikely to have been avoidable for these patients. 86% of admissions were appropriate from a clinical perspective. Contact with primary care did not appear to affect the appropriateness of an admission. 20% of patients received a prescription for a rescue pack of antibiotics and oral corticosteroids in the

two weeks prior to their admission. This also did not appear to have any effect on admission appropriateness.

Receipt of a COPD discharge care bundle was associated with receipt of key items of best practice care (follow-up within two weeks, assessment for referral to pulmonary rehabilitation, referral for smoking cessation, inhaler technique check, and prescription of a rescue pack). However, this association was only present in analyses that included receipt of care items in secondary care. As receipt of care items in secondary care will have been part of the bundle completion process, this significant association may just be self-correlation. This potential self-correlation when including secondary care outcomes, and the limited power of the primary care only outcomes, means no conclusion could be drawn on whether discharge bundles increase receipt of best practice care after discharge. Likewise, no conclusion could be drawn on the impact of post-discharge best practice care on 30-day readmission due to the limited power of the study population.

This is an important area to explore further, and future work should include repeating these analyses using linked audit data over a period of at least one year to ensure sufficient power. It would also be useful to assess the accuracy of AECOPD recording in the audit. This could be done by matching audit admissions with HES admissions and confirming that the diagnosis codes used in HES are consistent with AECOPD.

9.1 Thesis conclusions

In this thesis I have found a few keys areas of COPD care that need addressing. Recording of post-bronchodilator spirometry and rates of referral to pulmonary rehabilitation are poor in primary care and could do with improvement. Education of GPs on the accurate clinical coding of spirometry in the electronic patient record, and ensuring there are sufficient pulmonary rehabilitation programmes available, and alerting GPs to their presence could improve receipt of these two items of COPD care.

The finding that women were less likely to be offered pulmonary rehabilitation than men is concerning, and GPs should be made aware of this observation so that they can take it in to consideration when assessing female COPD patients. While current smokers, older, and more deprived patients were not less likely to be offered PR, they were less likely to be referred. This suggests that they may be more likely to refuse PR and therefore targeted efforts should be made to inform these groups of the benefits that PR can provide them.

There appears to be a pattern of COPD discharge bundles not living up to expectations. While they are financially incentivised by the COPD BPT, I have not been able to find any evidence that they improve mortality, readmissions, or the quality of care received after discharge. It is possible that the financial incentivisation of bundles itself is causing issues, as there is an incentive to claim that a bundle has been completed even when it has not been fully implemented. This could explain the substantial difference found between the proportion of admissions that were stated to have received a bundle, and the proportion of admissions that received all bundle items. Alternatively, this difference could perhaps be explained by different interpretations of the make-up a discharge bundle by different care providers. Ensuring there is a clear definition of what constitutes a discharge bundle, and ensuring all care providers are aware of this, could improve recording of data in this area. Future analysis of bundles including the specific bundle items completed would help to clarify remaining questions around COPD discharge care bundles.

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Appendix A. Validation of AECOPD in EHRs search strategy

MEDLINE search

1. lung diseases, obstructive/ or exp bronchitis/ or exp pulmonary disease, chronic obstructive/

2. (COPD or COAD or emphysema or chronic bronchitis).ab,kf,ti.

3. (chronic obstructive adj (pulmonary or lung or airway$ or airflow) adj disease).ab,kf,ti.

4. 1 or 2 or 3

5. clinical deterioration/

6. (exacerbation$ or hospital$).ab,kf,ti.

7. 5 or 6

8. 4 and 7

9. (AECOPD or ECOPD or AECB).ab,kf,ti.

10. 8 or 9

11. database management systems/ or electronic data processing/ or exp health information management/ or databases as topic/ or databases, factual/ or health information systems/ or consumer health informatics/ or medical informatics/ or health information exchange/ or medical informatics applications/ or medical informatics computing/ or public health informatics/

12. medical records/ or health records, personal/ or patient generated health data/ or medical record linkage/ or medical records, problem-oriented/ or medical records systems, computerized/ or electronic health records/ or registries/

13. Clinical Coding/ or current procedural terminology/ or healthcare common procedure coding system/ or "international classification of diseases"/ or "logical observation identifiers names and codes"/ or rxnorm/ or "systematized nomenclature of medicine"/

14. (EHR$1 or EMR$1 or electronic health record$1 or electronic medical record$1).ab,kf,ti.

15. ((billing or claim$ or admin$ or utili?ation or patient or inpatient or in-patient or outpatient or out-patient or care or medical or clinical or health$ or hospital$ or electronic or digit$ or computer$) adj2 (data$ or record$1 or system$1)).ab,kf,ti.

16. (billing code or discharge code or Read code or SNOMED CT or ICD*).ab,kf,ti.

17. 11 or 12 or 13 or 14 or 15 or 16

18. Validation Studies as Topic/ or Validation Studies/

19. "sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/

20. (validation or validity or verification or verify or identification or identify).ab,kf,ti.

21. ((case or cases) adj2 (definition$ or define$ or evaluat$)).ab,kf,ti.

22. (sensitivity or specificity or PPV or PNV or NPV or positive predictive value$ or predictive positive value$ or predictive negative value$ or negative predictive value$ or likelihood ratio or precision or accuracy or ROC or receiver operating characteristic$ or kappa or "c-statistic" or (concordance adj statistic) or "c-index").ab,kf,ti.

23. 18 or 19 or 20 or 21 or 22

24. 10 and 17 and 23

Embase search

1. exp chronic obstructive lung disease/

2. emphysema/

3. exp chronic bronchitis/

4. (COPD or COAD or emphysema or chronic bronchitis).ab,kw,ti.

5. (chronic obstructive adj (pulmonary or lung or airway$ or airflow) adj disease).ab,kw,ti.

6. 1 or 2 or 3 or 4 or 5

7. exp disease exacerbation/

8. hospitalization/

9. (exacerbation$ or hospital$).ab,kw,ti.

10. 7 or 8 or 9

11. 6 and 10

12. (AECOPD or ECOPD or AECB).ab,kw,ti.

13. 11 or 12

14. data base/

15. medical informatics/ or medical information system/

16. exp medical record/ or electronic health record/ or electronic medical record/ or electronic medical record system/ or electronic patient record/ or register/

17. Current Procedural Terminology/ or coding/

18. exp "international classification of diseases"/ or "Systematized Nomenclature of Medicine"/ or "logical observation identifiers names and codes"/

19. (EHR$1 or EMR$1 or electronic health record$1 or electronic medical record$1).ab,kw,ti.

20. ((billing or claim$ or admin$ or utili?ation or patient or inpatient or in-patient or outpatient or out-patient or care or medical or clinical or health$ or hospital$ or electronic or digit$ or computer$) adj2 (data$ or record$1 or system$1)).ab,kw,ti.

21. (billing code or discharge code or Read code or SNOMED CT or ICD*).ab,kw,ti.

22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. validation study/

24. "sensitivity and specificity"/ or predictive value/ or receiver operating characteristic/

25. (validation or validity or verification or verify or identification or identify).ab,kw,ti.

26. ((case or cases) adj2 (definition$ or define$ or evaluat$)).ab,kw,ti.

27. (sensitivity or specificity or PPV or PNV or NPV or positive predictive value$ or predictive positive value$ or predictive negative value$ or negative predictive value$ or likelihood ratio or precision or accuracy or ROC or receiver operating characteristic$ or kappa or "c-statistic" or (concordance adj statistic) or "c-index").ab,kw,ti.

28. 23 or 24 or 25 or 26 or 27

29. 13 and 22 and 28

Appendix B. Tailored QUADAS-2 risk of bias assessment tool for use in validation studies of AECOPD detection algorithms in EHRs

Domain 1: Patient selection

A. Risk of bias

- Was a consecutive or random sample of patients enrolled?
- Was a case-control design avoided?
- Did the study avoid inappropriate exclusions?

B. Concerns regarding applicability

- Were patients from a single EHR database that comprised patients from one specific setting (e.g. primary or secondary care only patients)?
- Were patients aged 35 years or more (COPD population)?

Domain 2: Index test(s)

A. Risk of bias

- Was the AECOPD detection algorithm designed without knowledge of the result of the reference standard (in the final validated population)?

B. Concerns regarding applicability

- Were specific clinical codes used to identify patients (i.e. a free text search wasn't used as part of patient identification)?

Domain 3: Reference standard

A. Risk of bias

- Is the reference standard likely to correctly classify the target condition?
- Were the reference standard results interpreted without knowledge of the index test?

B. Concerns regarding applicability

- Was there confirmation of airways obstruction using spirometry?
- Was diagnosis confirmed by a physician reviewing the patient's medical record?
- Did more than one physician review the medical record to confirm diagnosis and was there strong agreement between the reviewing physicians?

Domain 4: Flow and timing

A. Risk of bias

- Did all patients receive a reference standard?
- Did patients receive the same reference standard?
- Were all patients included in the analysis?

Appendix C. COPD codelist

Medcode	Read V2 code	Read V2 5B code	Read term
4084	663K.00	663K.	Airways obstructn irreversible
9520	66YB.00	66YB.	Chronic obstructive pulmonary disease monitoring
37371	66YD.00	66YD.	Chronic obstructive pulmonary disease monitoring due
18621	66YL.00	66YL.	Chronic obstructive pulmonary disease follow-up
18476	66YL.11	66YL.	COPD follow-up
42624	66YL.12	66YL.	COAD follow-up
11287	66YM.00	66YM.	Chronic obstructive pulmonary disease annual review
26018	66YS.00	66YS.	Chronic obstructive pulmonary disease monitoring by nurse
45998	66YT.00	66YT.	Chronic obstructive pulmonary disease monitoring by doctor
45770	66Yg.00	66Yg.	Chronic obstructive pulmonary disease disturbs sleep
45771	66Yh.00	66Yh.	Chronic obstructive pulmonary disease does not disturb sleep
42313	679V.00	679V.	Health education - chronic obstructive pulmonary disease
45777	8CR1.00	8CR1.	Chronic obstructive pulmonary disease clini management plan
18792	9Oi..00	9Oi..	Chronic obstructive pulmonary disease monitoring admin
28755	9Oi0.00	9Oi0.	Chronic obstructive pulmonary disease monitoring 1st letter
34202	9Oi1.00	9Oi1.	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	9Oi2.00	9Oi2.	Chronic obstructive pulmonary disease monitoring 3rd letter
42258	9Oi3.00	9Oi3.	Chronic obstructive pulmonary disease monitoring verb invite
1001	H3...00	H3...	Chronic obstructive pulmonary disease
998	H3...11	H3...	Chronic obstructive airways disease
27819	H312.00	H312.	Obstructive chronic bronchitis
14798	H312100	H3121	Emphysematous bronchitis
44525	H312z00	H312z	Obstructive chronic bronchitis NOS
794	H32..00	H32..	Emphysema
26306	H320.00	H320.	Chronic bullous emphysema
23492	H320z00	H320z	Chronic bullous emphysema NOS
46578	H321.00	H321.	Panlobular emphysema
10980	H322.00	H322.	Centrilobular emphysema
33450	H32z.00	H32z.	Emphysema NOS
10863	H36..00	H36..	Mild chronic obstructive pulmonary disease
10802	H37..00	H37..	Moderate chronic obstructive pulmonary disease
9876	H38..00	H38..	Severe chronic obstructive pulmonary disease
93568	H39..00	H39..	Very severe chronic obstructive pulmonary disease
12166	H3y..00	H3y..	Other specified chronic obstructive airways disease
67040	H3y..11	H3y..	Other specified chronic obstructive pulmonary disease
5710	H3z..00	H3z..	Chronic obstructive airways disease NOS
37247	H3z..11	H3z..	Chronic obstructive pulmonary disease NOS

Appendix D. CPRD ISAC Protocol

ISAC APPLICATION FORM

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No.	.....	***IMPORTANT***
Submission date (DD/MM/YYYY)	.....	*Please refer to the **guidance** for '**Completing the ISAC application form**' found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*

Variation in patient pathways and hospital admissions for exacerbations of COPD: linking the National Asthma and COPD Audit Programme (NACAP) with CPRD data

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes* ☐ No ☒

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes* ☒ No ☐

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

This work forms part of a grant competitively won by a collaboration between Imperial College London, CPRD and the RCP. This work will be funded by The Health Foundation

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☒	Other*	☐

If Other, please specify the type of study here and in the lay summary below:

5. Health Outcomes to be Measured§

§*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Inappropriate hospital admission
- Avoidable hospital admission
- Best practice care of acute exacerbation of COPD post-discharge
- Readmission in the 30 days after discharge
- Death in the 30 days after discharge
- The 2017 National COPD Audit queries

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Jennifer Quint, Clinical Senior Lecturer in Respiratory Epidemiology, Imperial College London

j.quint@imperial.ac.uk

§*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC	☒ **CV number:**	042_15CEPSL
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

8. Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

National Heart and Lung Institute

Imperial College London

Manresa Road

London

SW3 6LR

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

Philip Stone, Imperial College London, p.stone@imperial.ac.uk

§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator	☐	
CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Viktoria McMillan, Royal College of Physicians, Viktoria.McMillan@rcplondon.ac.uk

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

Other investigator: Noel Baxter, NHS, Royal College of Physicians, noel.baxter@nhs.net

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

Other investigator: Christopher Michael Roberts, Royal College of Physicians, UCL Partners, Mike.Roberts@uclpartners.com

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☒	
An updated CV is being submitted with this protocol	☐	

Other investigator: Johanna Feary, Imperial College London, NHS, j.feary@imperial.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☒

An updated CV is being submitted with this protocol ☐

Other investigator: Puja Myles, Medicines and Healthcare products Regulatory Agency, puja.myles@mhra.gov.uk

CV has been previously submitted to ISAC ☒ **CV number:** 038_15CESL

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: Alex Bottle, Reader, Imperial College London, robert.bottle@imperial.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 491_15CES

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: Rebecca Ghosh, Medicines and Healthcare products Regulatory Agency, rebecca.ghosh@mhra.gov.uk

CV has been previously submitted to ISAC ☒ **CV number:** 068_17

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

Dr Quint's research group has received funding from the MRC, Wellcome Trust, BLF, GSK, BI, Bayer, Insmed and AZ for other projects, none of which relate to this work. Dr Bottle's research group has received funding from Dr Foster (a Telstra Health company), Medtronics and the NIHR for other projects, none of which relate to this work. Imperial College London performed the analysis required for the National COPD Audit Programme and Dr Quint is Analysis Lead for the NACAP programme. This work has been funded by a grant from The Health Foundation.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Stone, Bottle, Ghosh	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Stone, Bottle, Feary, Ghosh, Myles	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Baxter	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

Baxter N, McMillan V, Holzhauer-Barrie J, Robinson S, Stone P, Quint J, Roberts CM. *Planning for every breath. National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme: Primary care audit (Wales) 2015–17*. Data analysis and methodology. London: RCP, December 2017

Stone RA, McMillan V, Mortier K, Holzhauer-Barrie J, Riordan J, Stone P, Quint J, Roberts CM. *COPD: Working together. National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme: Clinical audit of COPD exacerbations admitted to acute hospitals in England and Wales 2017*. Data analysis and methodology. London: RCP, April 2018.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government / NHS	☐	*Please specify name and country:*

Charity	☒	*Please specify name and country:* The Health Foundation, UK
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government Department	☒	*Please specify name and country:* CPRD, UK
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data	☐
The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data**	☐
A data set will be provided by the CPRD¥€	☐
CPRD has been commissioned to extract the data and perform the analyses€	☐
Other:	☒

If Other, please specify: CPRD GOLD data will be extracted by the investigators under the Imperial licence and CPRD Aurum data will be provided by CPRD under a jointly funded grant from THF.

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*

¥*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*

€*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher	Reference number (where available)	Date of contact

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies	☐	Both Vision and EMIS®*	☒
EMIS® only*	☐		

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher **Puja Myles** Reference number (where available) Date of contact 20/04/18

18. Site Location of Data

a) Processing location(s):

Location area - UK / EEA / Worldwide: UK

Organisation address:

National Heart and Lung Institute

Manresa Road

London

SW3 6LR

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

Location area - UK / EEA / Worldwide: UK

Organisation address:

National Heart and Lung Institute

Manresa Road

London

SW3 6LR

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK / EEA / Worldwide:

UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data

☒ HES Admitted Patient Care

☐ HES Outpatient

☒ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset

☐ HES PROMS (Patient Reported Outcomes Measure)**

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *

☐ NCRAS Cancer Patient Experience Survey (CPES) data*

☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*

☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

☒ **Other: Bespoke linked NACAP (National COPD Audit data); this has been discussed and agreed with CPRD. CPRD are leading on the CAG application which is being submitted in parallel with this ISAC as ISAC approval is required before the DARS can be submitted.**

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Puja Myles Reference number (where available) Date of contact 20/04/18

21. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)*

5

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a <u>local</u>¥ dataset with <1 million patients being requested?

Yes* ☐ No ☒

**If yes, please provide further details:*

¥ *Data from defined geographical areas i.e. non-national datasets.*

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☒ No ☐

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* ☐ No** ☒

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

CPRD are submitting a CAG amendment to include linkage of NACAP data to CPRD data

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.

- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Jennifer Quint Date: 19/07/18 e-Signature (type name): JKQuint

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Variation in patient pathways and hospital admissions for exacerbations of COPD: linking the National Asthma and COPD Audit Programme (NACAP) with CPRD data

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

The National Asthma and Chronic Obstructive Pulmonary Disease (COPD) Audit Programme (NACAP) provides data on the care received by people with COPD (a group of progressive lung conditions that cause breathing problems) in the United Kingdom (UK). Most COPD patients experience episodes of worsening in respiratory symptoms, termed acute exacerbations of COPD (AECOPD). AECOPD is one of the most common reasons for adult emergency hospital admission in the UK, resulting in significant healthcare usage and cost. The COPD admission hospital data from NACAP (NACAP-SC) contains detailed information on AECOPD hospital admissions. Our study will create a new linkage between primary care data from CPRD and hospital data for AECOPD taken from NACAP-SC. This linked dataset will be used to explore how many admissions for AECOPD are avoidable, and whether receiving specific treatments or being seen within 24 hours of admission by the respiratory team reduce the likelihood of a patient being readmitted or dying.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

The National Asthma and Chronic Obstructive Pulmonary Disease (COPD) Audit Programme (NACAP) provides data on the care received by COPD patients in the United Kingdom (UK). Most COPD patients experience episodes of worsening in respiratory symptoms, termed acute exacerbations (AECOPD). AECOPD is one of the most common reasons for adult emergency hospital admission in the UK, resulting in significant healthcare usage and cost. The secondary care clinical arm of NACAP (NACAP-SC) contains detailed information on clinical features of AECOPD hospital admissions. The aim of this study will be to use routinely linked primary care data, Hospital Episode Statistics (HES), and ONS Death registration data from CPRD and bespoke linked secondary care data for AECOPD taken from NACAP-SC. Using logistic regression, this linked dataset will be used to explore the proportion of potentially avoidable admissions: whether contact with primary care in the 2 weeks prior to an AECOPD reduces the risk of an admission being severe; whether different regions of England have different numbers of inappropriate AECOPD admissions; whether receiving a discharge bundle (a completed checklist of best-practice actions to undertake at discharge) increases the odds of receiving best practice care post-discharge, or reduces the odds of 30-day readmission and death; and whether being seen within 24 hours of admission by the respiratory team increases the odds of receiving best-practice care post-discharge, or reduces 30-day mortality.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

D. Objectives, Specific Aims and Rationale

Aim:

To link the exacerbation of COPD arm (secondary care clinical audit) of the National Asthma and COPD Audit Programme (NACAP) with CPRD primary care GOLD and Aurum data, Hospital Episode Statistics (HES), and Office of National Statistics (ONS) Death registration data to explore how variations in patient pathways through healthcare across England affect hospital admissions for exacerbations of COPD.

Objectives:

1. Link data from the exacerbation of COPD arm of NACAP with CPRD primary care GOLD and Aurum, HES, and ONS data, undertake dataset characterisation, and develop guidance for using the linked dataset that will be available for other researchers.
    - The primary care audit from the 2017 analysis of NACAP (which was for COPD only) will be replicated as part of the dataset characterisation. This will involve replicating the 15 queries that comprised the primary care audit (included in appendix and available from the Royal College of Physicians (RCP) website (1)). **To avoid confusion, the primary care audit component of NACAP will be referred to as NACAP-PC in this protocol**.
2. Demonstrate the added value of the linked data by exploring how the management of patients with COPD and patient pathways vary across England, and how this relates to hospital admissions for exacerbations of COPD**. To avoid confusion, the secondary care clinical audit component of NACAP that will be linked with CPRD data will be referred to as NACAP-SC in this protocol.** As part of this objective the following will be investigated:
    - What proportion of AECOPD admissions are potentially inappropriate or avoidable?
    - How does management of AECOPD on and following discharge from hospital affect disease outcomes, future admission events and mortality?
    - How accurate is the recording of AECOPD in HES and how do hospital admissions for other reasons affect admissions and readmission for AECOPD?

Rationale:

Acute exacerbations of COPD (AECOPD) pose a significant burden for patients both during the time of the acute event and in terms of affecting the natural history of the disease. They are a leading cause of adult emergency admission to hospital in the UK, resulting in significant health care usage and cost. Some AECOPD events legitimately require hospital admission (patients with unpreventable respiratory failure), but others are potentially avoidable. There is significant geographic variation across England for admissions for AECOPD (irrespective of the underlying area prevalence). Some of this variation may be due to patient factors (how engaged they are with their disease) and some health system factors (ease of primary care access when unwell).

NACAP is the gold standard for AECOPD hospital admissions, containing detailed information on clinical features associated with admission, allowing ascertainment of how unwell a patient is on hospitalisation and whether the admission could potentially have been avoided. Linkage of NACAP with primary care data from CPRD would allow the whole patient pathway to be investigated including visits to primary care preceding an admission, medications prescribed and previous AECOPD events. This would allow exploration of factors that may explain variations in admissions for AECOPD across England and highlight areas for action to reduce unwarranted variations and improve care for patients with COPD.

Currently, NACAP is linked intermittently to HES and ONS mortality data, but there is no primary care linkage. Therefore, the generation of a novel linkage between primary care data in CPRD and NACAP will allow clinical and health care system questions to be answered that would otherwise not be answerable.

E. Study Background

Chronic Obstructive Pulmonary Disease (COPD) is the term for a group of lung diseases that cause narrowing of the airways, making breathing difficult (2). The airflow obstruction that characterises COPD is not fully reversible, and is usually progressive in the long term (3). There is no simple diagnostic test for COPD; diagnosis is a clinical judgement based on historical exposures, physical examination, and airflow obstruction confirmed through spirometry (3). Many patients experience episodes of sustained worsening in symptoms termed acute exacerbations of COPD (AECOPD), or simply 'exacerbations' (3).

It is estimated 1.2 million people in the UK have diagnosed COPD, making it the second most common lung disease in terms of diagnoses (4). UK healthcare costs related to COPD are estimated to be £1.8 billion annually (5). In 2013 in England and Wales COPD was the 4th and 5th most common cause of death for men and women, respectively (6). The UK has the 12th highest mortality rate for COPD in the world, and the 3rd highest in Europe (4). AECOPD is one of the most common reasons for emergency hospital admission in England with approximately 115,000 admissions annually (7). Patients with more frequent exacerbations have faster decline in lung function and increased mortality (8,9). Patients with exacerbations that require oxygen or non-invasive ventilation (NIV) legitimately require hospitalisation, however other hospitalisations are potentially avoidable (3).

The National Asthma and COPD Audit Programme (NACAP) (formerly the National COPD Audit Programme) aims to improve the quality of care for people with COPD in the UK by following patients through their treatment pathways and highlighting instances where best practice care isn't received (10). The 2017 audit programme had 4 main components (10), the first of which, the primary care audit (NACAP-PC), was published in December 2017 (11). NACAP-PC analysed the quality of care received in 407 out of 435 (94%) practices in Wales for the period of 1st April 2015 to 31st March 2017 (11). Specifically the analysis looked at (i) demographics, (ii) quality of diagnosis, (iii) assessment of severity, (iv) quality of treatment, and (v) equitable care (11).

The secondary care workstream component of NACAP (NACAP-SC) consists of a continuous (from February 2017) clinical audit of patients admitted to hospital in England and Wales with an exacerbation of COPD (12). Data are gathered from patient case notes and entered in to a secure audit tool, with particular focus on gathering detailed information on whether a patient has been reviewed by a specialist, prescribed oxygen, whether NIV is required, lung function (via spirometry), whether smoking cessation services have been offered, and the discharge bundle offered (12).

Unfortunately, due to concerns over patient confidentiality, NACAP-PC was unable to proceed with data collection from English practices, and therefore primary care analysis has only been possible in Wales so far (13,14). This means that by using pseudonymised data from CPRD, we will be able to give an estimate of the quality of COPD care received in primary care for England and the rest of the UK. This study will also enable us to design a more methodologically-sound analysis of the quality of COPD care in the UK which will be subjected to peer review and can then be used for subsequent national COPD audits. In addition, linking NACAP-SC with primary care data from CPRD gives the opportunity to investigate how differences in diagnosis and treatment of COPD affect risk of hospitalisation. Linkage to CPRD primary care data that has Section 251 support from the Confidentiality Advisory Group (CAG) and is accomplished via NHS Digital acting as the Trusted Third Party (TTP) would ensure that these data can be accessed within a robust data

governance framework such that the risk to patient confidentiality is minimised. This information then has the potential to be used to formulate strategies that can reduce the risk of hospitalisation due to an AECOPD in the future.

F. Study Type

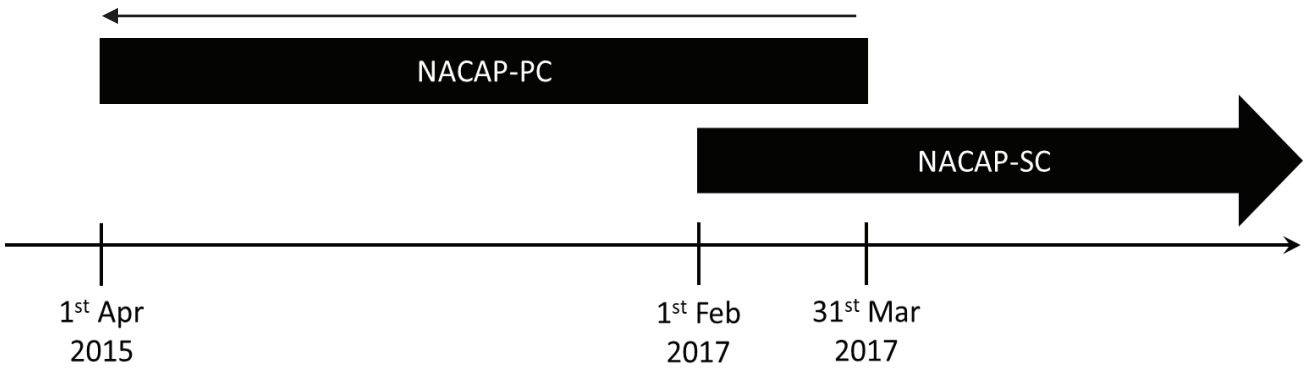
This study will be descriptive and hypothesis testing.

G. Study Design

This study will be cross-sectional, analysing care received by COPD patients (see section K). The period used in this study will be 1st April 2015 to 31st March 2017 inclusive (the exact same period as studied in NACAP-PC) for the analysis that replicates NACAP-PC using primary care data (linked only with Index of Multiple Deprivation (IMD) data for certain analyses [see section N]). The index date of the study will be 31st March 2017, and the study will look at the care patients alive on that date received in the previous 2 years. This adds a bias to the study as patients that are studied will be healthier than the general COPD population, however this is exactly what was done in NACAP-PC (see section K for how we will address this bias).

Analysis using the bespoke linked secondary care data from NACAP-SC (also linked with HES APC, HES A&E, ONS, and IMD data) will be from 1st February 2017 onwards as this is when continuous data collection began for NACAP-SC.

See diagram below for a visualisation of the timeline for each study period:



Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

H. Feasibility counts

For the NACAP-PC replication (objective 1), Initial feasibility calculations in CPRD GOLD have found there to be approximately 55,587 alive and currently registered patients with COPD (using validated COPD Read codes (15)) on the study index date of 31st March 2017 (26,282 of which were in England and therefore eligible for linkage to IMD data) (13,326 in Wales and therefore available for analysis of Welsh practices only (see section N)).

Feasibility counts for the NACAP-PC replication (objective 1) in CPRD Aurum have found there to be 289,194 patients with a record of COPD between 01/01/1987-31/03/2017 (prevalent cases).

As of 23rd May 2018, there are 90,112 admissions recorded in NACAP-SC (from 1st February 2017), however the number of individual patients contained in NACAP-SC will be lower due to readmissions. For the period 1st February 2017 to December 2017, there are 29,335 English COPD patients (prevalent & incident) present in CPRD GOLD, and 99,714 prevalent and 10,826 incident COPD cases in CPRD Aurum.

I. Sample size considerations

As mentioned in section H, the expected number of patients in the NACAP-PC replication component (objective 1) of this study is approximately 55,587 with approximately 26,282 English patients that are eligible for the required IMD linkage (see section N).

As an example: Assuming the same proportion of recording in CPRD as found in the Welsh National COPD Audit, a sample size of 26,488 COPD patients would allow us to detect a change in proportions of post-bronchodilator FEV1/FVC ratio recording of −0.0108 (0.0853 to 0.0745) between patients with a serious mental illness and those without with 90% power and $\alpha = 0.05$. This is the change that likely requires the greatest sample size, so with 77,698 patients available to study, we should have sufficient power in this study.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

IMD is required to analyse the effect of socioeconomic status on quality of COPD diagnosis, management and treatment.

HES APC is required to ascertain the validity of AECOPD recording in HES APC relative to the audit, how hospitalisations for reasons other than AECOPD relate to the hospitalisation for AECOPD.

HES A&E is required to determine the frequency of A&E attendances for patients.

ONS data is needed for mortality as an outcome as part of the investigation of the patient pathway.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

A bespoke linkage with NACAP-SC will also be created so that events in primary care before and after a hospital admission for an AECOPD can be analysed. Approval for this bespoke linkage is being sought from the Confidentiality Advisory Group via CPRD.

K. Study population

The objective 1 replication of NACAP-PC in CPRD GOLD and CPRD Aurum (separately) will be conducted in individuals with a validated (15) COPD diagnosis (exact same Read codes as used in NACAP-PC – see appendix or (1)) who are alive and registered with a practice and aged at least 35 on 31st March 2017. In CPRD GOLD, this population will be split in to 3 sub-populations: Welsh practices only (to exactly replicate NACAP-PC), all UK practices, and English practices only (so that linked IMD data can be used for logistic regression models – see section N). In CPRD Aurum, the analysis will be conducted in England only and linked IMD data will not be required. The study period will be 1st April 2015 to 31st March 2017 (identical to NACAP-PC).

As a result of looking at the treatment received by an alive population in the preceding 2 years there is risk the results won't be representative of the treatment received by all COPD patients (as mentioned in section G). To address this, once we have replicated NACAP-PC, we will repeat the study using a better-defined population (mentioned as part of sensitivity analyses in section N). The definition for this population will be: individuals from 1st April 2015 to 31st March 2017 with a validated COPD diagnosis (defined using same Read codes as above) who are alive, currently registered, up to research standard, and received their first COPD diagnosis at the age of 35 or more. These patients will then be followed-up until 31st March 2017.

For the objective 2, where a bespoke linkage between NACAP-SC and both CPRD GOLD and CPRD Aurum will be created, COPD patients will be defined by their presence in NACAP-SC (only AECOPD hospitalisations are recorded in NACAP-SC). The start of the study will be 1st February 2017 (when data collection began for NACAP-SC) and the study will run until the date of last data collection. Objective 2 will only include English practices and in addition to the bespoke linkage, routine IMD, HES, and ONS Death linkages will be used.

L. Selection of comparison group(s) or controls

Our comparison groups will consist of the different exposure groups as defined in section M. As part of a sensitivity analysis we may also compare English patients who were admitted to hospital for an AECOPD (patients with linked data) to those who weren't (patients without linked data) to see how their treatment in primary care differs.

M. Exposures, Health Outcomes§ and Covariates

§*Please note: Summary information on health outcomes (as included on the ISAC application form above) will be published on CPRD's website as part of its transparency policy*

Code lists (Read v2 – will be mapped to the appropriate medcodes as required for CPRD GOLD and CPRD Aurum) used in NACAP-PC, and to be used in this study, can be found in the attached spreadsheet: Read code list_PC audit 2017_v3.4_0.xlsx

Exposures:

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Objective 1 (NACAP-PC):

- Serious mental illness (yes/no) ('Psychosis' category in 'Section 1 (comorbidities)' worksheet of attached spreadsheet) [data from CPRD].
- Socioeconomic group (quintiles of IMD) [data from CPRD].
- Smoking status (current/haven't smoked for at least 4 years) ('Section 3 (severity)' worksheet) [data from CPRD].

Objective 2 (NACAP-SC):

- Contact with primary care in the 2 weeks prior to AECOPD (defined by presence in NACAP-SC – NACAP-SC only contains AECOPD admissions) hospital admission (yes/no). Contact defined as any Read code indicating communication with primary care (see attached 'pc_contact' codelist) [data from CPRD].
- Clinical Commissioning Group (CCG) [data from CPRD]
- Receipt of a discharge bundle (a discharge care bundle is a list of best-practice actions to be undertaken before the patient is discharged to reduce the likelihood of the patient being readmitted (16)) (yes/no) [data from NACAP-SC].
- Seen within 24 hours of admission by respiratory team (yes/no) [data from NACAP-SC].

<u>Outcomes:</u>

Objective 1 (NACAP-PC):

- The 2017 NACAP-PC audit queries (see appendix or RCP website for detailed list of queries (1)).

Objective 2 (NACAP-SC):

- AECOPD severity (high risk/low risk). High risk defined as DECAF score of 3-6 (the DECAF score is a validated predictor of mortality in patients with AECOPD (17,18). It measures extended MRC Dyspnoea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation.), or in the absence of a DECAF score, requirement for oxygen or NIV, or death (from linked ONS data). Low risk defined as DECAF score of 0-1 or, in the absence of a DECAF score, no requirement for oxygen or NIV. If there is sufficient DECAF data, a DECAF score of 2 can be used to create an 'intermediate risk' category [data from NACAP-SC].
- Avoidable hospital admission (defined as contact with primary care in the 2 weeks prior to AECOPD hospital admission [pc_contact codelist]) (yes/no).
- Best practice care of AECOPD post-discharge (yes/no). Defined as: A Read code indicating review within 2 weeks of discharge (see attached 'review' codelist), a Read code for pulmonary rehabilitation referral (see 'Section 4 (high value care)' worksheet of audit spreadsheet), prescription codes for a rescue pack of antibiotics and steroids ('Macrolides', 'Doxycycline', 'Broad spectrum Penicillins', and 'Oral Steroids' categories in 'Section 3 (severity)' worksheet), and a Read code for smoking cessation treatment referral (if a current smoker) ('Smoking Cessation' category in 'Section 4 (high value care)' worksheet) [data from CPRD].
- Readmission in the 30 days after discharge (yes/no) [data from NACAP-SC].
- Death in the 30 days after discharge (yes/no) [data from ONS Death Registration].

<u>Covariates:</u>

- Age (10-year age bands)
- Sex (male/female)
- Socioeconomic status (quintiles of IMD)
- Smoking status (current/ex/never) ('Section 3 (severity)')
- Comorbidities (yes/no) ('Section 1 (comorbidities)'):
  - Asthma
  - Bronchiectasis
  - Coronary heart disease
  - Diabetes
  - Heart failure

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

  - Hypertension
  - Lung cancer
  - Stroke
  - Osteoporosis
  - Anxiety
  - Depression
- Painful condition (yes/no) (defined as patients who had a record of four or more prescription analgesia medications in the past 12 months, or four or more specified anti-epileptics in the absence of an epilepsy Read code in the past 12 months ['Painful condition meds', 'Epilepsy', and 'Epilepsy resolved' categories in 'Section 1 (comorbidities)'])
- Diagnosed with AECOPD and prescribed antibiotics and/or steroids in the 2 to 4 weeks prior to AECOPD hospital admissions (yes/no) ('Exacerbations' [excluding 66Yf], 'Macrolides', 'Doxycycline', 'Broad spectrum Penicillins', and 'Oral Steroids' categories in 'Section 3 (severity)' worksheet).
- Inhaled therapies prescribed in the past year ('LABA/ICS', 'LABA', 'LAMA', and 'ICS' categories in 'Section 4 (high value care)' worksheet).
- Days since diagnosis of COPD (first occurrence of validated COPD diagnosis code ['COPD codes' worksheet]).
- Receipt of smoking cessation advice (yes/no) ('Section 4 (high value care').
- Referral for pulmonary rehabilitation (yes/no) ('Section 4 (high value care)').
- FEV1/FVC ratio ('Section 2 (diagnosis)').
- FEV1 % predicted ('Section 3 (severity)').
- MRC score ('Section 3 (severity)').
- Receipt of influenza immunisation (yes/no) ('Section 4 (high value care)').
- Invited for and attended annual review visit (yes/no) (review codelist)
- Exacerbation frequency (using same method as described in NACAP-PC (11)) ('Section 3 (severity)')
- Attendance at A&E in the 2 weeks prior to AECOPD hospital admission (yes/no) [from linked HES data]

N. Data/ Statistical Analysis

Data management and analysis will be performed in Stata 15 and R.

Objective 1 (NACAP-PC):

- Summary statistics (proportions & averages)
- The 2017 NACAP-PC audit queries (see Appendix for a copy of the National COPD Audit queries) will be conducted as part of the dataset characterisation. This will include checking the level of recording of various clinical events (e.g. spirometry result) in the primary care data, and the following statistical analysis:
  - Logistic regression to test whether patients with a serious mental illness are more likely to receive poorer care (defined as 'yes' to NACAP-PC audit queries (see appendix or (1)): 1, 2, 3, 4, 5, 6, 9, 10, 11) than those without a serious mental illness.
  - Logistic regression to test whether patients from a lower socioeconomic group are more likely to receive poorer care than those from a higher socioeconomic group.
  - Logistic regression to test whether patients who smoke receive poorer care than patients who haven't smoked for at least 4 years.

  As part of a sensitivity analysis this analysis will be performed in different populations:

  - In Welsh practices only (to emulate the Wales-only analysis of NACAP-PC). Only summary statistics will be calculated and therefore IMD data will not be required.
  - In all CPRD practices (to see if Welsh results are representative of the entire UK population).

- In a better-defined COPD population (see section K). The study population for NACAP-PC was poorly defined so this should give more representative results.
- In English practices only (so that linked IMD data can be used in the logistic regression models).
- In both CPRD GOLD and CPRD Aurum to see if the usage of a different GP software package (i.e. Vision vs. EMIS Web) gives different results.
- In COPD patients defined using the 2014 National COPD Audit Read codes (see Appendix or (19)). The Read codes used in 2014 were the QOF codes rather than the validated codes used in 2017 so it will be useful to see if or how much results differ.

Objective 2 (NACAP-SC):

- Summary statistics
- Are there management changes after discharge: changes in treatment, referral for pulmonary rehabilitation, prescription of rescue packs of antibiotics and steroids, and inhaler technique checked?
- Is data recording consistent across primary and secondary care for smoking cessation, pulmonary rehabilitation, and spirometry?
- Misclassification of AECOPD in HES. The recording of AECOPD in NACAP-SC can be compared with the diagnosis recorded in HES to ascertain the validity of AECOPD recording in HES.
- Logistic regression will be used to test the following:
  - Whether contact with primary care in the 2 weeks prior to an AECOPD reduces the risk of the admission being severe.
  - Whether different regions (CCGs) of England have differing levels of inappropriate (low risk AECOPD severity) AECOPD hospital admissions.
  - Whether different regions (CCGs) of England have differing levels of avoidable AECOPD hospital admissions.
  - Whether receipt of a discharge bundle increases the odds of receiving best practice care of the AECOPD post-discharge.
  - Whether receipt of a discharge bundle reduces the odds of readmission in 30 days following discharge.
  - Whether receipt of a discharge bundle reduces the odds of death in the 30 days following discharge.
  - Whether being seen by the respiratory team within 24 hours of admission increases the odds of receiving best practice care of the AECOPD post-discharge.
  - Whether being seen by the respiratory team within 24 hours of admission reduces the odds of death in the 30 days following discharge.

O. Plan for addressing confounding

In both objective 1 (NACAP-PC) and 2 (NACAP-SC) we will adjust for age, sex, socioeconomic status, smoking status, comorbidities (see appendix for full list), and painful conditions. It will also be investigated whether the following are potential confounders: time since first diagnosis of COPD, receipt of smoking cessation services, referral for pulmonary rehabilitation, FEV1/FVC ratio, FEV1 % predicted, MRC score, receipt of flu vaccine, and exacerbation frequency.

P. Plans for addressing missing data

Where appropriate, and where data are missing at random, we will undertake both a complete case analysis and we will consider using multiple imputation. Where data are not missing at random, but where we expect the data to be 80% complete, we will use a complete case analysis but will discuss biases that may occur as a result of adopting that approach. Where multiple imputation is not appropriate and there

are large quantities of data missing, we will report this in the write-up and discuss any biases and limitations that occur as a result of that. Variables likely to have missing data are BMI and spirometry results, however previous studies by our team have found that spirometry data are not missing at random.

Q. Patient or user group involvement (if applicable)

The project summary has been shared with patients, the public and health care professionals, including those involved in audit data collection through a range of different avenues. This has included Breathe Easy groups, patients attending COPD outpatient clinics at the Royal Brompton hospital and Imperial NHS Trust, the PPI team at the Royal Brompton and the RCP. In addition, the study summary will be sent out to the CPRD user group.

As a programme, the RCP National COPD Audit works closely with the BLF and ensures that all new material (e.g. consent forms) are reviewed by their patient Think Tank. In addition, they have patient representation on senior governance groups (Steering Committee).

In patient and public involvement discussions to date, no concerns have been raised regarding the linkage of detailed Audit and primary care data or the fact that pseudonymised data will be made available for research. In fact, patients have described it as "making perfect sense to help understand everything that is going on as what happens in and out of hospital is all related".

Following feedback, we have amended the clinical questions to be answered in this study and we will continue to involve patients and service users in the advisory group. In addition, they will assist with dissemination of findings and ideas for future work with the linked dataset.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals and will be presented at appropriate conferences and other meetings; the latter will include scientific meetings externally, for example the American Thoracic Society and European Respiratory Society meetings and internally within Imperial College London.

S. Limitations of the study design, data sources, and analytic methods

Possible limitations of the study are that as it uses a cross-sectional design, it may not be good for the analysis of rare exposures or outcomes. The short duration of the study may mean that we aren't able to capture quite as many patients and events as may be desirable. There is likely to be some misclassification of COPD, however using validated Read codes should help mitigate against this. The design of NACAP-PC wasn't very precise, so it may be difficult to accurately replicate the audit and results may be slightly unpredictable. Using Aurum data might give different and unexpected results due to the use of a different software system for the recording of patient primary care data. It is possible the Vision and EMIS Web software packages may persuade GPs to record the same event in different ways. However, using Aurum data will increase coverage of English practices in the study, but the study still won't include all English GP

practices. As CPRD seems to have a bias towards larger practices (20) this may mean the results from this study aren't generalisable to smaller practices in England.

T. References

1. Royal College of Physicians. *National COPD primary care audit (Wales) 2015–17: resources*. [Online] RCP London. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-copd-primary-care-audit-wales-2015-17-resources [Accessed: 5th June 2018]

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11. Royal College of Physicians. *Primary care audit (Wales) 2015–17: Planning for every breath*. [Online] RCP London. Available from: https://www.rcplondon.ac.uk/projects/outputs/primary-care-audit-wales-2015-17-planning-every-breath [Accessed: 23rd January 2018]

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Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

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15. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open*. [Online] 2014;4(7): e005540. Available from: doi:10.1136/bmjopen-2014-005540

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List of Appendices *(Submit all appendices as separate documents to this application)*

National COPD Audit questions (Nat COPD Primary Care Audit 2017_Audit Queries_v6.6_0.pdf)

National COPD Audit codes (Read code list_PC audit 2017_v3.4_0.xlsx)

Contact with primary care code list (pc_contact.txt)

Review codelist (review.txt)

Appendix E. NACAP Primary Care Audit: comorbidity codelists

NACAP Primary Care Audit Read V2 codelists can be found at:

https://github.com/pstone22/PhD/tree/main/codelists/Chapter%204

Appendix F. NACAP Primary Care Audit: audit query codelists

NACAP Primary Care Audit Read V2 codelists can be found at:

https://github.com/pstone22/PhD/tree/main/codelists/Chapter%204

Appendix G. Extended Output Scope form: Predictors of referral to pulmonary rehabilitation

Extended output scope and decision template V1.

(to be used in conjunction with the self-assessment tool for academic papers and other extended outputs)

OVERVIEW: please provide a title for and detail of the extended analysis and planned output proposed

What factors measured in primary care are associated with referral to pulmonary rehabilitation?

Using the primary care audit data from 2015-2017 (published in late 2017), we will look at factors (e.g. age, sex, co-morbidities) that may influence the likelihood of being referred for pulmonary rehabilitation (PR). This results of this work will be submitted as an abstract to be presented at the American Thoracic Society annual meeting which will take place in May 2019.

As there is no cure for COPD, management focuses on reducing symptoms and abating disease development through a range of treatments, one of which is PR; a multidisciplinary intervention which combines exercise training with education, psychosocial support and dietary advice (Spruit et al, 2013). There is considerable evidence for the benefits of PR in patients with both stable and post exacerbation COPD (Steiner et al, 2017). This is best summarised by a Cochrane meta-analysis of 65 randomised controlled trials (RCTs) of PR versus usual care, which concluded it is a safe and effective treatment, associated with clinically important benefits in exercise capacity and health related quality of life, as well as reduced risk of exacerbations, hospital admissions and mortality (McCarthy et al, 2015).

Despite the known benefits of PR, low rates of referral to PR (from both primary and secondary care), as well as poor patient uptake and completion have been widely reported, which considerably undermines the effectiveness of the intervention (Hogg et al, 2012). This work attempts to look at some of the factors that may influence referral of patients to PR from primary care. Our aim is to understand patterns of referral to help health care professionals to target others who are likely to benefit from PR.

Datasets
This work will utilise patient level data from the National Asthma and COPD Audit Programme (NACAP)'s primary care audit dataset. The national report was published in December 2017 and can be accessed here: **https://www.rcplondon.ac.uk/projects/outputs/primary-care-audit-wales-2015-17-planning-every-breath.** LHB and cluster level reports are available on the same site.

These data were extracted automatically from GP surgeries in Wales in June 2017 to capture activity between April 2015 and March 2017.

In order to answer the question, the following variables will be required:

- **Age**
- **Gender**
- **WIMD score (derived for the audit already)**
- **Co-morbidities (i.e. presence of diagnosis codes for diabetes, hypertension, coronary heart disease, stroke, heart failure, lung cancer, asthma, bronchiectasis, depression, anxiety, severe mental illness, osteoporosis)**
- **Breathlessness score, according to the MRC scale**
- **Smoking status**
- **Number of exacerbations in the last year**
- **Inhaled treatment therapy (i.e. whether the patient has been prescribed LAMAs, LABAs, ICS etc.)**
- **Flu vaccination**
- **Referral to PR**

No identifiers are required and it is important to note that no identifiable data is held for this audit –data is pseudonymised at source, which means no identifiers leave the practice.

References
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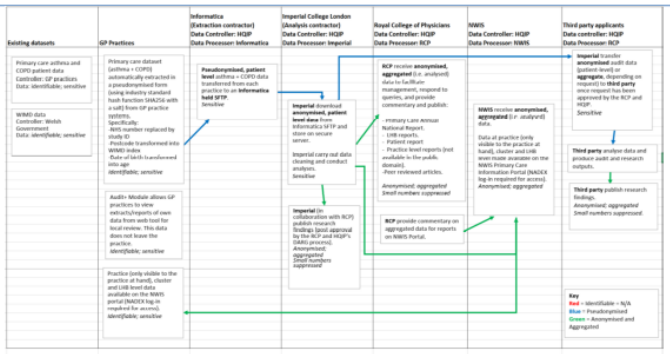
Question	Audit provider response – Yes/No, and if Yes then please provide rationale and detail (initialled and dated)	HQIP position – agreed or not agreed and why. (Initialled and dated)

1. Is the purpose of the data processing *explicitly included* in the HQIP contract specification or tender response? **If yes, provide evidence and go to question 3.** **If no go to question 2.**	No	
2. Is the purpose of the data processing *implicit* in the contract specification or tender response?	Yes The NACAP tender response stated: *We will identify areas of variation and deficiencies in care by collecting process measures (agreed by patients and clinical experts) that map to guidelines and standards. We will support improvement by providing timely and relevant data feedback, supplemented by a comprehensive QI programme. The RCP's key improvement aims for NACAP, based on results from the National COPD Audit Programme and Asthma Audit Development Project (AADP), are to:* • *COPD:* o ***Increase accuracy and timeliness of diagnosis**. The 2014-15 COPD Welsh primary care audit (https://www.rcplondon.ac.uk/projects/outputs/primary-care-time-take-breath) demonstrated only 20% of patients had a recorded spirometry confirmed diagnosis and, of these, 27% had a result that was inconsistent with COPD.*	Agreed YS 18 Dec 2018
	o ***Reduce hospital readmissions** by increasing the use of high-value, clinically effective interventions. The 2015 pulmonary rehabilitation (PR) audit (https://www.rcplondon.ac.uk/projects/outputs/pulmonary-rehabilitation-steps-breathe-better), showed that only 42% of patients referred completed the programme.* This work looks to identify variations and deficiencies in care (i.e. by understanding factors why some patients are less likely to be referred to PR) and also addresses one of the aims listed for COPD, namely, to increase the use of high-value, clinically effective interventions.	
3. Do the data flows and locations for the processing of the data to achieve this output exactly match the normal project pattern as reflected in the project's Data Flow Map?	Yes –the data flow is the same as the normal project flow, as per the data flow diagram below, which is also available at https://www.rcplondon.ac.uk/projects/outputs/national-asthma-and-copd-audit-programme-nacap-primary-care-workstream-resources. The only people who will be processing/analysing the data will be members of the Imperial College London analysis team, who are included in the primary care data flow chart.	Agreed. YS 18 Dec 2018

		
4. Is the legal basis for this processing of personal data (or data derived from personal data) clearly established? (e.g. within the NCAPOP project's S.251 application (research or non-research), fair processing information and / or consent materials and / or legal requirements	Please note, the primary care audit **does not** involve transfer of any patient identifiers – data is anonymised at source. However, fair processing activities are still conducted. As such, the patient information sheet stated: Overarching aims of the audit *This audit collects information to measure the delivery and quality of care which COPD patients receive at their general practice (GP) surgery* What information will be collected *This GP surgery will provide information on the care you receive if you have been diagnosed with COPD. Information on your diagnosis, care and treatment will be collected.* Why the information is useful *The information collected in this audit will help to highlight areas where COPD care for patients is good*	Agreed – clearly in keeping with the patient information provided and the DQS approval YS 18 Dec 2018
outside England and Wales)	*and where improvements need to be made.* What will happen to the information *The non-identifiable information collected will be analysed by the RCP, in collaboration with Imperial College London. Each GP surgery will receive a report about the care they are providing to people with COPD. This will help GP surgeries to see where they need to improve the care they provide. In addition, national and local health board reports will be made available on the National COPD Audit Programme website. The data collected may also be used to produce academic papers for publication. Any such use of the data will always be in line with the overall aims of improving care and services for people with COPD.* DQS approval (needed for Wales) also reiterated the overarching aims of the audit, as well as the fact that process data would be used for academic outputs, as long as these were in line with the overall aim of improving care for people with COPD. See below: *This customer requirement relates to the primary care element of the audit only. We seek to enable the improvement of the quality of care for COPD and asthma delivered in primary care settings through the provision of high quality data, linked to quality improvement initiatives. The data collection is designed to support reporting on indicators selected to map to relevant National Institute for Health and Care Excellence (NICE)'s Quality Standards. These include, but are not limited to, diagnosis, provision of high-value care (e.g. pulmonary rehabilitation and smoking cessation), and appropriate risk assessment (e.g. annual review, personalised asthma action plans).* *At some stage in the future the data collected through this audit may be used to produce academic papers for publication but these would not include any information that can be used to identify individual patients or individual practices. Any such use of the data will always be in line with the overall aims of improving care and services for COPD and asthma patients and will be subject to HQIP data access procedures/requirements.*	

HQIP position: one option only must be selected

☒ I confirm HQIP's agreement that this proposal for extended analysis and output **does not** require HQIP DARG approval

☐ The audit provider **must seek HQIP DARG approval** before commencing the work outlined above

HQIP Associate Director: Name……Yvonne Silove……Signature…… ……Date……18th December, 2018……

Appendix H. Extended Output Scope form: COPD BPT

Extended output scope and decision template V1.1.

(to be used in conjunction with the self-assessment tool for academic papers and other extended outputs)

OVERVIEW: please provide a title for and detail of the extended analysis and planned output proposed. Include dates for the relevant patient cohort and the associated audit report publication date for that cohort.

To investigate whether seven day working and the use of the best practice tariff are associated with better management and outcomes of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) admitted to hospital

COPD is a common chronic respiratory disease; approximately 3 million people in the UK have COPD and it is the fifth largest cause of death. Mortality rates are higher in the UK than in most of Europe and the USA (1,2). Over 10% of adult hospital emergency admissions in England have been attributed to AECOPD (accounting for ~94,000 admissions annually), and over 30% of COPD patients admitted to hospital with an AECOPD are readmitted within 3 months (3,4). AECOPD are a significant burden for patients both during the time of the acute event; increasing symptom burden and decreasing quality of life; and in terms of affecting the natural history of the disease (5).

Thus readmissions to hospital for AECOPD events and other reasons pose a significant healthcare burden. It is possible that readmissions may be lower and length of stay may be shorter in hospitals that have better staffing across the week, and also in those hospitals that have better integration with community teams.

This project will investigate:
1) Whether patients admitted to hospital with an AECOPD have better management (i.e time to NIV, time to specialist respiratory review, presence of a discharge bundle) and outcomes (reduced length of stay, readmissions and mortality) if they are admitted to a hospital where there is seven day working compared to one where there is not.

2) Whether patients admitted to those hospitals fulfilling the requirements for the best practice tariff (BPT) have better management and outcomes than those who do not.

3) Whether day of discharge affects mortality and readmission and is influenced by 7 day working and communication with integrated care teams.

Datasets
This work will utilise patient level data from the National Asthma and COPD Audit Programme (NACAP)'s COPD audit, as follows:

- COPD clinical data: cohort discharged between February 2017 and September 2017 (published April 2018 and available here: https://www.rcplondon.ac.uk/projects/outputs/copd-working-together-clinical-audit-2017)
- COPD outcome data: cohort discharged between February 2017 and September 2017 (due to be published in April 2019)
- COPD organisational data: collected in 2017 (published April 2018 and available here: https://www.rcplondon.ac.uk/projects/outputs/copd-time-integrate-care-organisational-audit-2017)

We are not intending to publish any output from this work prior to the publication of the outcome data report, which is currently scheduled to be April 2019.

In order to answer the questions, the following variables will be required:

Clinical audit:

Hospital
#1.2a Age At Admission
1.3 Gender
IMD Rank
1.6a Arrival Date
1.6b Arrival Time
1.7a Admission Date
1.7b Admission Time
2.1 Acute Physician Review
3.1 Respiratory Review
3.2a Respiratory Review Date
3.2b Respiratory Review Time
4.1 DECAF Score Recorded
4.2 DECAF Score
5.1 Oxygen Prescribed
5.2 Oxygen Target
6.1 NIV
6.2a NIV Start Date
NIV Start Date Not Recorded
6.2b NIV Start Time

NIV Start Time Not Recorded
7.1 Spirometry Result
7.2 FEV1 (Litres)
7.3 FVC (Litres)
7.4 Spirometry Date
8.1 Smoking Status
8.2 Smoking Cessation Therapy
9.1 Hospital Discharge Date
9.2 Date Of Death
9.3 BTS Discharge Bundle
9.4 Follow up Arrangements

Outcomes data:

Length of stay
Readmission rates
Mortality at 30 days
Mortality at 90 days

Organisational audit:

Unit
Unit Name
Q1.1 medEmergCount
Q1.2 emergCodAdmitCount
Q1.3 copdCodAdmitcount
Q1.4 emCodedRespAdmins
Q1.5 unitBeds
Q1.6 unitRespBedCount

Q1.7 wardRespBedCount
Q1.8 highDepAreas
Q1.9 unitHDUBedCount
Q1.10 unitGenCareBedCount
Q1.11 unitEarlyWarnDect
Q1.12 icuOutreachService
Q1.13 CAPhy
Q1.13 CGeria
Q1.13 RespConsult
Q1.13 OMedConsult
Q1.13 SpRs
Q1.14 consultInterest
Q1.15 weekdays
Q1.15 weekends
Q1.16 FY1_116
Q1.16 FY2_116
Q1.16 CT_116
Q1.16 ST3_116
Q1.16 AssSpec_116
Q1.16 StaffGrade_116
Q1.16 RespPhy_116
Q1.16 RespNur_116
Q1.16 COPDNur_116
Q1.16 OtherRepSpec_116
Q1.16 SpecRespPhy_116
Q1.16 ResReg_116
Q1.16 ResNur_116

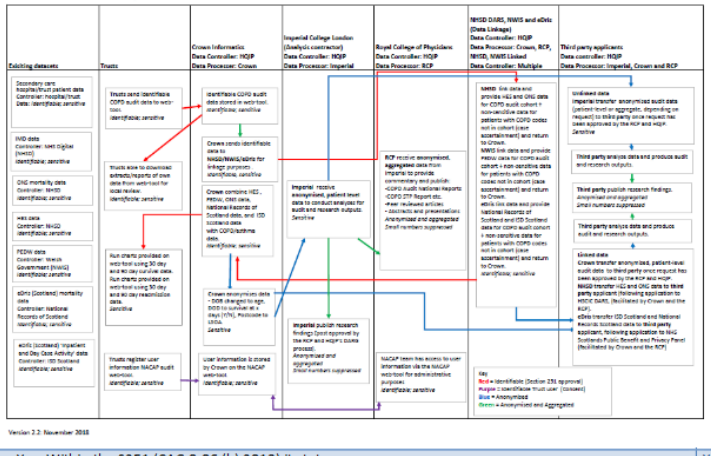
Q1.16 ResCon_116	
Q1.16 Other_116	
Q2.1 unResp2_1	
Q2.2 specialtyTriage	
Q2.3 respConsultAvail	
Q2.4 respSpRTrainee	
Q2.5 seniorDesMakerMau	
Q2.6 seniorDesMakerResp	
Q2.7 seniorDesMakerOther	
Q2.8 respNurse	
Q2.9 respNurseAccess	
Q2.10 availPhysio	
Q2.11 physioAccess	
Q3.1 leadClinicainNIV	
Q3.2 nivSetting	
Q3.3 nivChart	
Q3.4 nivtraining	
Q3.5 BTSparticipation	
Q4.1 oxygenPolicy	
Q4.2 prescriptions	
Q4.3 oxygenPrescrib	
Q4.4 monChart	
Q4.5 oxygenTraining	
Q4.6 respTrain	
Q4.6a respTrainPC	

Q5.1 dischargeBundles	
Q5.2 teamDischarge	
Q5.2.1 teamDischargeDays	
Q5.3 servicesProvided	
Q5.3 outReach	
Q5.3 inReach	
Q5.3 adminAvoid	
Q5.3 pulRehab	
Q5.3 oxyAss	
Q5.3 medChronDis	
Q5.3 nebServ	
Q5.3 smoCesAd	
Q5.4 rehabService	
Q5.4.1 rehabServiceTime	
Q5.5 mdtMeet	
Q5.5.1 mdtMeetAttend	
Q5.6 homeNivServices	
Q5.7 sessionTime	
Q5.8 pathway	

References

1. Report on inquiry into respiratory deaths. All Party Parliamentary Group on Respiratory Health. (2014).
2. An Outcomes Strategy for COPD and Asthma: NHS Companion Document. (2012).
3. Department of Health. Consultation on a Strategy for Services for Chronic Obstructive Pulmonary Disease (COPD) in England Title Consultation on a Strategy for Services for Chronic Obstructive Pulmonary Disease (COPD) in England: Draft Equality Impact Assessment. (2010).
4. https://www.england.nhs.uk/wp-content/uploads/2014/02/rm-fs-6.pdf
5. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012;67:957-963.

Question	Audit provider response – Yes/No, and if Yes then please provide rationale and detail (initialled and dated)	HQIP position – agreed or not agreed and why. (Initialled and dated)
1. Is the purpose of the data processing *explicitly included* in the HQIP contract specification or tender response? **If yes, provide evidence and go to question 3.** **If no go to question 2.**	No	
2. Is the purpose of the data processing *implicit* in the contract specification or tender response?	Yes The NACAP tender response stated: *We will identify areas of variation and deficiencies in care by collecting process measures (agreed by patients and clinical experts) that map to guidelines and standards. We will support improvement by providing timely and relevant data feedback, supplemented by a comprehensive QI programme. The RCP's key improvement aims for NACAP, based on results from the National COPD Audit Programme and Asthma Audit Development Project (AADP), are to:* • *COPD:* ○ ***Increase accuracy and timeliness of diagnosis**. The 2014-15 COPD Welsh primary care audit (https://www.rcplondon.ac.uk/projects/outputs/primary-care-time-take-breath) demonstrated only 20% of patients had a recorded spirometry confirmed diagnosis and, of these, 27% had a result that was inconsistent with COPD.* ○ ***Reduce hospital readmissions** by increasing the use of high-value, clinically effective interventions. The 2015 pulmonary rehabilitation (PR) audit (https://www.rcplondon.ac.uk/projects/outputs/pulmonary-rehabilitation-steps-breathe-better), showed that only 42% of patients referred completed the programme.* This work looks to identify variations and deficiencies in care (i.e. by understanding why some patients are more likely to be readmitted to hospitals) and also addresses one of the aims listed for COPD, namely, to reduce hospital readmissions.	YS 16/1/19 Agreed – this project is within keeping of the stated intention to identify variation and its association with system structures and processes.
3. Regarding the processing of record level data and / or aggregate data which cannot be fully anonymised: Do the data flows and locations for the processing of the data to achieve this output exactly match the normal project pattern as reflected in the project's Data Flow Map?	Yes, the data flow is the same as the normal project flow, as per the data flow diagram below, which is also available at https://www.rcplondon.ac.uk/projects/outputs/national-asthma-and-copd-audit-programme-nacap-secondary-care-workstream-copd. The only people who will be processing/analysing the data will be members of the Imperial College London analysis team, who are included in the COPD data flow chart (as receiving both audit and linked data).	YS 16/1/19 compliant

		
4. a. Is the legal basis for this processing of personal data (or data derived from personal data) clearly established? (e.g. within the NCAPOP project's S.251 application (research or non-research), fair processing information and / or consent materials and / or legal requirements outside England and Wales). **b. If data from another data controller (such as NHSD or NWIS) will be processed, please insert evidence from the relevant data sharing agreement that the processing will be permitted.**	a. Yes. Within the S251 (CAG 8-06 (b) 2013) it states: *Secondary use of de-identified data for the purpose of audit, service evaluation and research (with appropriate ethical approvals) by approved third parties is also permitted. This involves Imperial College London securely transferring de-identified data (either patient-level or aggregated) to credible applicants (i.e. those whose request has been approved by both Healthcare Quality Improvement Partnership (HQIP) (as data controller) and the RCP). In addition, should the applicant organisation require both audit data and outcome data (i.e. linked data), identifiable data is sent from Crown Informatics to NHS Digital and NWIS for the purposes of data linkage (e.g. with HES/PEDW or ONS) with subsequent flow of a linked (de-identified) dataset from NHS Digital to the applicant organisation.* b. Yes, within the DSA with NHS Digital (DARS-NIC-349273-T3L4K-v3.7) it states: *Future outputs:* *-Publications in peer-reviewed journals. These are essential to a) broadly disseminate important findings regarding the outcomes of people admitted to hospital with acute exacerbations of COPD and to; b) inform quality improvement at a local and national level.* *The publications will only present aggregated data and will not include patient level data.* The data **will not** at any point leave Imperial College London for this work to be undertaken.	YS 16/1/19 Whilst the CAG wording describes cover for third parties to undertake service evaluation, the implication would be that Imperial would be included as contracted NACAP processor also.

Confirmation from the NCAPOP project manager and clinical lead that the information provided is complete and accurate

HQIP position: one option only must be selected

☒ I confirm HQIP's agreement that this proposal for extended analysis and output **does not** require HQIP DARG approval

☐ The audit provider **must seek HQIP DARG approval** before commencing the work outlined above

HQIP Associate Director: Name…Yvonne Silove…..Signature… ……Date……16 Jan 2019……..

Appendix I.Extended Output Scope form: NEWS2

Extended output scope and decision template V1.4.

(to be used in conjunction with the 'Decision Aid for Accessing and Publishing Data Commissioned by HQIP')

1. PROPOSAL OVERVIEW: please summarise: • ***project title*** • ***the question(s) to be investigated*** • ***the dates for the relevant patient cohort being processed, and the associated audit report publication date for that cohort.*** • ***the sources of data to be used: England / Wales / other as well as from which data provider: audit dataset / NHSD / NWIS / other NCA*** • ***which (if any) personal data fields will be processed for the purposes of this project*** • ***the methodology proposed*** • ***the anticipated outputs and benefits*** • ***the anticipated project completion date***
Proposal overview: **TITLE:** Use of NEWS2 to predict length of stay and in hospital mortality at exacerbation of COPD **QUESTION:** Can NEWS2 be used to predict short term outcomes at exacerbation of COPD, including inpatient mortality, need for non-invasive ventilation (NIV), and length of stay. **DATES:** Most recent COPD clinical audit data cut is for patients discharged between 01/10/2018 and 30/09/2019, but this includes patients that were admitted from as early as 01/01/2018 so we will only include patients with available NEWS2 datafollowing its introduction into the data refresh in 2018. PERSONAL DATA FIELDS not required. **DATA SOURCE:** English NACAP COPD secondary care clinical audit 2019 data **METHODOLOGY:** Distribution of NEWS2 scores across the cohort and across units using general summary statistics.

Associations between NEWS2 (categorise into low, medium and high risk (0-4, 5/6, 7 or higher and if possible undertake a sensitivity analysis as a continuous variable and aforementioned outcomes; inpatient mortality, need for non-invasive ventilation (NIV), and length of stay (expressed as above and below median and explore categorical), univariable and corrected for known associations. Associations between NEWS2 and COPD disease severity (spirometry) FEV1% predicted (30/50/80) Associations between NEWS2 and presence of cardiovascular and mental health co-morbidity (yes/no) Association between NEWS2 as an acuity measure and social deprivation (LSOA) as we have seen better outcomes in more deprived patients and wonder if there is a difference in admission severity. Confounders to be adjusted for as appropriate include: age, sex, deprivation and we will test for further confounders (e.g. disease severity, comorbidity). We will use logistic regression. **OUTPUT/BENEFIT:** Conference abstract / paper Benefit: utility (or not) of NEWS2 as a predictor of outcome in COPD. This is important as the utility of NEWS2 scoring in COPD has been questioned and NACAP provides the largest dataset to inform clinical practice on the utility of this assessment in COPD. If NEWS2 is under or over-estimating risk in COPD then that could adversely affect patient care. **PROJECT COMPLETION DATE:** In time for submission to 2020 ERS Congress (Quarter 1 2020), followed by preparation of a manuscript. The expected publication date of the NEWS2 data from which this is drawn is in May-June 2020 so this proposed analysis will not be publicly available prior to release of that report.

Additional Questions	Audit provider response
2. Is the purpose of the data processing *explicitly included* in the HQIP contract specification or tender response? **If yes, provide evidence and go to question 4.** **If no go to question 3.**	No

3. Is the purpose of the data processing *implicit* in the contract specification or tender response?	Yes Audit data fields are chosen to reflect important variables and or outcomes. There has been a national move to NEWS2 as an acuity measure, but this was not explicitly developed in COPD and respiratory diseases are complex in relation to oxygen scoring in NEWS2. We therefore have the ability to demonstrate the utility of NEWS2 in COPD. Whether we do or do not find positive association between NEWS2 and outcomes is important both in the clinical utility of NEWS2 for COPD, and inclusion of this variable in the audit dataset.
4. Regarding the flows and processing locations of all record level data and / or aggregate data for this output which cannot be fully anonymised…	☒ **I confirm that the data flows and locations for the processing for this output exactly match the normal project pattern as reflected in the project's Data Flow Map?** ***(initialled and dated) JRH 13/12/2019***
5. Regarding the legal basis, other information governance requirements and any requirements from third party data providers (e.g. NHS Digital, Public Health England, NWIS, other registries and audits)	☒ **I confirm that all proposed processing activities have an established legal basis (e.g. within the NCAPOP project's S.251 application (research or non-research), fair processing information and / or consent materials and / or legal requirements outside England and Wales).** ☒ **I confirm that any proposed processing of data from a third party data controller is permitted under the agreement by which that data has been accessed.** ***(initialled and dated) JRH 13/12/2019***

Confirmation from the NCAPOP project manager and clinical lead that the information provided is complete and accurate

NCAPOP Project Manager: Name……Kirsty MacLean Steel……..Signature……. ……Date……5/3/20……..

NCAPOP Clinical Lead: Name……John Hurst……Signature…… …23/01/2020……..

HQIP position: one option only must be selected

☒ I confirm HQIP's agreement that this proposal for extended analysis and output is approved and **does not** require HQIP DARG approval

☐ The NCAPOP provider **must seek HQIP DARG approval** before commencing the work outlined above

HQIP Associate Director: Name……Yvonne Silove……Signature…… ……Date……09/03/2020

Appendix J. CPRD GOLD primary care audit replication codelists

CPRD GOLD Read V2 codes used to replicate the NACAP primary care audit in CPRD GOLD can be found at: https://github.com/pstone22/PhD/tree/main/codelists/Chapter%205

Appendix K. Charlson Comorbidity Index ICD-10 codes

Comorbidity (score)	ICD-10 codes
Diabetes without complications (1 point)	E100, E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149
Diabetes with complications (2 points)	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147
Mild Liver Disease (1 point)	B18, K73, K74, K700, K701, K702, K703, K709, K717, K713, K714, K715, K760, K762, K763, K764, K768, K769, Z944
Moderate or Severe Liver Disease (3 points)	K704, K711, K721, K729, K765, K766, K767, I850, I859, I864, I982
Cancer (2 points)	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97
Metastatic Carcinoma (6 points)	C77, C78, C79, C80
AIDS/HIV (6 points)	B20, B21, B22, B24
Renal Disease (2 points)	N18, N19, N052, N053, N054, N055, N056, N057, N250, I120, I131, N032, N033, N034, N035, N036, N037, Z490, Z491, Z492, Z940, Z992
Congestive Heart Failure & Hypertension (1 point)	I43, I50, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, P290
Myocardial Infarction (1 point)	I21, I22, I252
Peripheral Vascular Disease (1 point)	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Cerebrovascular Disease (1 point)	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340
Dementia & Depression (1 point)	F00, F01, F02, F03, G30, F051, G311, F33
Paraplegia and Hemiplegia (2 points)	G81, G82, G041, G114, G801, G802, G830, G831, G832, G833, G834, G839
Connective Tissue Disease-Rheumatic Disease (1 point)	M05, M32, M33, M34, M06, M315, M351, M353, M360
Peptic Ulcer Disease (1 point)	K25, K26, K27, K28

Appendix L. Mental illness ICD-10 codes

Mild/moderate mental illness (depression or anxiety)

All sub-codes were included for each code.

ICD-10 Code	Description
F32	Depressive episode
F33	Recurrent depressive disorder
F34	Persistent mood [affective] disorders
F38	Other mood [affective] disorders
F39	Unspecified mood [affective] disorder
F40	Phobic anxiety disorders
F41	Other anxiety disorders

Severe mental illness (schizophrenia, bipolar or other psychotic disorder)

All sub-codes were included for each code.

ICD-10 Code	Description
F06	Other mental disorders due to brain damage and dysfunction and to physical disease
F10	Mental and behavioural disorders due to use of alcohol
F11	Mental and behavioural disorders due to use of opioids
F12	Mental and behavioural disorders due to use of cannabinoids
F13	Mental and behavioural disorders due to use of sedatives or hypnotics
F14	Mental and behavioural disorders due to use of cocaine
F15	Mental and behavioural disorders due to use of other stimulants, including caffeine
F16	Mental and behavioural disorders due to use of hallucinogens
F18	Mental and behavioural disorders due to use of volatile solvents
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
F20	Schizophrenia
F23	Acute and transient psychotic disorders
F24	Induced delusional disorder
F25	Schizoaffective disorders
F28	Other nonorganic psychotic disorders
F30	Manic episode
F31	Bipolar affective disorder
F60	Specific personality disorders

Appendix M. HQIP Data Access Request Form (DARF) approval

HQIP
Healthcare Quality Improvement Partnership

Data Access Request Form (DARF)

Applicants should ensure that they have reviewed the accompanying HQIP guidance and have discussed this request with the organisation(s) commissioned by HQIP to deliver the relevant clinical audit or clinical outcome review programme. The audit or clinical outcome review programme acts as data processor to HQIP and is referred to as the 'data provider' for the purpose of this data access request.

Once completed please return this signed form to datasharing@hqip.org.uk

All sections within this form are mandatory unless specifically stated otherwise. Unless this form is completed in full, it will be returned to the applicant which will extend the time to data receipt.

For HQIP office use only			
HQIP application number	HQIP323	**Date of submission to HQIP**	06/12/2019
If applicable, any linked application number(s)	Click or tap here to enter text.	**Charging category**	Complexed
Tracking history	02/12/10 Yvonne complete pre-DARG checks 06/12/19 Application submitted Pro forma submitted 10/12/19 Pro forma sent to Finance 13/02/20 Submitted to DARG for review 19/2/20 REVIEWED AT DARG: Clarifications requested: Section 4: We note ONS is now Civil registration (noted here– form does not need to be modified) N/A Section 7: Lead application also has a role with audit provider (lead analyst) please declare. Completed Section 10: Please include a list of fields requested from other data controllers which will be linked and provided to the applicant (to be		

DARF Form v2 – 22 October 2019

	embedded) HES fields added to S. 10; CPRD fields already listed in the methodology section – therefore Complete Section 13: Needs updating as previous registration now expired Complete Section 14: Tick to indicate that the S.251 provided covers the **'Transfer/access personal data'** **Complete** Section 21: Needs signing by audit clinical lead has signed but audit signature still required – now complete also For Chair's Action when clarifications completed 10/3/20 - Clarifications received and reviewed by YS. Audit signature outstanding therefore returned to applicant 20/3/20 - YS Reviewed – signatures now in order – recommended now for Chair's Action please **20/03/20 – Approved by Chair's Action**
Expiry date	Click or tap to enter a date.

Section 1	Primary applicant information			
Title of project	Variation in patient pathways and hospital admissions for exacerbations of COPD: linking the National Asthma and COPD Audit Programme (NACAP) with CPRD data			
Name of primary applicant organisation	Imperial College London			
Name of any partner organisation (s) if applicable *(ensure partner form also completed)*	Clinical Practice Research Datalink			
Address of primary applicant organisation	Respiratory Epidemiology, Occupational Medicine and Public Health Emmanuel Kaye Building National Heart and Lung Institute Imperial College London Manresa Road London SW3 6LR			
Primary contact *(must be a permanent senior member of staff)*	Jennifer Quint	**Job title**	Reader in Respiratory Epidemiology	
Telephone	0207 594 8821	**Email**	j.quint@imperial.ac.uk	
Organisation type	**NHS Healthcare Provider**	**Academic Institution**	**Healthcare Regulator**	**Other Healthcare Body**
	☐	☒	☐	☐
	Local Authority	**Individual Citizen(s)**	**Commercial Body**	**Other (please state)**
	☐	☐	☐	☐
HQIP projects from which data is requested *(For reference a list of HQIP projects and their Project Managers are listed on the HQIP website)*	**Please list below the name(s) of each of the HQIP-commissioned projects from which you are requesting data.**			
	National Asthma and COPD Audit Programme – COPD secondary care clinical audit			

Section 2	Application type

Please tick at least one box below confirming whether the application is for a new application, extension or amendment. For extensions or amendments, you must highlight the specific information within this form that has been updated and provide updated signatures in order for the request to be processed.		
Request	**Provide original HQIP application number and approval date and any subsequent amendment approval dates.**	**Summary of changes and rationale for the change to your original application. In addition all changes must be made as highlighted edits within this form.**
☒ **New Application** Including applications that have not previously been approved by HQIP.	**N/A**	**N/A**
☐ **Extension** Request to extend the term of a current data sharing agreement.	Click or tap here to enter text.	Click or tap here to enter text.
☐ **Amendment** Request to change the scope, data fields requested or any other change to an application previously approved by DARG.	Click or tap here to enter text.	Click or tap here to enter text.

Section 3	**Project type**				
Please select the most appropriate answer	**Research**	**Service Evaluation**	**Clinical Audit**	**Other (please state)**	
	☒	☐	☐	☐	Click or tap here to enter text.
Is ethics approval required?	**If the request is for research purposes you must enclose evidence of NHS ethics approval or evidence that this is not required**				
	YES Confirmation of NHS ethics needs to be submitted with this application.				☐
	NOT REQUIRED Confirmation needs to be submitted with this application from the HRA decision tool http://www.hra-decisiontools.org.uk/ethics/ or confirmation from your local Research and Development Department that NHS ethics is not required. HRA decision tool_JKQ.PDF				☒

Section 4	Project details
Please provide full details of the project below. You should describe and justify the project's objectives, rationale and methodology.	
Objective/Rationale	Aim To link the exacerbation of COPD arm (secondary care clinical audit) of the National Asthma and COPD Audit Programme (NACAP) with CPRD primary care GOLD and Aurum data, Hospital Episode Statistics (HES), and Office of National Statistics (ONS) Death registration data to explore how variations in patient pathways through healthcare across England affect hospital admissions for exacerbations of COPD. CPRD consists of routinely collected anonymized electronic healthcare record data from general practices in the United Kingdom (GOLD and Aurum databases), HES contains data on patients admitted to National Health Service (NHS) hospitals in England, and the ONS data has information on date and cause of death. 75% of English practices in CPRD have provide information allowing for linkage to other data sources, include HES and ONS data. Objectives 1. Demonstrate the added value of the linked data by exploring how the management of patients with COPD and patient pathways vary across England, and how this relates to hospital admissions for exacerbations of COPD. For the sake of brevity, the secondary care clinical audit component of NACAP that will be linked with CPRD data will be referred to as NACAP-SC in this Data Access Request Form. As part of this objective the following will be investigated: • What proportion of AECOPD admissions are potentially inappropriate or avoidable? • How does management of AECOPD on and following discharge from hospital affect disease outcomes, future admission events and mortality? • How accurate is the recording of AECOPD in HES and how do hospital admissions for other reasons affect admissions and readmission for AECOPD? 2. Using the linked data from the exacerbation of COPD arm of NACAP with CPRD primary care GOLD and Aurum, HES, and ONS data, undertake dataset characterisation, and develop guidance for using the linked dataset. This may in the future be of benefit to other researchers. Rationale Acute exacerbations of COPD (AECOPD) pose a significant burden for patients both during the time of the acute event and in terms of affecting the natural history of the disease. They are a leading cause of adult emergency admission to hospital in the UK, resulting in significant health care usage and cost. Some AECOPD events legitimately require hospital admission (patients with unpreventable respiratory failure), but others are potentially avoidable. There is significant geographic variation across England for admissions for AECOPD (irrespective of the underlying area prevalence).

	Some of this variation may be due to patient factors (how engaged they are with their disease) and some health system factors (ease of primary care access when unwell). NACAP is the gold standard for AECOPD hospital admissions, containing detailed information on clinical features associated with admission, allowing ascertainment of how unwell a patient is on hospitalisation and whether the admission could potentially have been avoided. Linkage of NACAP with primary care data from CPRD would allow the whole patient pathway to be investigated including visits to primary care preceding an admission, medications prescribed and previous AECOPD events. This would allow exploration of factors that may explain variations in admissions for AECOPD across England and highlight areas for action to reduce unwarranted variations and improve care for patients with COPD. Currently, NACAP is linked intermittently to HES and ONS mortality data, but there is no primary care linkage. Therefore, the generation of a novel linkage between primary care data in CPRD and NACAP will allow clinical and health care system questions to be answered that would otherwise not be answerable.
Methodology	**Please include:** ▪ **A summary of your project methodology, ensuring this description aligns with the dataset requested** ▪ **A justification of sample size, analyses proposed and plans for patient and/or user group involvement**
	<u>Study Design</u> This study will be cross-sectional, analysing care received by COPD patients (see Study Population). The period used in this study will be 1st October 2018 to the 30th September 2019. <u>Sample Size</u> As of 23rd May 2018, there are 90,112 admissions recorded in NACAP-SC (from 1st February 2017), however the number of individual patients contained in NACAP-SC will be lower due to readmissions. For the period 1st February 2017 to December 2017, there are 29,335 English COPD patients (prevalent & incident) present in CPRD GOLD, and 99,714 prevalent and 10,826 incident COPD cases in CPRD Aurum. <u>Study Population</u> COPD patients will be defined by their presence in NACAP-SC (only AECOPD hospitalisations are recorded in NACAP-SC). The start of the study will be 1st October 2018 and the study will run until 30th September 2019, the date of last data collection. Analyses required routinely linked IMD, HES, and ONS Death data will be performed using English patients only. <u>Variables</u> ***Exposures:*** • Contact with primary care in the 2 weeks prior to AECOPD (defined by presence in NACAP-SC – NACAP-SC only contains AECOPD admissions) hospital admission (yes/no). Contact defined as any Read code indicating communication with primary care [data from CPRD]. • Clinical Commissioning Group (CCG) [data from CPRD]. • Receipt of a discharge bundle (a discharge care bundle is a list of best-practice actions to be undertaken before the patient is discharged to reduce the likelihood of the patient being readmitted) (yes/no) [data from NACAP-SC].

- Seen within 24 hours of admission by respiratory team (yes/no) [data from NACAP-SC].

Outcomes:

- AECOPD severity (high risk/low risk). High risk defined as DECAF score of 3-6 (the DECAF score is a validated predictor of mortality in patients with AECOPD (17,18). It measures extended MRC Dyspnoea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation.), or in the absence of a DECAF score, requirement for oxygen or NIV, or death (from linked ONS data). Low risk defined as DECAF score of 0-1 or, in the absence of a DECAF score, no requirement for oxygen or NIV. If there is sufficient DECAF data, a DECAF score of 2 can be used to create an 'intermediate risk' category [data from NACAP-SC]. We will also use NEWS2 as a marker of severity.
- Avoidable hospital admission (defined as contact with primary care in the 2 weeks prior to AECOPD hospital admission (yes/no) [data from CPRD].
- Best practice care of AECOPD post-discharge (yes/no). Defined as: A Read code indicating review within 2 weeks of discharge, a Read code for pulmonary rehabilitation referral, prescription codes for a rescue pack of antibiotics (macrolides, doxycycline, and broad spectrum penicillins) and oral corticosteroids, and a Read code for smoking cessation treatment referral (if a current smoker) [data from CPRD].
- Readmission in the 30 days after discharge (yes/no) [data from NACAP-SC].
- Death in the 30 days after discharge (yes/no) [data from ONS Death Registration].

Covariates [from CPRD data unless otherwise specified]:

- Age (10-year age bands)
- Sex (male/female)
- Socioeconomic status (quintiles of IMD)
- Smoking status (current/ex/never)
- Comorbidities (yes/no):
  - Asthma
  - Bronchiectasis
  - Coronary heart disease
  - Diabetes
  - Heart failure
  - Hypertension
  - Lung cancer
  - Stroke
  - Osteoporosis
  - Anxiety
  - Depression
- Painful condition (yes/no) (defined as patients who had a record of four or more prescription analgesia medications in the past 12 months, or four or more specified anti-epileptics in the absence of an epilepsy Read code in the past 12 months).
- Diagnosed with AECOPD and prescribed antibiotics and/or steroids in the 2 to 4 weeks prior to AECOPD hospital admissions (yes/no).
- Inhaled therapies prescribed in the past year.
- Days since diagnosis of COPD (first occurrence of validated COPD diagnosis code).

	• Receipt of smoking cessation advice (yes/no). • Referral for pulmonary rehabilitation (yes/no). • FEV1/FVC ratio. • FEV1 % predicted. • MRC score. • Receipt of influenza immunisation (yes/no). • Invited for and attended annual review visit (yes/no). • Exacerbation frequency (using validated method (Rothnie et al., 2016; PLOS ONE)). • Attendance at A&E in the 2 weeks prior to AECOPD hospital admission (yes/no) [from linked HES data] **Statistical Analysis** Data management and analysis will be performed in Stata 15. The following analysis will be done: • Summary statistics. • Are there management changes after discharge: changes in treatment, referral for pulmonary rehabilitation, prescription of rescue packs of antibiotics and steroids, and inhaler technique checked? • Is data recording consistent across primary and secondary care for smoking cessation, pulmonary rehabilitation, and spirometry? • Misclassification of AECOPD in HES. The recording of AECOPD in NACAP-SC can be compared with the diagnosis recorded in HES to ascertain the validity of AECOPD recording in HES. • Logistic regression will be used to test the following: ➢ Whether contact with primary care in the 2 weeks prior to an AECOPD reduces the odds of the admission being inappropriate (low risk severity). ➢ Whether different regions (CCGs) of England have differing levels of inappropriate (low risk AECOPD severity) AECOPD hospital admissions. ➢ Whether different regions (CCGs) of England have differing levels of avoidable AECOPD hospital admissions. ➢ Whether receipt of a discharge bundle increases the odds of receiving best practice care of the AECOPD post-discharge. ➢ Whether receipt of a discharge bundle reduces the odds of readmission in 30 days following discharge. ➢ Whether receipt of a discharge bundle reduces the odds of death in the 30 days following discharge. ➢ Whether being seen by the respiratory team within 24 hours of admission increases the odds of receiving best practice care of the AECOPD post-discharge. ➢ Whether being seen by the respiratory team within 24 hours of admission reduces the odds of death in the 30 days following discharge.
Please describe the expected measurable benefits to health and/or social care including target date	This work will impact on patients, health care providers, health care funders, National Clinical Audit schemes and research communities. Patients and health care providers: The full patient pathway will be explored, variations in care identified and relationship to hospitalisation for AECOPD determined highlighting areas for reduction in variation and improvement in quality of patient care.

	Researchers: Development of a new linked dataset may be available to others in the future with appropriate permissions, and may allow more detailed understanding of the pathways leading to hospital admission, subsequent outcomes and validation of HES recorded AECOPD events. COPD is one of the most popular research areas using CPRD data as evidenced by the growing number of ISAC protocols submitted in this area. Given the enormous health burden associated with AECOPD, the number of research questions that can be answered using a linked dataset is high. The linked COPD Audit dataset will possibly be available in the future for other researchers (HQIP permitting) through the CPRD routine linkage scheme. CPRD, HQIP, Audits: Once the legal gateway for this linkage is established it may be that it will be easier to link other audit datasets under the HQIP umbrella with primary care data. This particular linkage will provide insight into the benefit of primary care data which is important given the primary care arm of the National COPD Audit could not be done in England. This should in turn impact on the thinking, planning and implementation of future national clinical audits. We will disseminate our work and findings through leading peer review journals, conferences and the Future Hospital Commission website. We will also disseminate information through patient groups to encourage audit participation
Proposed completion date of the project	30/06/2021
Lay Title and Summary	**Please provide a lay summary of your project (max 300 words).** The lay summary should be written in plain English and must enable a non- medical audience to understand the research question and aims of the project. If your request is approved, this paragraph (title and summary) will be published on the HQIP website.
	The National Asthma and Chronic Obstructive Pulmonary Disease (COPD) Audit Programme (NACAP) provides data on the care received by people with COPD (a group of progressive lung conditions that cause breathing problems) in the United Kingdom (UK). Most COPD patients experience episodes of worsening in respiratory symptoms, known as a flare-up of COPD. A COPD flare-up is one of the most common reasons for adult emergency hospital admission in the UK, resulting in significant healthcare usage and cost. The COPD admission hospital data from NACAP (NACAP-SC) contains detailed information on COPD flare-up hospital admissions. Our study will create a new linkage between a large UK database of GP medical records (the Clinical Practice Research Datalink (CPRD)) and hospital data for COPD flare-ups taken from NACAP-SC. This linked dataset will be used to explore how many admissions for COPD flare-ups are avoidable, and whether receiving specific treatments or being seen within 24 hours of admission by the respiratory team reduce the likelihood of a patient being readmitted or dying.

Section 5	**Publications and other outputs**
Please include all intended outputs of the project including publications. Outputs include all types of disseminations produced from the project data. For each output include the highest level of detail of data/information that will be displayed.	

Outputs including publications *(add more rows if required)*	What is the highest level of detail that will be displayed in the output *(e.g. case record, unit, hospital, trust, network, regional, national, whole study, study group)*	Will this output be published?	Expected Date of Publication	Confirm that published output will be anonymised to the level required by ISB1523: Anonymisation Standard for Publishing Health and Social Care Data
abstract to a respiratory conference (BTS, ERS or ATS)	trust	Yes	01/10/2021	Yes
A paper associated to the project	trust	Yes	10/01/2021	Yes
PhD thesis chapter	trust	yes	03/01/2021	Yes
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.
Add more rows if needed				

Section 6	**Project funding**	
Please indicate whether your project has received dedicated funding. Please also indicate whether there is a commercial interest in the project, either by funding or direct input into project design or team.		
Funding *(please select one answer)*	**No** ☐	
	Yes ☒	**If yes**, please provide the name of the funding body below The Health Foundation
Commercial interest *(please select one answer)*	**No** ☒	
	Yes ☐	**If yes**, please provide the name of the organisation and the nature of any interest into the project design below. Please also note information required in Section 7 Click or tap here to enter text.

Section 7	Declaration of Interest	
Please indicate whether any individuals named in this application have an interest to declare about this application. All interests that might unduly influence an individual's judgement and objectivity in the use of the data being requested from DARG are of relevance. Particular consideration should be given to declaring interests involving payment or financial inducement for use of the data being requested. These will be considered by DARG to determine if there is any potential conflict of interest identified as part of the request.		
Declaration of interest ***(please select one answer)***	**No** ☐	
	Yes ☒	**If yes**, please provide the name and details of the declaration for each individual below Dr Quint is the analysis lead for the NACAP. She does not receive any personal funding for this role but Imperial College receive funding as a result which part funds two individuals to analyse the audit data.

Section 8	Data Summary		
Please tick the box(es) confirming the geographical coverage of the data you are requesting. Coverage is defined as the location of the healthcare services who originated / initially provided the extract of data you are requesting. *NB. HQIP's DARG can only approve applications for access to the datasets which HQIP commission and thereby act as Data Controller.*			
Geographical coverage	☒ **England**	☐ **Wales**	☐ **Scotland**
	☐ **Northern Ireland**	☐ **Republic of Ireland**	☐ **Other**, please state: Click or tap here to enter text.
Inclusion and exclusion criteria (including date parameters)	**Describe precisely the criteria which define the patients to be included and to be excluded from the data extract you are requesting.** Please include precise date parameters for the start and end of the range requested (dd/mm/yy) and explain which dated project field will be used to define the requested cohort (e.g. date of admission or date of operation).		
	All patients in the COPD Secondary Care Clinical Audit of NACAP (NACAP-SC) will be required for linkage. This will include all patients from the 1st October 2018 to 30th September 2019. After creation of the bespoke linkage between NACAP-SC and primary care data from both CPRD GOLD and CPRD Aurum, COPD patients will be defined by their presence in NACAP-SC (only AECOPD hospitalisations are recorded in NACAP-SC). The start of the study will be 1st October 2018 and the study will run until 30th September 2019. Where data are further linked with the routine linkages of IMD, HES, and ONS Death data, only English patients will be included (routine linkages are only available for England).		

Periodic updates	**Periodic updates may sometimes be available.** These must be agreed with the HQIP data provider in advance and any falling outside of the term of the Data Sharing Agreement will be subject to an application extension being agreed. Please provide details below including reasons.	
	☒ **None** ☐ **Monthly** ☐ **Quarterly** ☐ **Bi-annual (6 monthly)** ☐ **Annual** ☐ **Other**, please state: Click or tap here to enter text.	
Project/linked data *(please tick all that apply)*	**HQIP commissioned projects routinely link the data that they collect to other external datasets. The requirements of each data controller vary and there may not be an agreed process for onward sharing of linked project data. Please contact HQIP for advice before completing this form if you wish to apply for project data that has been linked with other datasets.** Please confirm whether you are applying for unlinked project data, or project data that has been linked to an external dataset.	
	☒ **Unlinked project data**	☐ **Project data linked with HES**
	☐ **Project data linked with ONS**	☐ **Project data linked with PEDW**
	☐ **Project data linked with Civil Registration data**	☐ **Project data linked with another dataset** Please provide details below: whilst we are applying to HQIP for unlinked audit data, CPRD permissions will allow us to receive linked, de-personalised record level data as per dataflow diagram in section 11

Section 9	**Data Type**
First discuss your request with the data provider and then indicate in this section the type of data you are requesting (tick all that apply). Note that what is relevant here is the identifiability of the data you are requesting at the point it leaves the HQIP data provider and not the level disclosed in any future publication. For further information on these categories of identifiability please see the Understanding patient data guidance https://understandingpatientdata.org.uk/what-does-anonymised-mean	

☐ **Anonymous data** This is information from many people combined together (aggregated), so that it would not be possible to identify an individual from the data. Information about small groups or people with rare conditions could potentially allow someone to be identified and so would not be considered anonymous. Individual patient level data may also very occasionally be categorised as anonymous. In this case, the information in each record requested would also potentially be true for many other similar individuals, and so could not be used to deduce the person's identity.	Click or tap here to enter text.
☒ **De-personalised data** This is information that does not identify an individual, because identifiers have been removed or encrypted. However the information is still about an individual person and so needs to be handled with care. It might, in theory, be possible to re-identify the individual if the data was not adequately protected, for example if it was combined with different sources of information.	**HQIP data provider to provide a description for how the data will be de-identified to reduce any risk of re-identification.** NHS Digital will use the identifiers to create a bridging file which contains the Crown Informatic record key pseudonym and the CPRD GP practice record key. This bridging file will be sent to CPRD. CPRD will send the Crown Informatics Pseudonyms to Crown Informatics, requesting the relevant the clinical variables required for the study. Once CPRD receives the variables, it will link the COPD data+ CPRD primary care data + HES + ONS and anonymise the data (eg only provide age and LSOA) to Imperial College London. Before this is released, risk assessment will be conducted to ensure the risk of re-identification is low. If required mitigation measures will be applied based on standard CPRD procedures
☒ **Personally identifiable data** This is information that identifies a specific person. Identifiers might include: name, address, full postcode, date of birth or NHS number. Personally identifiable data fields that are requested solely for the purpose of linkage still need to be described here and in Section 10, even if they are removed before the data reaches the applicant.	Crown informatics will send the following identifiers to NHS Digital (Full Postcodes, date of birth, NHS Number and Gender and a Crown Informatic record key pseudonym. Personal fields will be deleted before transfer to CPRD and Imperial College London (see dataflow diagram section 11).

Section 10	**Data Fields**

Please detail in the table below the data fields required as part of this request. All fields required to leave the data provider must be included here including linkage fields. Justification for these should include whether they will be retained or destroyed once linkage is complete. This should also be clear on the data flow map in Section 11. Applicants should only request the minimum data set required to address the purpose stated within this application.			
Data field requested	**Data source** *(Audit/project, HES, ONS, PEDW etc.)*	**Transformation applied** **This must be completed for every data field requested:** ▪ **None** ▪ **Explain the transformation applied** (e.g. pseudonymisation (including who holds the key to reverse), time elapsed, age banding etc.)	**Justification** *Please justify your use of each data item requested*
EXAMPLE – NHS Number	*EXAMPLE - Audit*	*EXAMPLE – Pseudonymisation and encryption with key held only by HQIP data provider*	*EXAMPLE - For tracking single patients within multiple audit entries*
See attached 2019 CPRD Copy of 2019 COPD SCC Variables.xlsx SCC Variables spreadsheet	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Data_Minimisation_Variable_Restriction		Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Add more rows as needed			

Section 11	**Processing locations and data flows**			
Please list all locations where processing will be undertaken, for the avoidance of doubt storage is considered processing. For each separate organisation processing data which is not fully anonymous a separate partner organisation form must also be completed.				
Processing location	**Organisation name**	**Processing or storage**	**Data type processed** *(anonymous, de-personalised,*	**How will data be transferred to this location?**

			personally identifiable)	
Canary Wharf, London, UK	Clinical Practice Research Datalink	Processing	De-personalised	Secure File Transfer Protocol
Boar Lane Leeds, UK	NHS Digital	Processing	Personally identifiable	Secure File Transfer Protocol
London, UK	Imperial College London	Storage	Anonymous	Secure File Transfer Protocol

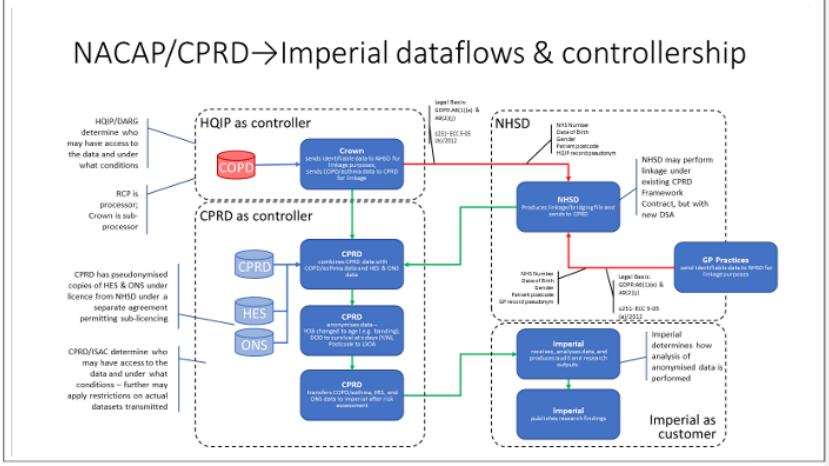
Will data be transferred outside of the European Economic Area? *If yes please state to where and give details of how that will be in compliance with the Data Protection Act 2018.*	☒ **No**	☐ **Yes**
	If yes, please provide details: Click or tap here to enter text.	

Data Flows

Please insert a data flow diagram which graphically describes:

1. **All locations where data is processed**
2. **All transfers that take place between locations and organisations**
3. **Data linkages to other data sets**

Please insert data flow diagram here



Section 12	**Project team employed by the applicant organisation**

Please list the name and job title of each member of the applicant organisation who will have access to the data for the purposes of this request. Please also confirm that they have a formal contract with the applicant organisation and will therefore be covered by the HQIP Data Sharing Agreement. Please add additional rows if necessary. Where the data map in Section 11 details processing of data which is not anonymous by additional organisations, a partner organisation form is required to be completed for each.			
Team member	**Name**	**Job title**	**Contract in place with applicant organisation**
Principal investigator	Dr Jennifer K Quint	Reader in Respiratory Epidemiology	☐ **No** ☒ **Yes**
Project member 1	Philip Stone	Research Assistant	☐ **No** ☒ **Yes**
Project member 2	Click or tap here to enter text.	Click or tap here to enter text.	☐ **No** ☐ **Yes**
Project member 3	Click or tap here to enter text.	Click or tap here to enter text.	☐ **No** ☐ **Yes**
Project member 4	Click or tap here to enter text.	Click or tap here to enter text.	☐ **No** ☐ **Yes**
Project member 5	Click or tap here to enter text.	Click or tap here to enter text.	☐ **No** ☐ **Yes**

Section 13	**Data Protection**
As a data controller your organisation should be registered with the Information Commissioners Office (ICO). Please provide the following information.	
Registered name *(if different to applicant name, please state reason)*	Imperial College
Registration number	Z5940050
Expiry date	22/10/2020

Section 14	**Legal basis (of the processing you intend to undertake)**
If you are requesting data that is fully anonymous, please proceed to section 20	
GDPR Legal Basis	Section 14 explanation .docx **Article 6 legal basis:** Article 6 (1)(e)

	Justification: Research and processing is conducted in the public's interest in the area of public health
	Article 9 legal basis: Article 9 (2)(j) **Justification:** Research and processing is conducted for scientific purposes .
Common law of duty of confidentiality is addressed by	**If the data you are requesting is personally identifiable please explain how you have addressed the common law duty of confidentiality below.**
	☐ **Explicit informed consent** *(please enclose consent form and patient information sheet with this application)*
	☒ **Approval under section 251 of the NHS Act 2006** *(please enclose both the application and the approval letter)* NACAP_Amendment_request_FINAL(Sign ECC 5-05(a) 2012 Conditionally Suppo RE_ ECC 5-05(a)_2012 Conditi REf CAG 8-06(b)_2013) AND E
	The section 251 approval enables the applicant to: ☐ **Hold/receive personal data** ☒ **Transfer/access personal data** ☒ **Operate on and link personal data** **Commented [MA1]:** Clicked on both
	☐ **Other legal basis** If other legal basis selected, please provide further information here with reference to the statute, regulation or other provision relied upon: Click or tap here to enter text.

Section 15	**Fair Processing**
Please describe what transparency information has been provided to the data subjects that the data requested relates to. Please ensure you enclose copies of any privacy notices and other material you rely on when submitting this application.	
Information provided by the HQIP project	https://www.rcplondon.ac.uk/projects/outputs/national-asthma-and-copd-audit-programme-nacap-secondary-care-workstream-copd
Information provided by the applicant	https://www.imperial.ac.uk/media/imperial-college/research-and-innovation/research-office/public/Privacy-Notice-For-Research-Partners,-Co-Applicants-And-Collaborators.pdf

Section 16	**Security**

Each organisation processing data that is not fully anonymous as part of this project must demonstrate that they have appropriate security arrangements are in place. Please confirm whether the applicant organisation has a compliant Data Security and Protection Toolkit. *(Please note that additional organisations processing data which is not fully anonymous must complete a partner organisation form and evidence of security arrangements)*			
Applicant organisation *(please select one answer)*	☒ **Yes** *If yes, please provide evidence with this application.*	**ODS code**	EE133887-SPHTR
		Status	Standards met
		Published date	09/04/2019
	☐ **No**	**If no, please provide below alternative evidence of adequate organisational and technical measures; to ensure the security of processing and preserve the confidentiality, integrity and availability of data.**	
		Click or tap here to enter text.	

Section 17	**Retention and destruction**
Please state the date until which you are seeking to retain the data and the reason. ***NB. That the requirement to extend the Data Sharing Agreement*** *(if retention is requested for longer than its original term) would still apply.*	Until 12 months after receipt of the linked dataset Click or tap here to enter text.
Please provide details of how you intend to destroy the data at the end of the retention period.	We will delete all copies of the data and any backups, including emptying the deleted items files. This will include secure file shredding
Please confirm that you will submit a certificate of destruction to HQIP within 5 business days of destruction of the data.	☒ **Yes**

Section 18	**Intention to link data**
Do you intend for the requested data set to be linked with any additional data sets? If yes, please provide full details of the data controller(s) of the secondary dataset(s) and a description of which organisation will perform the linkage and how the linkage will take place. HQIP will work to the principle that other relevant requests are in process. *(Please select one answer)*	

☐ No intended linkage	☒ Intention to link the data. *Please provide full details of linkage below.*
If there is an intention to link the data, please provide full details here: Audit data will be linked with data from the Clinical Practice Research Datalink (CPRD). CPRD will act as data controller and NHS Digital (NHSD) will produce linking file to enable linkage of CPRD and NACAP audit data. See Data flow diagram	

Section 19	**Further information**
Please use the section below to add any additional information to support your request.	
CPRD has pseudonymised copies of HES & ONS under licence from NHSD under separate agreement permitting sub-licencing	

Section 20	Attachments Checklist							
Please use the table below to ensure that the documents / information listed are either contained within the application or submitted as attachments.								
	Applicant organisation(s)						Data provider	
Type of data / Level of data	Data items spreadsheet	Evidence of Data Security and Protection (DSPT) Toolkit or equivalent	Data flow map	Ethics approval OR confirmation that it is not required	Fair processing information	Legal basis supporting evidence (such as, consent form and patient leaflet, s251 application and approval letter or any other evidence)	Description for how the data will be de-identified to reduce any risk of re-identification	Fair processing information
Anonymous	✓		✓					
De-personalised	✓	✓	✓	✓	✓	✓	✓	✓
Personally Identifiable	✓	✓	✓	✓	✓	✓		✓

Terms and Conditions for Use of HQIP Data

BACKGROUND

(A) HQIP agrees to share the HQIP Data (defined below) with the Applicant on the terms set out in the Contract (as defined below).

(B) The Applicant agrees to use the HQIP Data on the terms set out in the Contract.

(C) The Applicant has submitted a request to HQIP using the Data Access Request Form (defined below) for access to the HQIP Data. These Conditions together with the Data Access Request Form comprise the Contract.

AGREED TERMS

1. Interpretation

The following definitions and rules of interpretation apply:

1.1 Definitions:

Agreed Purpose: the purpose(s) for which the Applicant wishes to use the HQIP Data, as set out in section 3, section 4 and section 5 of the Data Access Request Form as such purposes may be amended by written agreement from HQIP from time to time, subject to the payment of any related Charges.

Anonymous Data: has the meaning set out in the Data Access Request Form.

Applicant: the party named as such in the Data Access Request Form.

Business Day: a day other than a Saturday, Sunday or public holiday in England when banks in London are open for business.

Change Fees: the fees notified by HQIP to the Applicant, to be paid by the Applicant to HQIP, in relation to a change in the HQIP Data that the Applicant wishes to access.

Conditions: the terms and conditions set out in this document as amended from time to time in accordance with condition 27.

Contract: the contract between HQIP and the Applicant for the sharing of the HQIP Data by HQIP with the Applicant in accordance with these Conditions, the Data Access Request Form and any attachments to the Data Access Request Form.

Data Access Request Form: the Applicant's request to HQIP for access to the HQIP Data set out on the form attached to these Conditions and approved by HQIP and any subsequent form(s) as completed by the Applicant and approved by HQIP which refer to these Conditions.

Data Destruction Certificate: HQIP's required form of certificate in relation to data destruction as set out in the Schedule to these Conditions.

Data Sharing Code: the Information Commissioner's Data Sharing Code of Practice of May 2011, as updated or amended from time to time.

Data Protection Legislation: all applicable data protection and privacy legislation in force from time to time in the UK including the General Data Protection Regulation (*(EU) 2016/679*) (**GDPR**); the Data Protection Act 2018 (**DPA 2018**); the Privacy and Electronic Communications Directive 2002/58/EC (as updated by Directive 2009/136/EC) and the Privacy and Electronic Communications Regulations 2003 (SI 2003 No. 2426) as amended; any other European Union legislation relating to personal data and all other legislation and regulatory requirements in force from time to time which apply to a party relating to the use of Personal Data (including, without limitation, the privacy of electronic communications); and the guidance and codes of practice issued by the relevant data protection or supervisory authority and applicable to a party, including the Data Sharing Code.

De-personalised Data: has the meaning set out in the Data Access Request Form.

EEA: European Economic Area.

Fees: the Initial Fees, the Renewal Fees and the Change Fees, as the case may be.

FOIA: the Freedom of Information Act 2000.

HQIP: Healthcare Quality Improvement Partnership (company number 6498947) whose registered office is at 70 Wimpole Street, London W1G 8AX.

HQIP Data: the Anonymous Data, De-personalised Data and Shared Personal Data to be shared with the Applicant by HQIP.

Initial Fees: the fees notified by HQIP to the Applicant, to be paid by the Applicant to HQIP prior to the relevant data sharing taking place, in relation to the Basic, Standard and Complex HQIP Data (identified in the Data Access Request Form) that the Applicant wishes to access.

Personal Data Breach: a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to the Shared Personal Data.

Personally Identifiable Data: has the meaning set out in the Data Access Request Form.

Renewal Fees: the annual renewal fees notified by HQIP to the Applicant, to be paid by the Applicant to HQIP prior to each anniversary of the date of the initial sharing of the HQIP Data by HQIP with the Applicant.

Shared Personal Data: the Personally Identifiable Data (including Personal Data and Special Category Personal Data) and De-personalised data which can be reverse engineered to be Personally Identifiable Data to be shared between the parties under condition 5 of these Conditions.

Subject Access Request: the exercise by a data subject of his or her rights under Article 15 of the GDPR and the DPA 2018.

Supervisory Authority: the relevant supervisory authority in the territories where the parties to the Contract are established.

Transfer Dates: the date or dates when the HQIP Data is transferred to the Applicant.

Term: the length of time for the data sharing with the expiry date specified by HQIP in the Data Access Request Form.

1.2 **Controller**, **Processor**, **Data Subject** and **Personal Data**, **Special Categories of Personal Data**, **Processing** and "appropriate technical and organisational measures" shall have the meanings given to them in the Data Protection Legislation.

1.3 A reference to a company shall include any company, corporation or other body corporate, wherever and however incorporated or established.

1.4 A reference to a statue or statutory provision shall include all subordinate legislation made from time to time under that statute or statutory provision.

1.5 References to conditions and schedules are to the conditions and schedules of these Conditions.

1.6 Any words following the terms **including**, **include**, **in particular** or **for example** or any similar phrase shall be construed as illustrative and shall not limit the generality of the related general words.

1.7 A reference to **writing** or **written** includes email.

1.8 In the event of any inconsistency, discrepancy or conflict between a Data Access Request Form, these Conditions and the Schedule, the conflict in relation to the HQIP Data covered by that Data Access Request Form should be resolved in the following descending order of priority:

(a) the Data Access Request Form (including any attachments to the Data Access Request Form);

(b) these Conditions;

(c) the Schedule.

2. Commencement and Term

2.1 The data sharing shall commence on the date set out in the Data Access Request Form and shall continue for the Term, unless terminated earlier in accordance with condition 12, condition 14 and condition 17, when it shall terminate automatically without notice.

2.2 Without prejudice to condition 2.1 it is the Applicant's responsibility to instigate any request for an extension to the Term in good time to allow for HQIP to consider whether to approve the Applicant's request and HQIP cannot be held responsible if the Applicant's request is not made to allow sufficient time for the HQIP approval process.

3. Purpose

3.1 The Applicant shall only process that HQIP Data for the Agreed Purpose.

4. Compliance with data protection laws

4.1 The Contract sets out the framework for the sharing of HQIP Data between HQIP, and the Applicant. Where HQIP is sharing Shared Personal Data with the Applicant HQIP acts as a Controller when it discloses such Shared Personal Data and the Applicant acts as a Controller when it receives such Shared Personal Data. It defines the principles and procedures that the parties shall adhere to and the responsibilities the parties owe to each other.

4.2 Each Party must ensure compliance with applicable national data protection laws at all times.

4.3 In the event the data protection law or approach to compliance of two or more countries conflict, the requirements of the country that necessitates stricter or additional requirements to protect data subjects' privacy and personal data shall be applied.

4.4 Each party has such valid registrations and or paid such fees as are required by its national Supervisory Authority which, by the time that the data sharing is expected to commence, covers the intended data sharing pursuant to the Contract, unless an exemption applies.

5. Shared Personal Data

5.1 The categories of HQIP Data that will be shared by HQIP with the Applicant are set out in the Data Access Request Form at section 9 and section 10 together with any access and processing restrictions required by HQIP.

6. Lawful, fair and transparent processing

6.1 The Applicant shall ensure that it processes the Shared Personal Data fairly and lawfully in accordance with condition 6.2 while the sharing of the Shared Personal Data is taking place.

6.2 The Applicant shall ensure that it has legitimate grounds under the Data Protection Legislation for the processing of Shared Personal Data.

6.3 The Applicant undertakes to inform the Data Subjects, in accordance with the Data Protection Legislation, of the purposes for which it will process their Personal Data, the legal basis for such purposes and such other information as is required by Article 14 of the GDPR including:

(a) if Shared Personal Data will be transferred to a third party, that fact and sufficient information about such transfer and the purpose of such transfer to enable the data subject to understand the purpose and risks of such transfer; and

(b) if Shared Personal Data will be transferred outside the EEA pursuant to condition 10, that fact and sufficient information about such transfer, the purpose of such transfer and the safeguards put in place by the Applicant to enable the data subject to understand the purpose and risks of such transfer.

6.4 HQIP Data is provided on the understanding that it will not be matched to any other datasets, even to depersonalised or aggregated datasets, unless HQIP has agreed to the proposed processing matching.

6.5 The Applicant is the Controller of Shared Personal Data that HQIP has supplied. The Applicant is responsible for complying with the Data Protection Legislation, all other applicable laws and its own internal policies and procedures in relation to the Applicant's processing of the Shared Personal Data.

7. Data quality

7.1 Shared Personal Data shall be limited to the Personal Data and Special Category Data listed at section 9 and section 10 of the Data Access Request Form.

7.2 The Shared Personal Data shall not be irrelevant or excessive with regard to the Agreed Purpose.

8. Data subjects' rights

8.1 The parties each agree to provide such assistance as is reasonably required to enable the other party to comply with requests from Data Subjects to exercise their rights under the Data Protection Legislation within the time limits imposed by the Data Protection Legislation.

8.2 Each party is responsible for maintaining a record of individual requests for information, the decisions made and any information that was exchanged. Records must include copies of the request for information, details of the data accessed and shared and where relevant, notes of any meeting, correspondence or phone calls relating to the request.

9. Data retention and deletion

9.1 The Applicant shall not retain or process HQIP Data for longer than is necessary to carry out the Agreed Purposes.

9.2 The Applicant shall not retain HQIP Data after the end of the Term.

9.3 The Applicant shall ensure that any HQIP Data are, unless otherwise required by HQIP, destroyed securely and in accordance with the Applicant's organisational policy and standards of best practice at the end of the Term or, if earlier, once processing of the HQIP Data is no longer necessary for the Agreed Purposes.

9.4 Following the deletion of HQIP Data in accordance with condition 9.3, the Applicant shall notify HQIP that the HQIP Data in question has been deleted and provide HQIP with a data destruction certificate in the form of the Data Destruction Certificate within five (5) Business Days.

10. Transfers

10.1 For the purposes of this condition, transfers of Shared Personal Data shall mean any sharing of Shared Personal Data by the Applicant with a third party, and shall include, but is not limited to, the following:

(a) subcontracting the processing of Shared Personal Data;

(b) granting a third party controller access to the Shared Personal Data.

10.2 Shared Personal Data must not be shared by the Applicant with any other organisations or individuals unless such sharing is included on the Data Access Request Form and agreed to in writing by HQIP.

10.3 If, with HQIP's prior consent, the Applicant appoints a third party processor to process the Shared Personal Data it shall comply with Article 28 and Article 30 of the GDPR and shall remain liable to HQIP for the acts and/or omissions of the processor.

10.4 The Applicant may not transfer Shared Personal Data to a third party located outside the EEA unless this has been requested by the Applicant in the Data Access Request Form and it has been approved by HQIP in writing subject to such conditions as HQIP may impose in relation to such a transfer which (as a minimum) shall include that it;

(a) complies with the provisions of Articles 26 of the GDPR (in the event the third party is a joint controller); and.

(b) ensures that (i) the transfer is to a country approved by the European Commission as providing adequate protection pursuant to Article 45 of the GDPR; (ii) there are appropriate safeguards in place pursuant to Article 46 of the GDPR; or (iii) one of the derogations for specific situations in Article 49 of the GDPR applies to the transfer.

11. Security and training

11.1 HQIP shall only provide the Shared Personal Data to the Applicant by using secure methods.

11.2 The Applicant undertakes to have in place appropriate technical and organisational security measures to:

(a) prevent:

(i) unauthorised or unlawful processing of the Shared Personal Data; and

(ii) the accidental loss or destruction of, or damage to, the Shared Personal Data

(b) ensure a level of security appropriate to:

(i) the harm that might result from such unauthorised or unlawful processing or accidental loss, destruction or damage; and

(ii) the nature of the Shared Personal Data to be protected.

11.3 It is the responsibility of the Applicant to ensure that its staff members are appropriately trained to handle and process the Shared Personal Data in accordance with any applicable national data protection laws and the Data Protection Legislation and guidance and have entered into confidentiality agreements with such staff relating to the processing of personal data.

11.4 The level, content and regularity of training referred to in condition 11.3 shall be proportionate to the staff members' role, responsibility and frequency with respect to their handling and processing of the Shared Personal Data.

11.5 Consistent with the Applicant's responsibilities as a Controller in accordance with applicable national data protection laws and the Data Protection Legislation the Applicant shall implement and comply with its own security policy as evidence of the Applicant's management's commitment to information security and the security measures to be taken to cover the temporary removal of any Shared Personal Data or confidential information from the Applicant's premises.

11.6 The Applicant shall ensure that access to any buildings or rooms within the Applicant's premises where Shared Personal Data is stored and/or can be accessed is controlled and that casual passers-by cannot read information off screens or documents.

11.7 The Applicant shall not disclose or allow access to any HQIP Data other than to a person placed by the Applicant under the same obligations as those set out in the Contract who is variously employed or engaged by the Applicant or any sub-contractor, contractor, servant, agent or other person within the control of the Applicant.

11.8 Confidential information (including Shared Personal Data) transferred between HQIP and the Applicant in electronic form must be encrypted and if sent by email must be password protected with the password sent in a separate email or text message.

11.9 The Applicant will have in place appropriate security on external routes into its organisation, for example internet firewalls and secure dial-in facilities.

11.10 The Applicant shall ensure that any system whereby any Shared Personal Data may be disclosed over the telephone is protected by a procedure for authenticating identity prior to the disclosure of that Personal Data.

11.11 The Applicant's computer systems must be password protected. Passwords must give access only to Shared Personal Data which an employee has a proper need to access and not to all levels of the system. Passwords must be known only to authorised people and changed regularly.

11.12 The Applicant shall have a satisfactory procedure for cleaning media (such as hard drives and disks) before they are reused or new data written over old. The Applicant shall ensure that printed material is disposed of securely, for example by shredding.

11.13 The Applicant confirms that the Shared Personal Data will not be removed from the Applicant's secure premises nor worked on by employees on their own electronic devices unless this is permitted by the Applicants Bring Your Own Device Policy and subject to the Applicant's requirements in relation to secure Virtual Private Networks. The Applicant shall take adequate precautions against burglary, fire or natural disaster. The Applicant shall ensure that all HQIP Data is protected against corruption by viruses or other forms of intrusion.

11.14 All duplicate copies or back-up copies of the Shared Personal Data are held by the Applicant subject to the terms of the Contract and shall be securely destroyed when they are no longer required to be processed for the Agreed Purpose.

11.15 The Applicant shall ensure that proper weight is given to the discretion and integrity of staff when they are being considered by the Applicant for employment or promotion or for a move to an area of work where they will have access to Shared Personal Data. The Applicant shall ensure staff are aware of their responsibilities and given training to ensure their knowledge is up to date.

11.16 The Applicant shall ensure that disciplinary rules and procedures take account of the requirements of the Data Protection Legislation. In the case of an employee of the Applicant being found to be unreliable or unsuitable for access to Shared Personal Data, the Applicant shall ensure that his or her access to Shared Personal Data is withdrawn immediately

11.17 The Applicant shall ensure that its staff are aware that Shared Personal Data should only be accessed for the Agreed Purpose and not for their own private purposes.

11.18 The Applicant shall ensure that audit trails are kept so that access to Shared Personal Data is logged and can be attributed to a particular person.

12. Personal data breaches and reporting procedures

12.1 The Applicant shall ensure that any Personal Data Breaches are properly investigated and remedied as soon as possible, particularly when damage or distress could be caused to an individual. The Applicant shall notify HQIP immediately should such a breach occur. Upon receipt of such a notification HQIP shall have the right:

(a) to immediately suspend provision of the HQIP Data under the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(b) to terminate immediately the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(c) to terminate immediately all other contracts for the sharing of HQIP Data with the Applicant that are entered into under this Contract; and/or

(d) to immediately suspend and/or terminate any existing applications by the Applicant to access the HQIP Data.

12.2 Each party shall comply with its obligation as controller to report a Personal Data Breach to the appropriate Supervisory Authority and (where applicable) data subjects under Article 33 of the GDPR.

13. Resolution of disputes with data subjects or the Supervisory Authority

13.1 In the event of a dispute or claim brought by a data subject or the Supervisory Authority concerning the processing of Shared Personal Data against either or both parties, the parties will inform each other about any such disputes or claims, and will cooperate with a view to settling them amicably in a timely fashion.

13.2 The parties agree to respond to any generally available non-binding mediation procedure initiated by a data subject or by the Supervisory Authority. If they do participate in the proceedings, the parties may elect to do so remotely (such as by telephone or other electronic means). The parties also agree to consider participating in any other arbitration, mediation or other dispute resolution proceedings developed for data protection disputes.

13.3 Each party shall abide by a decision of a competent court of HQIP's country of establishment or of the Supervisory Authority.

13.4 Subject to conditions 13.1 to 13.3 the Parties shall attempt to resolve any disagreement arising from the Contract informally and promptly by officers who have day-to-day responsibility for the operation of the Contract.

13.5 If the disagreement cannot be resolved further to condition 13.4 within fourteen (14) days of it arising, the matter shall be referred to the Chief Executives (or the corresponding individuals) of the Parties.

14. Fees

14.1 The Applicant shall pay to HQIP the Fees to cover the cost to HQIP of considering the Applicant's request to access the HQIP Data and, if approved by HQIP, the cost of providing access to the Applicant of the HQIP Data during the Term.

14.2 All Fees shall be paid by the Applicant to HQIP to its nominated bank account detailed below within thirty (30) days of the due date, in cleared funds, without withholding, set-off or deduction are non-refundable and time for payment is of the essence. The Fees shall be due and payable in full to HQIP annually in advance.

14.3 The Initial Fees for the first year of the HQIP Data sharing shall be paid within thirty (30) days of the Applicant's submission of the signed Pro Forma Invoice which will be sent to them once the completed Data Access Request Form has been received and approved by HQIP;

14.4 The Renewal Fees for the second and subsequent years of the HQIP Data sharing shall be paid within thirty (30) days of HQIP's submission of the invoice for those fees;

14.5 The Change Fees shall be paid within thirty (30) days of HQIP's submission of the invoice for those fees;

14.6 HQIP'S bank details are:

Lloyds Bank plc

(Threadneedle Street Branch)

Account No. 00322010

Sort Code 30-00-09.

14.7 Where the Applicant fails to make payment of any Fees by the due date, HQIP shall be entitled (but shall not be obliged) to withhold the HQIP Data requested until payment is made. Where the Applicant fails to make payment within a further fourteen (14) days from the first date that any sums are due, HQIP shall be entitled (but shall not be obliged) to do any, or a combination of, the following on written notice to the Applicant:

(a) to immediately suspend provision of the HQIP Data under the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(b) to terminate immediately the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(c) to terminate immediately all other contracts for the sharing of HQIP Data with the Applicant that are entered into under this Contract; and/or

(d) to immediately suspend and/or terminate any existing applications by the Applicant to access the HQIP Data.

14.8 HQIP may charge interest at an annual rate of 4% above the base rate of Lloyds Bank, calculated on a daily basis in respect of any sum which is due and unpaid, that interest to run from the date on which that sum is due and payable until receipt by HQIP of the full amount, whether before or after judgment.

14.9 All Fees are to be paid in pounds sterling (£) and are exclusive of VAT or any other applicable sales tax, which shall be paid by the Applicant at the rate and in the manner for the time being prescribed by law, unless a current proof of VAT exemption is provided to HQIP.

14.10 HQIP may, at any time after the date of the initial sharing of the HQIP Data by HQIP with the Applicant, by giving 90 days' prior written notice, vary the Renewal Fees and the Change Fees and the basis on which they are calculated. The Applicant may terminate the Contract for the HQIP Data Sharing from the date on which that variation is intended to take effect, provided that the Applicant gives HQIP written notice of termination of the Contract within 60 days of the date of HQIP's notice.

14.11 Where an amendment to the provisions of the Contract (other than the Fees or the basis on which they are calculated) is required as a result of an addition to the HQIP Data sharing service or the relevant HQIP Data sharing service (including, for example, an amendment to acknowledge third party rights), HQIP may give the Applicant reasonable notice in writing of the Change Fees that will take effect on the date specified in that notice.

15. Confidentiality

15.1 Each party undertakes that it shall not at any time disclose to any person any Shared Personal Data or confidential information concerning the business, affairs, customers, clients or suppliers of the other party or of any member of the group of companies to which the other party belongs, except as permitted by Condition 15.2;

15.2 Each party may disclose the other party's confidential information:

(a) to its employees, officers, representatives or advisers who need to know such information for the purposes of exercising the party's rights or carrying out its obligations under or in connection with the Contract. Each party shall ensure that its employees, officers, representatives or advisers to whom it discloses the other party's confidential information comply with this condition 15; and

(b) as may be required by law, a court of competent jurisdiction or any governmental or regulatory authority.

15.3 HQIP may disclose details of the Applicant's Data Access Request Form to bodies who licence the HQIP Data to HQIP.

15.4 HQIP may publish details of the Applicant's Data Access Request Form on a public register of HQIP's data sharing activities.

15.5 The Applicant may discuss adverse device outcomes findings with competent authorities (e.g. MHRA).

15.6 No party shall use any other party's confidential information for any purpose other than to exercise its rights and perform its obligations under or in connection with the Contract.

16. Publication

16.1 This condition only applies to HQIP Data supplied by the National Joint Registry. The Applicant shall provide a copy of any paper proposed for publication to HQIP approval at least one (1) month before submitting for publication or making public any information that has been derived utilising the HQIP Data.

16.2 The Applicant shall acknowledge HQIP and all such bodies who licence the HQIP Data to HQIP and set out in the attachment to the Data Access Request Form, in all work published arising from any research undertaken on the HQIP data and will provide copies of such published work to HQIP. The applicant shall use the following wording for the HQIP acknowledgement:

'Data has been provided by the Healthcare Quality Improvement Partnership from the xxx Programme'

Separate wording will be required for applications relating to HQIP Data supplied by the National Joint Registry. Applicants must use the NJR acknowledgement guidance located at http://www.njrcentre.org.uk/njrcentre/Research/Research-requests.

16.3 Where HQIP shares Shared Personal Data with the Applicant, data shall not be published, except in compliance with all subsisting legal requirements as to confidentiality and provided that there is a lawful basis for such publishing.

17. Rights to inspection and withdrawal of data sharing

17.1 HQIP reserves its rights to inspect the Applicant's arrangements for the processing of the shared Personal Data at any time without prior notice, at the Applicant's cost, and shall be entitled (but shall not be obliged) to do any, or a combination of, the following on written notice to the Applicant:

(a) to immediately suspend provision of the HQIP Data under the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(b) to terminate immediately the Contract or any other contract for the sharing of HQIP Data with the Applicant; and/or

(c) to terminate immediately all other contracts for the sharing of HQIP Data with the Applicant that are entered into under this Contract; and/or

(d) to immediately suspend and/or terminate any existing applications by the Applicant to access the HQIP Data.

where it considers the Applicant is not processing the Personal Data in accordance with the Contract.

18. Freedom of Information

18.1 The Applicant acknowledges that HQIP, although not itself a public authority subject to the FOIA, HQIP may be required to facilitate FOI requests for information made by third parties on such bodies who licence the HQIP Data to HQIP where such bodies are subject to FOIA.

18.2 If the Applicant is a public authority and it receives an FOIA request regarding the HQIP Data, the Applicant must consult with the body that licences the HQIP Data to HQIP (as notified by HQIP to the Applicant in any attachment to the Data Access Request Form) prior to any release of the HQIP Data and shall take into account such licensee's views before responding to any FOIA request. Notwithstanding this condition 18.2, bodies who licence the HQIP Data to HQIP acknowledge and the Applicant accepts that the Applicant is responsible in its absolute discretion for determining whether information regarding the HQIP Data is exempt from disclosure under FOIA.

18.3 The Applicant shall ensure that its sub-contractors, servants, suppliers, agents or any other person in the control of the Applicant shall adhere to the terms of this condition 18.

19. Research

19.1 Article 89 of the GDPR and Part 6 of Schedule 2 of the DPA 2018 contain various exemptions and relaxations in relation to the processing of Personal Data only for research purposes in compliance with the relevant conditions (as such terms are defined in the GDPR and the DPA 2018), including in relation to the second Data Protection Principle, the keeping of Personal Data indefinitely and the right of access to Personal Data.

19.2 If the Applicant intends to claim its use of any Personal Data is covered by Article 89 of the GDPR and Part 6 of Schedule 2 of the DPA 2018, the Applicant warrants to HQIP that its use

of Personal Data conforms with the required conditions of Article 89 of the GDPR and Part 6 of Schedule 2 of the DPA 2018 and the Data Access Request Form shall set out the relevant information.

20. Reporting Requirements

20.1 The Applicant will comply with any reporting requirements made known to it by HQIP when the Applicant submits its Data Access Request Form and which are reflected in an attachment to the signed Data Access Request form signed by both of the parties.

20.2 HQIP reserves the right to request a written update from the Applicant at any stage during the Term.

20.3 This condition only applies to HQIP Data supplied by the National Joint Registry. The Applicant shall provide a written project summary update to the National Joint Registry in the form and detail required by the National Joint Registry. The written summary shall be submitted to National Joint Registry six (6) months after the Transfer Dates and then at six (6) monthly intervals ('**Six Monthly Updates**') until the HQIP Data has been deleted. After the Applicant has finished processing the HQIP Data in accordance with the Agreed Purposes, a final written report shall be sent to National Joint Registry within three (3) months after the end of the Term.

21. Language

21.1 The Contract is drafted in the English language. If the Contract is translated into any other language, the English language version shall prevail.

21.2 Any notice given under or in connection with this Contract shall be in English. All other documents provided under or in connection with this Contract shall be in English, or accompanied by an English translation certified as accurate by a notary experienced in the relevant foreign language and with the appropriate technical and legal experience in relation to the relevant document to be translated.

21.3 The English language version of this Contract and any notice or other document relating to this Contract shall prevail if there is a conflict.

22. Warranties

22.1 The Applicant warrants and undertakes that it will:

(a) Process the Shared Personal Data in compliance with all applicable laws, enactments, regulations, orders, standards and other similar instruments that apply to its personal data processing operations.

(b) Make available on request to the data subjects who are third party beneficiaries a copy of the Contract, unless the Contract contains confidential information.

(c) Respond within a reasonable time and as far as reasonably possible to enquiries from the relevant Supervisory Authority in relation to the Shared Personal Data.

(d) Respond to Subject Access Requests in accordance with the Data Protection Legislation.

(e) Where applicable, maintain registration or pay the appropriate fees with all relevant Supervisory Authorities to process all Shared Personal Data for the Agreed Purpose.

(f) Take all appropriate steps to ensure compliance with the security measures set out in condition 11 above.

22.2 HQIP warrants and undertakes that it is entitled to provide the Shared Personal Data to the Applicant. The Applicant warrants and undertakes that it will not disclose or transfer the Shared Personal Data to a third party controller located outside the EEA unless it complies with the obligations set out in condition 10.4 above.

22.3 Except as expressly stated in the Contract, all warranties, conditions and terms, whether express or implied by statute, common law or otherwise are hereby excluded to the extent permitted by law.

23. Indemnity

23.1 The Applicant indemnifies, and shall keep indemnified, HQIP against any liability, costs, damages, expenses (including legal fees), losses, claims, administrative sanction, fine, penalty, action or other liability or proceedings whatsoever arising under any statute or at common law or for breach of contract in respect of:

(a) damage to property, real or personal, including any infringement of third party intellectual property rights; and

(b) injury to persons, including injury resulting in death; and

(c) any direct economic or financial loss; and

(d) any enquiry or complaint by a Data Subject; and

(e) any enquiry or investigation by the Supervisory Authority; and

(f) any claim or action brought by any third party against HQIP

arising out of, in connection with any act, omission or default of the Applicant, its staff, agents or sub-contractors in relation to the HQIP Data. The indemnity in this condition shall be separate, distinct from and not subject to any exclusions and limitations on liability in the Contract.

24. Allocation of cost

24.1 Except as otherwise stated each party shall perform its obligations under the Contract at its own cost.

25. Limitation of liability

25.1 Neither party excludes or limits liability to the other party for:

(a) fraud or fraudulent misrepresentation;

(b) death or personal injury caused by negligence;

(c) a breach of any obligations implied by section 12 of the Sale of Goods Act 1979 or section 2 of the Supply of Goods and Services Act 1982;

(d) any matter for which it would be unlawful for the parties to exclude liability; or

(e) in relation to the indemnity in condition 23.

25.2 Subject to condition 25.1, neither party shall in any circumstances be liable whether in contract, tort (including for negligence and breach of statutory duty howsoever arising), misrepresentation (whether innocent or negligent), restitution or otherwise, for:

(a) any loss (whether direct or indirect) of profits, business, business opportunities, revenue, turnover, reputation or goodwill;

(b) loss (whether direct or indirect) of anticipated savings or wasted expenditure (including management time); or

(c) any loss or liability (whether direct or indirect) under or in relation to any other contract.

25.3 HQIP takes no responsibility for the accuracy, currency, reliability and correctness of the HQIP Data, nor for the accuracy, currency, reliability and correctness of links or references to other information sources and disclaims all warranties in relation to such data, links and references to the maximum extent permitted by legislation. The Applicant uses or relies on the HQIP Data at its own risk.

26. Third party rights

26.1 Except as expressly provided in condition 8 (data subjects rights) and such bodies who licence the HQIP Data to HQIP, set out in the attachment to the Data Access Request Form and to the extent required by such bodies in that attachment, contract holders with, and funders to, HQIP, a person who is not a party to the Contract shall not have any rights under the Contracts (Rights of Third Parties) Act 1999 to enforce any term of the Contract. This does not affect any right or remedy of a third party which exists, or is available, apart from that Act.

27. Variation

27.1 Except as set out in the Contract, no variation of the Contract, including the introduction of any additional terms and conditions shall be effective unless it is agreed in writing and signed by the Applicant.

28. Waiver

28.1 No failure or delay by a party to exercise any right or remedy provided under the Contract or by law shall constitute a waiver of that or any other right or remedy, nor shall it prevent or restrict the further exercise of that or any other right or remedy. No single or partial exercise of such right or remedy shall prevent or restrict the further exercise of that or any other right or remedy.

29. Severance

29.1 If any provision or part-provision of the Contract is or becomes invalid, illegal or unenforceable, it shall be deemed deleted, but that shall not affect the validity and enforceability of the rest of the Contract. If any provision or part-provision of this Contract is deemed deleted under condition 29, the parties shall negotiate in good faith to agree a replacement provision that, to the greatest extent possible, achieves the intended commercial result of the original provision.

30. Changes to the applicable law

30.1 If the Data Protection Legislation change in a way that the Contract is no longer adequate for the purpose of governing lawful data sharing exercises, the Parties agree that they will negotiate in good faith to review the Contract in the light of the new legislation.

31. No partnership or agency

31.1 Nothing in the Contract is intended to, or shall be deemed to, establish any partnership or joint venture between any of the parties, constitute any party the agent of another party, or authorise any party to make or enter into any commitments for or on behalf of any other party. Each party confirms it is acting on its own behalf and not for the benefit of any other

person except that HQIP enters into the Contract for the benefit of such bodies who licence the HQIP Data to HQIP, set out in the attachment to the Data Access Request Form and to the extent required by such bodies in that attachment.

32. Entire agreement

32.1 The Contract constitutes the entire agreement between the parties and supersedes and extinguishes all previous agreements, promises, assurances, warranties, representations and understandings between them, whether written or oral, relating to its subject matter. Each party acknowledges that in entering into the Contract it does not rely on, and shall have no remedies in respect of any statement, representation, assurance or warranty (whether made innocently or negligently) that is not set out in the Contract. Each party agrees that it shall have no claim for innocent or negligent misrepresentation or negligent misrepresentation based on any statement in the Contract.

33. Further assurance

33.1 Each party shall, and shall use all reasonable endeavours to procure that any necessary third party shall, promptly execute and deliver such documents and perform such acts as may reasonably be required for the purpose of giving full effect to the Contract.

34. Rights and remedies

34.1 The rights and remedies provided under the Contract are in addition to, and not exclusive of, any rights or remedies provided by law.

35. Notice

35.1 Any notice or other communication given to a party under or in connection with the Contract shall be in writing, addressed to the Data Protection Officer and shall be:

(a) delivered by hand or by pre-paid first-class post or other next working day delivery service at its registered office (if a company) or its principal place of business (in any other case); or

(b) sent by email to HQIP at datasharing@hqip.org.uk and to the email address provided by the Applicant in the Data Access Request Form.

35.2 Any notice or communication shall be deemed to have been received:

(a) if delivered by hand, on signature of a delivery receipt or at the time the notice is left at the proper address;

(b) if sent by pre-paid first-class post or other next working day delivery service, at 9.00 am on the second Business Day after posting or at the time recorded by the delivery service; and

(c) if sent by email, at the time of transmission, or if this time falls outside business hours in the place of receipt, when business hours resume. In this condition 35.2(c) business hours means 9:00 am to 5:00 pm Monday to Friday on a day that is not a public holiday in the place of receipt.

35.3 This condition does not apply to the service of any proceedings or other documents in any legal action or, where applicable, any arbitration or other method of dispute resolution.

36. Governing law

36.1 The Contract and any dispute or claim (including non-contractual disputes or claims) arising out of or in connection with it or its subject matter or formation shall be governed by and construed in accordance with the law of England and Wales.

37. Jurisdiction

37.1 Each party irrevocably agrees that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim (including non-contractual disputes or claims), arising out of or in connection with the Contract or its subject matter or formation.

The Schedule: Data Deletion Certificate

Certificate of Destruction

Certificate of Destruction	
In accordance with the Data Access Request Form and Data Sharing Agreement, this form must be completed by applicants at the end of their data retention period and a copy sent to HQIP at datasharing@hqip.org.uk.	
Data Access Request Form reference number	Click or tap here to enter text.
Organisation	Click or tap here to enter text.
Method of destruction	Click or tap here to enter text.
Please detail the method used for destruction of the data	Click or tap here to enter text.
Date of destruction	Click or tap to enter a date.

Name:	Click or tap here to enter text.
Position:	Click or tap here to enter text.
Signature:	
Date of signature:	Click or tap to enter a date.

Section 21	Authorised signatories		
Please note that this agreement is not valid until all parties have signed and agreed this document.			
Applicant *The applicant confirms that the details provided in the application above are accurate, valid and true. HQIP reserves the right at all times to confirm that it is so. The applicant will give HQIP all reasonable assistance and access in order to confirm any matters arising from this applicant whether now or in the future. The applicant acknowledges and agrees that the application is made on and subject to the terms and conditions for use of HQIP Data and any grant of access to the data will at all times be subject also to that agreement.*		**Name**	Dr Jennifer Quint
		Position	Reader in Respiratory Epidemiology
		Date of signature	12/03/2019
Clinical lead or appropriate project scientific committee chairman *The clinical lead / Chair of an appropriate audit or Outcome Review Programme Scientific Committee confirms that the information included within this application would represent a clinically appropriate usage of the data requested.*		**Name**	Prof Mike Roberts
		Position	Managing Director, UCLPartners
		Date of signature	09/03/2020
Data provider (statistician, methodologist or project manager): *The provider confirms that the information included within this application represents a methodologically appropriate usage of the data requested. Where de-personalised data has been requested, the data provider confirms that the data will be appropriately de-identified before release to minimise any risk of re-identification.*		**Name**	Kirsty MacLean Steel
		Position	Project Manager
		Date of signature	10/03/2020
HQIP / data controller: *Authorises release of the data described in this application as data controller.*		**Name**	Jane Ingham
		Position	CEO
		Date of signature	20/03/2020
For HQIP use only *Comments to note (if applicable)*		Click or tap here to enter text.	

Once completed please return this signed form to datasharing@hqip.org.uk

Partner Organisation Form

applicant	
project	Variation in patient pathways and hospital admissions for exacerbations of COPD: linking the National Asthma and COPD Audit Programme (NACAP) with CPRD data
contact within organisation e a permanent ember of staff)	Dr Puja Miles
f partner t organisation	Clinical Practice Research Datalink
of partner t organisation	10 S Colonnade, Canary Wharf, London E14 4PU

otection	
a controller your organisation should be registered with the Information Commissioners Office (ICO). Please provide the following tion.	
ed name ent to applicant lease state reason)	Department Of Health & Social Care
tion number	Z5571792
ate	12/07/2020

asis (of the processing you intend to undertake)	
gal	**Article 6 legal basis:** Article 6(1)(e) **Justification:** Research and processing are conducted in the public's interest in the area of public health
	Article 9 legal basis: Article 9(2)(j) **Justification:** Research and processing are conducted for scientific purposes.
n law of ntiality ssed	**If the data you are requesting is personally identifiable please explain how you have addressed the common law duty of confidentiality below.**
	☐ **Explicit informed consent** *(please enclose consent form and patient information sheet with this application)*

	☒ **Approval under section 251 of the NHS Act 2006** *(please enclose both the application and the approval letter)*
	The section 251 approval enables the applicant to: ☐ **Hold/receive personal data** ☒ **Transfer/access personal data** ☐ **Operate on and link personal data**
	☐ **Other legal basis** **If other legal basis selected,** please provide further information here with reference to the statute, regulation or other provision relied upon: Click or tap here to enter text.

y			
ganisation processing data that is not fully anonymous as part of this project must demonstrate that they have appropriate security ments are in place. Please confirm whether the partner organisation has a compliant Data Security and Protection Toolkit.			
nt ation select wer)	☒ **Yes** ***If yes,*** *please provide evidence with this application.*	**ODS code**	☒ **Yes** ***If yes,*** *please provide evidence with this application.*
		Status	Standards Met
		Published date	27/03/2019
	☐ **No**	**If no, please provide below alternative evidence of adequate organisational and technical measures; to ensure the security of processing and preserve the confidentiality, integrity and availability of data.**	
		Click or tap here to enter text.	

on and destruction

tate the date until ou are seeking to he data (MM/YY) reason. Note also requirement to the Data Sharing ent (if retention is ed for longer than nal term) would ly	Keeping in good practice, CPRD will keep the extract it receives 12 months after receipt of bridging file from NHSD and clinical variables from Crown Informatics (see data flow diagram). This will be deleted once Imperial College who require the linked data is satisfied their data is appropriate for their study
rovide details of u intend to destroy at the end of the n period?	The clinical variables from Crown Informatics will be kept locally on the CPRD domain network. At the end of the retention period, CPRD will delete the bridging file created by NHS Digital for the study and the clinical variables. Blancco File eraser will be used to remove the filed from the local network. Confirmation will be provided in the form of a data destruction certificate.
onfirm that you mit a certificate of tion to HQIP business days of tion of the data	☒ Yes

ised signatories		
ote that this agreement is not valid until all parties have signed and agreed the HQIP application.		
Applicant ner applicant s that the details d in the application re accurate, valid and IP reserves the right	Name	Dr Janet Valentine
	Position	Director of CPRD
n the future. The applicant ledges and agrees application is made ubject to the terms ditions for use of HQIP d any grant of access ata will at all times be also to that ent.	Date of signature	04/12/2019

Appendix N. CPRD and NACAP linkage Read V2 codelists

CPRD GOLD Read V2 codelists are available at:

https://github.com/pstone22/PhD/tree/main/codelists/Chapter%208/CPRD%20GOLD

Appendix O. CPRD and NACAP linkage SNOMED CT codelists

CPRD Aurum SNOMED CT codelists are available at:

https://github.com/pstone22/PhD/tree/main/codelists/Chapter%208/CPRD%20Aurum