# Risk Prediction and Domiciliary Care in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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# Abstract

## Background

Acute exacerbations of COPD (AECOPD) requiring admission have high mortality, readmission rates and healthcare costs. The DECAF score (Dyspnoea, Eosinopenia, chest radiograph Consolidation, Acidaemia and atrial Fibrillation) risk stratifies for acute mortality in these patients, but no validation or implementation study has been performed. Low risk patients may be suitable for Hospital at Home treatment.

No risk stratification score to predict 90 day readmission/ death without readmission has been developed and validated in this patient group.

## Methods

Consecutive patients with AECOPD were admitted to one of six hospitals. Predictors of mortality and readmission were collected. Data were combined with the DECAF derivation study to create a score to predict 90 day readmission/ death without readmission. Discrimination was assessed with the area under the receiver operator curve characteristic (AUROC).

A non-inferiority, randomised controlled trial was performed to compare usual care to Hospital at Home (HAH) with patient selection by low risk DECAF score (0 or 1). The primary outcome was cost, with a cost-utility analysis as a secondary outcome.

## Results

In 1,725 patients, the DECAF AUROC curve for inhospital mortality was 0.82 (95% CI 0.79 to 0.85), with a mortality risk of 1.0% in the DECAF 0 or 1 group and an overall mortality risk of 7.7%.

In those that survived to discharge (n=2417), the strongest predictors of readmission/ death without readmission in the final model were: **P**revious admissions, **e**MRCD score, **A**ge, **R**ight-sided heart failure and **L**eft sided heart failure (PEARL). The PEARL AUROC was 0.70 (95% CI 0.66 to 0.72).

In 118 patients in the RCT, mean 90-day costs were £1,016 lower in HAH than usual care, but the one sided 95% cost interval crossed the non-inferiority limit (CI -2343 to

312). A sensitivity analysis assuming an extra days' stay in usual care met the inferiority limit: cost difference £-1262, (CI -2590 to 66). HAH had a 90% chance of cost-effectiveness at a threshold of £30,000 per quality adjusted life year.

## Discussion

The DECAF and PEARL score are simple tools that can be used at the bed side to risk stratify patients with AECOPD for inpatient mortality and readmission/ death without readmission respectively. Patient selection for Hospital at Home services using DECAF is cost effective.

## Dedication

To my wife, Rebecca, and my boys, Leonardo and Benicio.

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# Glossary of abbreviations

| | |
|---|---|
| AECOPD | Acute exacerbation of COPD |
| APACHE II | Acute Physiology and Chronic Health Evaluation |
| AUROC | Area Under the Receiver Operator Characteristic (Curve) |
| BAP-65 | Blood urea nitrogen, Acute mental status change, Pulse rate and age 65 |
| BTS | British Thoracic Society |
| CAP | Community Acquired Pneumonia |
| CAPS | COPD and Asthma Physiology Score |
| CAT | COPD Assessment Tool |
| CEAC | Cost effectiveness acceptability curves |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| CT-PA | Computed Tomography Pulmonary Angiogram |
| CURB-65 | Confusion, Urea, Respiratory rate, Blood pressure and age 65 |
| CXR | Chest x-ray |
| DECAF score | Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation |
| DVT | Deep Vein Thrombosis |
| ECG | Electrocardiogram |
| eMRCD score | Extended Medical Research Council Dyspnoea score |

| | |
|---|---|
| ICD 10 | International Classification of Diseases 10 |
| EQ-5D-5L | European Quality of Life-5 Dimensions |
| ESD | Early supported discharge |
| EXACT-PRO | EXAcerbation of Chronic Pulmonary Disease Tool- Patient Reported Outcomes |
| FEV1 | Forced expiratory volume in one second |
| FEV1% predicted | Forced expiratory volume in one second, per cent predicted |
| FVC | Forced Expiratory Volume |
| GCS | Glasgow Coma Score |
| GOLD | Global Initiative for COPD |
| HADS | Hospital Anxiety and Depression Score |
| HAH | Hospital at Home |
| HRQoL | Health Related Quality of Life |
| ICER | Incremental cost effectiveness ratio |
| IMV | Intubation and mechanical ventilation |
| MAR | Missing at Random |
| MCAR | Missing Completely at Random |
| MCID | Minimum clinical important difference |
| MNAR | Missing Not at Random |
| mMRCD score | Modified Medical Research Council Dyspnoea score |

| | |
|---|---|
| NICE | The National Institute for Health and Care Excellence |
| NIV | Non-invasive ventilation |
| pAECOPD | Pneumonic AECOPD |
| PEARL score | Previous admissions, eMRCD, Age, Right sided heart failure and Left sided heart failure |
| PE | Pulmonary thromboembolism |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| RRMH | Risk Ratio Mantel-Haenszel |
| RSN | Respiratory Specialist Nurses |
| SGRQ | St George's Respiratory Questionnaire |
| UC | Usual care |
| VTE | Veno-thromboembolism |

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# Overview of programme of research

In prognostic research, there are three key steps in creating a prognostic score:

1) Derivation
2) Validation
3) Implementation

Derivation refers to the development of a prognostic score. Validation refers to testing the developed score in: the same population ("internal validation") or a different population at a different time ("external validation"). "Implementation" refers to the assessment of the tool in clinical practice to quantify its impact on patient care.

This thesis is part of a larger programme of research which aims to derive, validate and implement prognostic scores for patients admitted with a COPD exacerbation (AECOPD) with respect to:

a) Inpatient mortality
b) Readmission or death without readmission within 90 days

This thesis includes: 1) the internal and external validation of the **D**yspnoea, **E**osinopenia, **C**onsolidation, **A**cidaemia and atrial **F**ibrillation (DECAF) score; 2) an RCT of the implementation of the DECAF score ("HoT DECAF"); and 3) the development, and internal and external validation of the **P**revious admissions, **e**MRCD, **A**ge, **R**ight sided heart failure and **L**eft sided heart failure (PEARL) score.

| | **OUTCOME,** name of prognostic score | |
|---|---|---|
| | **INPATIENT MORTALITY,** The DECAF score | **READMISSION/ DEATH WITHOUT READMISSION,** The PEARL score |
| Derivation cohort | Previous research[1, 2] | This thesis |
| Validation cohorts | This thesis | This thesis |
| Implementation study | This thesis | Future research |

*Table 0.1 showing overview of programme of research and work included in this thesis*

The DECAF score was developed and published prior to this work in the DECAF derivation study.[1, 2] An a priori aim of this work was to derive tools to predict readmission, or death without readmission, within 90 days of discharge and one year mortality. This study cohort was used in this thesis in the development of the PEARL

scores. The DECAF derivation study cohort will be referred to as the “derivation cohort” throughout this thesis.

The validation study comprises an internal and external validation cohort. All tools were validated in these cohorts, and the terms “internal validation cohort” and “external validation cohort” will be used throughout.

# Thesis overview

The main topics of this thesis are the validation of prognostic tools to risk stratify acute exacerbations of COPD (AECOPD) requiring hospital admission for in-hospital mortality (DECAF) and post-discharge readmission risk (PEARL), and an implementation RCT assessing Hospital at Home (HAH) selected by low risk DECAF score.

Five key aspects will be covered:

- AECOPD requiring hospitalisation
- Hospital at Home as a therapy for patients admitted with AECOPD
- The validation of the DECAF score
- The impact of the DECAF score when used to select patients for Hospital at Home therapy
- The development and validation of the PEARL score to predict 90 day readmission or death

Chapter 1 is a literature search which covers: COPD; AECOPD requiring hospitalisation; and tools that predict death or readmission following hospital admission with an AECOPD. We (Karen Brewin, Hazel Horobin, Andrew Bryant, Sally Corbett, John Steer, Stephen C. Bourke, and I) have published a meta-analysis of Hospital at Home for AECOPD which forms chapter 2.[3]

Within the methods section (chapter 3 to 5) the development, validation and impact assessment of prognostic scores are discussed together in that order to avoid repetition as we have developed and validated both the DECAF score and the PEARL score. The order of the results section (chapter 6 to 10) differs so that the DECAF implementation study (HoT DECAF RCT) follows the DECAF validation study, with the PEARL score reported afterwards. The studies appear in the following order in the results section:

1) The validation of the DECAF

The performance of the DECAF score was assessed in two large cohorts (an internal and external validation cohorts) comprised of six hospitals throughout the UK (1,725 patients). The DECAF score predicts in-hospital mortality.

2) HoT DECAF (Home Treatment for low DECAF risk AECOPD)
This is a randomised controlled trial (RCT) of 118 patients, in which patients admitted to hospital with a low risk DECAF score were allocated to receive Hospital at Home or usual care. Clinical and cost outcomes are described.

3) The PEARL score
The PEARL score was developed and validated to predict 90 day readmission or death without readmission in 2,417 consecutive admissions surviving to discharge. This includes 824 patients from the DECAF derivation cohort.

At the end of each results section follows a discussion, which summaries the key results, discusses the strengths and limitation of the research, and places the findings in the context of the existing literature.

The conclusion section synthesises the key results from the thesis.

# BACKGROUND

# Chapter 1 Introduction

## Chapter introduction

All patients included in the studies in this thesis had an acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) that required hospital admission. This chapter will include a brief overview of COPD, and then a more detailed exploration of AECOPD with regards to the impact of AECOPD on the patient and society, and prevention and treatment.

An overview is provided of prognostic scores which may be used for risk stratification and to guide management in patients admitted with an AECOPD.

## 1.1 Chronic Obstructive Pulmonary Disease (COPD)

This section begins with the definition and epidemiology of COPD and, then discusses the impact of COPD both globally and on the individual. The extended Medical Research Council Dyspnoea (eMRCD) score forms part of the DECAF score, and is therefore outlined along with the original MRCD score, the modified MRCD (mMRCD) score, the COPD Assessment Tool (CAT) and European Quality of Life-5 Dimensions (EQ-5D-5L). Lastly "1.1.7 Co-morbidity in COPD" discusses the importance of investigating and diagnosing co-morbidity which frequently complicate COPD.

### *1.1.1 Definition and diagnosis*

The National Institute for Health and Care Excellence (NICE) and the Global Initiative for COPD (GOLD) [4, 5] describe chronic obstructive pulmonary disease as a multi-system condition characterised by airflow obstruction that is usually progressive, but not fully reversible, and is commonly associated with respiratory symptoms such as breathlessness, cough and sputum production. Definitions include:

- Respiratory symptoms (e.g. breathless, cough sputum production), functional impairment and impaired health status (partly through exacerbations)
- Aetiological factors (smoking, occupational and environmental exposure)
- Abnormal lung physiology and function (primarily airflow obstruction)
- Chronic inflammation and structural lung changes (including emphysema)

Symptoms alone cannot define COPD, as they are non-specific and may occur in non-respiratory conditions. Breathlessness, cough and chronic sputum production (e.g. chronic bronchitis) may occur without airflow obstruction. Furthermore, symptomatic smokers/ former smokers (based on a CAT score of 10 or more) with normal spirometry suffer from acute exacerbations. This result was unchanged despite using various Forced Expiratory Volume in one second/ Forced Vital Capacity (FEV1/FVC) cut-offs (0.66, 0.7, 0.75 and the lower limit of normal).[6]

Airflow obstruction and radiographic features of COPD may exist in the absence of symptoms. Emphysema and airflow obstruction usually co-exist, but patients with emphysema, especially younger patients, may lack airflow obstruction as defined by an FEV1/ FVC ratio of less than 0.7. Conversely, the normal FEV1/(F)VC ratio slowly falls with age and older individuals who are otherwise well may have spirometric values which meet this criterion for airflow obstruction. For this reason, use of the lower limit of normal has been advocated by some.

Other respiratory diseases, such as asthma and bronchiectasis commonly co-exist with COPD and have several features which overlap.

### *1.1.2 Epidemiology*

In a systematic review and meta-analysis, the global prevalence of COPD was 9 to 10% in adults aged 40 year and over, though the reported prevalence varied considerably, partly due to methodological differences between studies.[7] Data from the United States shows that COPD affects more than one in twenty people, and more than one in ten in patients aged 65 and over.[8] In 2012, approximately 1.2 million people in the UK had been diagnosed with COPD. The proportion of people with COPD is highest in the North-East of England, and it is estimated that there are millions of patients with undiagnosed COPD in the UK.[9]

Historically, the reported prevalence of COPD has been higher in men, probably due to higher smoking rates. This remains true in some parts of Europe,[10] but COPD prevalence and AECOPD frequency (requiring hospitalisation) are similar between men and women in the US and UK.[8, 11]

Whilst the prevalence of COPD in the UK population is rising, new diagnosis rates have declined from around 226 per 100,000 in 2004 to 187 per 100,000 in 2013, coinciding with reduced smoking rates.

Estimates of prevalence and incidence are problematic, due to variation in diagnostic practice, and under- and over- reporting of the condition. A substantial proportion of patients with COPD remain undiagnosed [12, 13] and self-reported rates of COPD (or asthma) are twice the rate based on primary care records.[14] Globally, 80% of patients with COPD may be undiagnosed.[15] Under-reporting and undiagnosed COPD is associated with: older age (in the Netherlands);[14] younger age, smoking status (never or current smokers are at higher risk), lower education, and milder disease (globally);[15] and in low-income populations (US).[16] Most of the epidemiological data on COPD comes from higher income countries. The most important risk factor for COPD is tobacco smoke. Whilst the prevalence of smoking has reduced over the last 35 years, the world-wide absolute number of smokers has increased (there has been an increase in the global population).[17]

Typically, 10 or fewer pack years is unlikely to result in COPD in most individuals, whilst a 40 pack year history is a strong predictor of airflow obstruction.[18] Of interest, the higher the number of smoked cigarettes, the lower the median FEV1% predicted. This contradicts the commonly held view that susceptibility to smoke is binary. All individuals who smoke are at risk, though the extent varies between individuals.[18]

In developing countries, combustion of biomass for use as an energy source is associated with an increase in the risk of COPD.[19] The association between biomass smoke and COPD is higher in men than women, though smoking status may partly account for this difference; there is an especially high prevalence of smoking amongst middle-aged men in developing countries. In parts of the UK, industrial exposure, such as coal-dust, is an important risk factor for COPD.[7]

### *1.1.3 Impact of COPD*

The key symptoms in COPD are breathlessness, chronic cough and sputum production; wheeze or chest tightness may also be reported. Most patients (92.5%) with severe COPD (FEV1% predicted less than 50%) will report having experienced these symptoms within the previous seven days, with breathlessness being the most

frequently reported symptom (72.5%).[20] Despite this, many COPD patients underestimate the severity of their condition in relation to an objective breathlessness scale.[21] Symptoms can vary over the course of a day or week, and morning breathlessness is a key complaint,[20, 22] though some of this variation may be due to unreported exacerbation.[23] In severe and very severe COPD fatigue, weight loss and anorexia are common.[5]

Most patients will experience a general decline in lung function, which is accompanied by a deterioration in quality of life and worsening respiratory symptoms, and progressively more frequent exacerbations.[24, 25] The decline in FEV1 is greater amongst patients who have more frequent exacerbations.[26]

The burden of COPD is increasing and is predicted to be the fourth cause of death and seventh cause of disability-adjusted life years worldwide by 2030.[27] Morbidity in those with COPD increases as patients age, which may be partly due to worsening COPD as well as the progression and/or development of co-morbidity.[5]

The estimated annual healthcare cost of COPD is substantial;[5] in the UK COPD is the second commonest respiratory reason to attend the GP,[28] one of the commonest reasons for hospitalisation and total healthcare costs are close to one billion pounds.[29]

### *1.1.4 MRCD and CAT score*

The severity of COPD is based upon the degree of airflow obstruction, symptoms (as measured by the mMRCD scale or CAT) and frequency of exacerbations. The GOLD guidelines provide the following categories:[5]

- Group A have mild to moderate airflow obstructive, and/or 0 to 1 exacerbations per year, and an mMRCD score of 0 to 1 or CAT score of less than 10.
- Group B have mild to moderate airflow obstructive, and/or 0 to 1 exacerbations per year, and an mMRCD score of 2 or more or CAT score of 10 or more.
- Group C have severe or very severe airflow obstructive, and/or 2 or more exacerbations per year, and an mMRCD score of 0 to 1 or CAT score of less than 10.

- Group D have severe or very severe airflow obstructive, and/or 2 or more exacerbations per year, and an mMRCD score of 2 or more or CAT score of 10 or more.

It has been suggested that this guideline needs to be refined as an mMRCD score of 1 or more is approximately equivalent to a CAT of 10, and not an mMRCD score of 2 or more.[30] The Gold guide states that the CAT is the preferred method of assessment as it is more comprehensive, and this cut-off is associated with impaired health status.[31] The CAT is used as a secondary outcome in the DECAF implementation study (5.7 Overview of outcomes). It is a self-reported questionnaire that measures health-related quality of life. There have been numerous publications looking at the CAT in AECOPD.[32, 33] It has been shown to have good internal consistency and test-retest reliability.[32] Furthermore, scores worsen at the onset of AECOPD,[34] and improve with recovery.[35, 36] The minimum clinically important difference is 2.[37]

### *1.1.5 MRCD and eMRCD score*

Breathlessness is the most frequently reported symptom in COPD and can be assessed with respect to daily activities using standardised tools such as the MRC breathlessness score.[38] It shows good agreement between observers and with repeated use.[39] The primary measure of COPD severity previously was the degree of airflow obstruction. Symptoms have been added to the severity assessment in the GOLD guidelines because FEV1% predicted and breathlessness as measured by the MRCD are not closely associated, and the MRCD is associated with health status and mortality risk.[40, 41]

The extended MRC Dyspnoea score (Table 1.1) comprises one of the five indices in the DECAF score, which was developed to predict inpatient mortality; it is the strongest predictor of inpatient and 30 day mortality.[1, 2]

There are important differences between the eMRCD and traditional instrument: the transition point between levels is clearly defined, and the most severe category of breathlessness has been refined and sub-categorised. One of the criticisms of the traditional instrument is that there are no precise limits, and scoring can be unclear. For example, individuals who can leave the house but walk less than 100 yards could be scored MRCD 4 or 5.[42] Also, patients who can walk several hundred yards fall

between 3 and 4 for the traditional scale, whilst in the eMRCD it is clear they should be scored 3.

| Extended MRC Dyspnoea Score (eMRCD): "In the past 3 months, when you were feeling at your best, which of the following statements best describes your level of breathlessness?" (please circle) | |
|---|---|
| Only breathless on strenuous exertion | 1 |
| Breathless hurrying on the level or walking up a slight hill | 2 |
| Walks slower than contemporaries, or stops after walking on the level for 15 minutes | 3 |
| Stops for breath after walking 100 meters, or for a few minutes, on the level | 4 |
| Too breathless to leave the house unassisted but independent in washing and/or dressing | 5a |
| Too breathless to leave the house unassisted and requires help with washing and dressing | 5b |

**Guidance notes:**

Remember that you are asking the patient about their level of breathlessness ***on a good day over the preceding 3 months***, not breathlessness during an exacerbation/on admission.

A patient only achieves a higher grade if they are as breathless as defined in that higher grade.

- for example, if worse than defined in eMRCD 3, but not as bad as eMRCD 4, they remain eMRCD 3.

A key distinction is between eMRCD 4 and eMRCD 5a/5b:

- only score 5a or 5b if the patient cannot leave the house without assistance.
- if a patient can only walk 30 to 40 metres, but can leave the house unassisted, they are eMRCD 4.
- if a patient can walk 5 or 10 metres, perhaps from their front door to a car, but need a wheelchair

otherwise, they require assistance: eMRCD 5a or 5b. Simple walking aids do not constitute assistance.

If a patient requires assistance in personal washing *and* dressing they are eMRCD 5b. If they only require assistance in washing *or* dressing they are eMRCD 5a. Remember to ask about putting on socks and shoes.

If patients are limited for a reason other than breathlessness, score based on their functional limitation.

| DECAF Score | | Circle |
|---|---|---|
| D | eMRCD 5a (Too breathless to leave the house unassisted but independent in washing and/or dressing) | 1 |
| | eMRCD 5b (Too breathless to leave the house unassisted and requires help with washing and dressing) | 2 |
| E | **E**osinopenia (eosinophils < 0.05 x$10^9$/L) | 1 |
| C | CXR **C**onsolidation | 1 |
| A | Moderate or severe **A**cidaemia (pH < 7.3) | 1 |
| F | Atrial **F**ibrillation (including history of paroxysmal AF) | 1 |
| Total: | | |

*Table 1.1: eMRCD score, guidance notes for eMRCD, and DECAF score*

The traditional score reads: "Too breathless to leave the house…", sometimes referred to as housebound, "… or breathless when undressing". The eMRCD reads: "Too breathless to leave the house unassisted…" which better captures patients' functional limitations. Those only able to walk a few steps, but who routinely leave the house using a wheelchair or when driven by family, may not be considered/ consider themselves housebound, yet they clearly have very severe breathlessness and exercise limitation.

In our experience, many patients who can leave their home unassisted are breathless dressing and, according to the traditional scale, would be classified grade 5 (the most severe state); in the eMRCD score, patients must be unable to leave their home unassisted before scoring 5x. A range of activities of daily living were assessed during development of the eMRCD (including washing, dressing, feeding, cooking and cleaning), but crucially, if the patient experienced breathlessness but remained independent, they did not score: functional limitation is more clearly defined and probably offers more accurate prediction. The activities considered were then refined to optimise discrimination and ease of application. Level 5 is subcategorised into eMRCD 5a or 5b, with 5b referring to a person who requires assistance with both washing and dressing. This is essentially a composite assessment of breathlessness and frailty.

Numerous variations of the traditional MRCD scale are in clinical and academic use and each variation may have different interpretations. For example, descriptors to define MRCD grade 3 include: “people of the same age”, “contemporaries”, “peers” or “most people”. In addition, grade 5 traditionally includes breathlessness too severe to leave the house, with some versions including breathlessness on dressing/ undressing and some including breathlessness on eating.[38, 41, 43] Generally, such modified scores have not been compared to the traditional instrument, rendering their clinical relevance uncertain.

The 2014 COPD UK national audit [11] has recommended that the DECAF score, which includes the eMRCD score, is captured in all patients admitted with an exacerbation of COPD.

#### *1.1.6 EQ-5D-5L*

The EQ-5D-5L score allows health related quality of life (HRQoL) to be valued on a scale where perfect health and death are 1 and 0 respectively. The EQ-5D-5L is a generic, multi attribute, preference-based measure preferred by NICE for broader cost-effectiveness comparative purposes.[44] The EQ-5D-5L consists of two aspects. The first is a descriptive system, which defines HRQoL in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses to each of these dimensions are divided into five ordinal levels: first, no problems; second, slight problems; third, moderate problems; fourth, severe

problems; and fifth, unable to/extreme problems, generating a total of 3,125 possible health states. Index-based values (utilities) are a major feature of the EQ-5D instrument, facilitating the calculation of quality adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. The responses to the EQ-5D 5L questionnaire can be transformed using a standard algorithm to produce a health state utility score over various time points.[45]

The EQ-5D-5L has been validated in patients with COPD.[46] In a group of patients with stable COPD, and a group of COPD patients undergoing pulmonary rehabilitation, the validity of the EQ-5D-5L was compared to the St. George's Respiratory Questionnaire, the Chronic Respiratory Questionnaire, the Clinical COPD Questionnaire and the COPD Assessment Tool. The EQ-5D-5L was shown to be a valid and responsive measure of health status.

### *1.1.7 Co-morbidity in COPD*

The terms cardiovascular disease and metabolic syndrome (diabetes, high blood pressure, obesity and/or dyslipidaemia) cover the most common co-morbidities associated with COPD.[5, 47] Cardiovascular disease and metabolic syndrome are seen more frequently in the COPD population than the general population,[11, 47] including those with early stage COPD by GOLD classification.[48, 49] This is of importance, as the investigation and treatment of these conditions can improve morbidity and mortality across all stages of COPD severity. Such treatments should include smoking cessation. Metabolic syndrome and cardiovascular disease are not discrete diagnoses, and share smoking as a common risk factor. Systemic inflammation, which is increased by smoking, is a feature of COPD, cardiovascular disease and metabolic syndrome.[47, 50]

## 1.2 Acute Exacerbation of COPD

Section "1.2.1 Definition, diagnosis and aetiology" is an in-depth review of the definition and diagnosis of AECOPD. Thousands of patients were screened throughout this research, and AECOPD (as a provisional diagnosis prior to specialist confirmation) was over- and under-diagnosed. Three key differentials were under-recognised (heart failure and anxiety) or given undue attention (veno-thromboembolism) and are discussed. This section also justifies both the inclusion of

patients with “pneumonic AECOPD” and the use of this term in preference to “community acquired pneumonia”.

Measures of deprivation in AECOPD are shown in section “1.2.2 Epidemiology”, along with prevalence data.

Section “1.2.4 Impact of AECOPD on patients” looks at the impact of AECOPD on patients. Evidence is sought to justify the current emphasis on exacerbation prevention, which is partly based on the view that this will slow disease progression. Accurate baseline measures of mortality aid risk assessment. The reliability of mortality data is considered, which builds on points raised in the first section regarding the definitions of npAECOPD and pAECOPD. In Chapter 5, Hospital at Home is compared to usual care, and the primary outcome is cost. Potential harm due to hospital admission is reviewed, which could be avoided hypothetically with home treatment. Finally, there is a description of the overall cost of COPD, and the proportion attributed to AECOPD and hospitalisation.

Section “1.2.5 Management of AECOPD” examines the rationale for common in-hospital treatments, including the benefits and harms of corticosteroids and antibiotics which are perhaps too frequently provided to individuals with COPD. This expands on literature from the previous section looking at exacerbation prevention and disease progression. Hospital at Home treatment for AECOPD does not appear in this section, and is included in the meta-analysis (Chapter 2).

### *1.2.1 Definition, diagnosis and aetiology*

AECOPD are defined as a worsening of symptoms from baseline, which is beyond the typical daily variation. These symptoms include breathlessness, cough, or a change in sputum (increased volume or discolouration).[4] The definition sometimes includes the requirement of medication, or admission.[51] The GOLD 2017 guidelines classifies AECOPD as mild (treated with short acting bronchodilators only), moderate (treated with short acting bronchodilators plus antibiotics of oral corticosteroids), or severe (requires hospitalisation or visit to emergency room).[52] The majority of exacerbation are caused by bacterial and/or viral infections, though air pollution may also be an important aetiological factor in AECOPD and is associated with hospitalisation admission.[53]

Bacterial infection may follow as a consequence of viral infection.[54] Tests that confirm the presence of viruses tend only to be performed in the research setting.[24] In the clinical setting, excluding infection as the cause of AECOPD is difficult, though discoloured sputum as reported by microbacteriologists strongly suggests the presence of bacteria.[55, 56]

Bacteria are present in 4% of healthy adults, 29% of patients with stable COPD, and 54% of those with an AECOPD, with higher microbial loads seen during AECOPD.[57] This increased load may represent new acquisition of bacteria rather than proliferation of existing strains.[58]

49% (662 of 1,352) of patients with an AECOPD and purulent sputum have positive sputum cultures.[59] Within this group, multivariate analysis showed that pre-treatment clinical factors, including sputum colour and viscosity, were not strong predictors of the presence of bacteria either as individual predictors or in combination (area under the receiver operator characteristic curve = 0.59).[60]

In patients who meet the diagnostic criteria for chronic bronchitis and have an AECOPD and mucoid sputum, bacteria are commonly present. In one study, the rate of absence of bacterial growth was 22%,[56] though in another study it was 62%.[61] Variation in disease severity may explain this difference, as more severe COPD correlates with the presence of bacteria.[57, 60] High rates of bacterial growth in those with severe, stable COPD has been attributed to colonization. However, the presence of bacteria is associated with inflammation and an immune response, so chronic infection may be a more accurate description than colonization.[62]

Pneumonia commonly occurs with AECOPD, especially in patients who require hospitalisation. The proportion of patients with AECOPD who have pneumonia is unclear, in part due to reporting. In the International Classification of Diseases (ICD) 10 classification there are multiple possible codes for patients admitted with an AECOPD or a pneumonic AECOPD (pAECOPD). Furthermore, the term “pneumonia” may supersede pAECOPD, and “COPD” subsequently may not appear. Previous studies of COPD codes using ICD-9 or ICD-10 are limited in that they did not include pneumonia and/or patients did not require spirometric confirmation of COPD.[63-66] Many observational studies rely on administrative data to identify patients; accurate

identification of the population of interest is fundamentally important to the validity of their results.

Some clinicians regard pneumonia as a separate diagnosis to an AECOPD, or even take the extreme view that a diagnosis of pneumonia (parenchymal disease) invalidates a diagnosis of AECOPD (airway disease). This observation is supported by the differences in the rates of pneumonia reported in the national COPD audit compared to the DECAF derivation study. The DECAF derivation study captured 920 consecutive admissions with AECOPD, and included all those with co-existent pneumonia. Radiographic consolidation was seen in 32.5% in the DECAF cohort, compared to only 18% in the UK national audit.[2, 11]

Throughout this thesis, an AECOPD complicated by pneumonia will be called a pneumonic exacerbation (pAECOPD). The primary justification for this terminology is that patients with pAECOPD and non-pneumonic AECOPD share more similar treatments than those with community acquired pneumonia (CAP) without COPD. Patients with pAECOPD have similar sociodemographic details, severity of underlying COPD and range of organisms to those with non-pneumonic AECOPD.[67] Patients with CAP have higher rates of pulmonary effusion, empyema, legionella pneumophilia infection, and lower rate of pseudomonas aeruginosa infection than patients with pAECOPD.[68]

The recognition of pAECOPD is important because co-existent pneumonia is associated with worse outcome, and has important implications for treatment. In patients with acute hypercapnic respiratory failure and isolated CAP, most studies show non-invasive ventilation (NIV) does not improve outcome and current guidelines state NIV is not indicated.[69] In pAECOPD NIV reduces intubation rates and improves survival. In high risk patients, broad spectrum antibiotic therapy with anti-pseudomonal cover should be considered. However, the presence of consolidation depends on the timing and type of radiographic modality; lack of consolidation on chest radiograph does not exclude pneumonia.[70-72]

Blood eosinopenia (<0.05x10^9/l) is a marker of disease severity, and is a strong, independent predictor of inpatient mortality.[2] Airway eosinophilia is associated with response to corticosteroids, and a serum eosinophil count of 2% or less may have a role directing oral corticosteroid therapy for AECOPD.[73] Stable state eosinophil count

also appears to predict response to inhaled corticosteroids; consistent with earlier data, a threshold of 2% has been muted,[74] however a post-hoc analysis of the Wisdom study showed that it is principally those with an absolute count of 0.3 or more, or a relative count of 4% or more who benefit.[75] It is important to recognise that eosinophil counts may fall in the setting of sepsis and inflammation, and stability of eosinophil phenotype is uncertain. In the future, AECOPD may be classified based on eosinophil count, which may be used to direct corticosteroid therapy, and further research is awaited.

GOLD guidelines prior to the initiation of our RCT did not recommend (diagnostic) spirometry during an AECOPD because "it can be difficult to perform and measurements are not accurate enough."[5] One study specifically questioned the validity of this recommendation.[76] Whilst less than half of patients admitted with an AECOPD could perform spirometry, the mean FEV1% predicted was 38.7% (SD 14.4) at discharge and 40.6% (14.3) at one month (p = 0.18). Crucially, of 41 patients who met GOLD criteria for COPD at discharge, only 2 failed to meet the criteria at one month. In previously undiagnosed patients hospitalised with a clinical history consistent with AECOPD, this data supports using pre-discharge spirometry to confirm COPD. Patients are at particularly high risk of adverse events immediately after an exacerbation requiring hospitalisation; confirmation of airflow obstruction supports initiation of therapy to improve symptom control and reduce risk. Of interest, the recommendation not to perform diagnostic spirometry during an AECOPD does not appear in the 2017 GOLD guidelines.[52]

Clinical features which point towards underlying COPD in a patient presenting to hospital with a suspected AECOPD include: a heavy smoking history; progressive breathlessness, chronic cough, sputum production and onset after age 35 years. Physical examination may show hyper-inflation, hyper-resonance or decreased cardiac dullness on percussion; decreased breath sounds; wheeze; and a prolonged expiratory time.[77] Features suggestive of primary or co-existent asthma should be sought, and other differential diagnoses considered. Such factors are important, as there are a number of medical conditions which can mimic AECOPD and co-morbidity is common in patients with COPD.[5] An autopsy study of 43 inpatient COPD deaths who died within 24 hours of admission showed the primary cause of death to

be heart failure (n = 16), pneumonia (n = 12) and pulmonary thrombo-embolism (n = 9).[78]

In patients with known COPD who present with symptoms suggestive of AECOPD, pulmonary thromboembolism and heart failure are common final diagnoses.[79] It is not appropriate to label such episodes as AECOPD, not least because the required treatments are different.

### *Differential diagnosis for AECOPD*

AECOPD are the focus of this research and their correct identification is crucial. Common conditions that can mimic AECOPD will be considered in detail in the following section. The GOLD guidelines state that the diagnosis of an exacerbation relies exclusively on the presence of symptoms. However, the symptoms that define an AECOPD are non-specific, and not all patients with these symptoms should receive a diagnosis of AECOPD. A diagnosis of AECOPD also involves assessing patients for features that favour an alternative diagnosis.

#### Heart failure

Decompensated heart failure can cause or mask the symptoms and signs of an AECOPD.[80] Pulmonary congestion is associated with airflow obstruction, acute breathlessness, wheeze and cough.[81, 82] Bronchial hyper-responsiveness to acetylcholine provocation testing has been observed in patients with chronic pulmonary overload.[83] The prevalence of COPD is approximately 30% in stable heart failure, though estimates vary between 9 and 45%.[84] The proportion of never smokers is higher than might be expected.[85, 86] The lower COPD prevalence reported in some studies may be due to more aggressive treatment of heart failure in the acute and chronic setting. Variation in COPD prevalence may also reflect differences in study populations (such as smoking prevalence and age) and accuracy of diagnosis; most studies did not include spirometric testing.[84]

Few studies have performed serial spirometry to establish the prevalence of fixed airflow obstruction following admission due to heart failure. In an early study,[81] airflow obstruction was common at the time of decompensation, but improved rapidly in most patients over two weeks. After several months, only 8 of 15 patients had persistent airflow obstruction.

In another study of patients hospitalised with congestive heart failure,[86] 144 of 619 (23%) patients had a previous diagnosis of COPD at admission, of whom 79 of 144 (55%) were on COPD therapy. However, in those with a previous diagnosis of COPD, 112 of 144 (78%) had COPD excluded by pulmonary function testing at six months' follow-up. COPD was both over-diagnosed and under-recognised; an additional 26 new cases were identified. A previous history of asthma was an exclusion criterion, so is unlikely to account for the variability in lung function results.

Within this same study, 272 patients had lung function testing prior to discharge and at six months' follow-up. This showed significant increases in FEV1% predicted, FVC, residual volume and total lung capacity, showing that patients had a mixed obstructive and restrictive picture. The FEV1/FVC ratio improved, but did not reach statistical significance ($p = 0.12$). Of note, the authors used an FEV1/FVC cut off of 0.7 to define COPD, which tends to result in a higher prevalence of COPD compared to using the lower limit of normal in this group.[87]

It is important to differentiate between AECOPD and decompensated heart failure to ensure patients receive the correct treatment. Concerns have been raised regarding the use of beta-agonists in those with heart failure. In a cohort of 1,529 patients, a dose-response increase in risk was reported between beta-agonist use in heart failure and all-cause mortality, which persisted after adjusting for cofounders.[88] This cannot prove causation, as beta-agonist use may be a marker of disease severity. In a related example, an association between mortality and chronic beta-agonist has been reported in asthma,[89] [90] but was not seen in the 4 to 12 months prior to death, making a causal relationship more doubtful.[90]

### Pulmonary thromboembolism

Presenting symptoms and signs are similar between AECOPD and pulmonary thromboembolism (PE). A literature review from 2009 aimed to determine the prevalence of pulmonary thromboembolism during AECOPD.[91] Eligibility criteria included a diagnosis of COPD supported by symptoms and spirometry, and investigation of pulmonary thromboembolism based on CT angiography or pulmonary angiography within 48 hours of presentation. The review incorrectly concluded that one in four patients hospitalised with AECOPD may have PE. This is misleading as the selected studies largely looked at subpopulations of patients with AECOPD

without a clear cause, rather than consecutive unselected patients. Hartman et al. looked at consecutive patients with suspected pulmonary thromboembolism, not consecutive AECOPD, and the prevalence of PE was similar in patients with and without COPD.[92]

Lesser et al.[93] and Mispelaere et al.[94] looked at a select group of AECOPD, namely those in whom a diagnosis of pulmonary thromboembolism was suspected [93] and those with a COPD exacerbation without evidence of infection.[94] Tillie-Leblond et al. found 25% of patients with COPD exacerbation of unknown cause had pulmonary thromboembolism.[95]

Rutschmann et al.[96] may provide the most representative picture of the prevalence of pulmonary thromboembolism in patients thought to have an AECOPD. Consecutive patients with a diagnosis of AECOPD who had moderate to very severe COPD were recruited. AECOPD was defined as a worsening of breathlessness sufficiently severe to warrant admission to the emergency room, but, importantly, patients with an obvious alternative cause for their breathlessness were excluded. Clinicians reported whether pulmonary thromboembolism was clinically suspected or not, with no suspicion defined as a patient who would not have otherwise been investigated for a pulmonary thromboembolism. In those patients with an AECOPD in whom pulmonary thromboembolism was not clinically suspected, only 1 of 75 patients had a confirmed pulmonary thromboembolism. Also, the proportion of people with veno-thromboembolism (VTE) risk factors was appreciably lower compared to other studies.

Newer imaging techniques may have a higher pick up rate for pulmonary thromboembolism in AECOPD: recent studies of pulmonary thromboembolism in AECOPD report figures of 18% [97] and 30%.[98] Both of these studies have included patients in whom pulmonary thromboembolism was the favoured diagnosis.

Shapira-Rootman et al.[97] defined AECOPD broadly as any worsening of dyspnoea sufficiently severe to warrant admission to hospital, and alternative obvious causes of breathless were not part of the exclusion criteria. Similarly, Akpinar et al.[98] failed to exclude those whose likely diagnosis was not an AECOPD: 22% of patients diagnosed with pulmonary thromboembolism had leg asymmetry in whom the primary diagnosis perhaps should not have been an AECOPD.

Post-mortem studies show high proportions of pulmonary thromboembolism, but cannot provide an estimate of the prevalence of PE in AECOPD. In COPD patients admitted to a respiratory intensive care unit who died, 30% had VTE [99] and in patients admitted with an AECOPD who died within 24 hours of admission, 21% had VTE.[78] Both of these studies involve patients at especially high risk of VTE.

Whilst the prevalence of PE in AECOPD is probably overestimated, the risk of PE in COPD may be higher than in the general population. The risk of venous thromboembolism and adverse outcome (including risk of death, bleeding and VTE recurrence) is higher in patients with COPD than those without COPD. The ratio of pulmonary thromboembolism to deep vein thrombosis (DVT) is higher in COPD patients than the general public and COPD patients are also more likely to re-present with pulmonary thromboembolism rather than DVT.[100] This could be explained by a higher rate of in-situ thrombosis,[91] which has been implicated as a cause of pulmonary thrombosis in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.[101] COPD is associated with systemic inflammation, and hypothetically such patients may be more likely to produce DVTs that embolise. Lastly, patients with COPD are more likely to have a CT-PA and receive a diagnosis of PE, which includes incidental sub-segmental PE and false positive CT-PA results. The significance of incidental and/or isolated subsegmental PE is uncertain. Recent guidance recommends that they should be managed the same way as symptomatic and non-subsegmental PE, though the evidence is not clear-cut.[102]

### Anxiety

Anxiety is common in COPD and is associated with hospital admission.[103, 104] During an AECOPD that requires hospitalisation, patients have high levels of anxiety as measured by the Hospital Anxiety and Depression score (HADs), which improve with recovery.[105] AECOPD are characterised by breathlessness, which is a cause of anxiety.[5] A cycle of breathlessness, arousal, and worsening breathlessness forms the cognitive model of panic attacks and panic disorder.[106] The Diagnostic and Statistical Manual of Mental Disorders 4$^{th}$ Edition makes a distinction between panic attacks with and without an underlying general medical condition. Panic disorder involves recurrent, unexpected panic attacks with one month or more of persist concern about

further attacks, their consequences, and/or a change in behaviour. Anxiety disorder is the appropriate term for patients that experience symptoms akin to panic attacks at the time of an AECOPD. In practice, it may be difficult to distinguish between a COPD patient having a panic attack and patients with an AECOPD and high levels of coexistent anxiety.

Anxiety and panic attacks are important to identify in COPD patients. Corticosteroids may induce a range of psychiatric disorders, and are associated with increased risk for panic disorder in elderly patients.[107] Cognitive-based therapy is of benefit in those suffering panic attacks, and may stop the development of panic disorder.[106]

Panic attacks may be of particular concern in patients with COPD who are “flow limited”. This describes patients whose expiratory time is insufficient to allow the end expiratory lung volume to reach its natural relaxation volume, which leads to hyperinflation.[108] During AECOPD such patients are prone to worsening expiratory flow obstruction, dynamic hyperinflation and cardiorespiratory decompensation. In patients with severe hyperinflation, there are decreases in left and right ventricular end-diastolic volumes, and an impaired stroke volume and cardiac output compared to controls, due to changes in intrathoracic blood flow and mechanical compression.[109] Acute anxiety can contribute to this deterioration through an increase in respiratory rate, which can worsen flow limitation and dynamic hyperinflation.

### *1.2.2 Epidemiology*

The prevalence of AECOPD can vary substantially depending on whether the definition is symptom based, or includes the need for medication and/or admission.[110] Up to 50% of exacerbations are unreported to clinicians.[23, 111] Symptoms and the time-course to recovery is similar between reported and unreported exacerbation,[23, 112] so a definition that includes these important events is appropriate from the patients’ perspective. Previously unreported events have been captured by the use of symptom diary cards,[23] which pre-dated the EXAcerbation of Chronic Pulmonary Disease Tool- Patient Reported Outcomes (EXACT-PRO). The EXACT PRO has been used to identify the frequency, severity and duration of AECOPD and has been assessed in stable and exacerbating populations.[113]

Patients who do not report their exacerbations have worse health-related quality of life, and are more likely to be admitted to hospital; early treatment for AECOPD may shorten recovery.[114] Those that do not report exacerbations may represent a more unwell population.

Up to one in eight AECOPD may need emergency inpatient episodes.[115] The TORCH study selected patients aged 40 to 80 with a baseline pre-bronchodilator FEV1 of less than 60%; in the Seretide treatment arm, the annual rate of exacerbations requiring treatment was 0.85 and hospitalisation 0.16. The WISDOM study, another large RCT, reported 0.95 exacerbation per patient-year for moderate to severe exacerbation.[116] Such large RCTs may not be representative of the general population. In the US in 2010, there was an estimated 1.5 million emergency department visits (73.6 per 10,000 US population) and 699,000 hospital admissions (34.4 per 10,000 US population) for COPD.[117] In the UK, between 2006 and 2009, COPD admissions were 26.5 per 10,000 UK population.[118]

From a population perspective, data from Spain and Sweden show that the incidence of AECOPD is decreasing,[119, 120] though these figures may not be generalisable to other parts of the world.

COPD is associated with lower levels of education, lower income and employment rates, and higher health disability.[8, 11] The latest UK National COPD Audit [11] assessed deprivation in patients admitted with AECOPD using the Index of Multiple Deprivation which is based on postcode and includes seven different domains. In four domains, there was more than a three-fold difference in the proportion of the total COPD population living in the most deprived national quintile compared to the least deprived quintile (Table 1.2). This trend was seen in Wales, as well as England.

Patients with AECOPD have high levels of co-morbidity. In the most recent UK national audit,[11] the most frequently reported co-morbidities were hypertension (31%), ischaemic heart disease (21%), diabetes (16%) and atrial fibrillation (12%). High levels of comorbidity were also seen in the DECAF derivation study:[2] hypertension (40%), ischaemic heart disease (29%), diabetes (15%) and atrial fibrillation (13%). Furthermore, 34% of patients were housebound, with 6.5% admitted from institutional care. The findings in the DECAF validation cohorts (6.1 Patient characteristics) were consistent.

| | % of national audit sample living in postcode areas within English national quintiles, from most deprived (Q1) to least deprived (Q5), % (total n = 12,245) | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 |
| Index of multiple Deprivation | 33 | 24 | 19 | 15 | 10 |
| Income deprivation | 32 | 25 | 19 | 15 | 10 |
| Employment deprivation | 34 | 24 | 18 | 14 | 10 |
| Health deprivation and disability | 33 | 23 | 18 | 15 | 11 |
| Education, skill and training deprivation | 34 | 24 | 18 | 15 | 10 |
| Barriers to housing and services | 16 | 19 | 21 | 22 | 23 |
| Crime | 27 | 23 | 19 | 17 | 14 |
| Living environment deprivation | 23 | 21 | 21 | 19 | 15 |

*Table 1.2: Index of multiple deprivation measures by national quintile, England*

Most studies which look at severe AECOPD only (those that require hospitalisation) include all patients who present between discrete time points, and at different stages in their disease. One inception cohort studied 73,106 patients from their first ever hospitalisation for COPD.[25] The time between the first and second hospitalised exacerbation was around five years, and the gap between successive episodes shortened with time. Patients were followed up for a mean of 3.6 years, ranging from 1 day to 17 years. The mean rate of severe exacerbation requiring hospitalisation was 37.8 per 100 per year. As patients were recruited following their first admission with an AECOPD, these rates will be higher than the general population with COPD. In Spain and Sweden, the incidence of hospital admissions seems to have decreased.[119, 120]

### *1.2.3 Risk factors for AECOPD requiring hospitalisation*

Predictors of AECOPD requiring hospitalisation over six months include: age, FEV1 % predicted, unscheduled clinic/Emergency Department visits in the prior year, hospitalisations in the prior year, cardiovascular disease, and oral corticosteroids.[119-121] In the ECLIPSE study,[122] the best predictor of exacerbation was a previous history of exacerbations. One of the aims of COPD therapy is to reduce the risk of future AECOPD. Evidence from TORCH,[123] and the Eclipse study [122] (as quoted in the

GOLD guidelines[5]) show that more severe airflow obstruction is associated with more hospitalisations per year (GOLD 2 = 0.11 to 0.2, GOLD 3 = 0.25 to 0.30, and GOLD 4 = 0.40 to 0.54 hospitalisations per year). Consequently, therapy to reduce the frequency of AECOPD is directed by the number of exacerbations in the previous year, and the FEV1% predicted.[5] One study of 107 patients with COPD reported the following potentially modifiable risk factors of AECOPD requiring admission: ACE inhibitor or angiotensin receptor blocker use, gastro-oesophageal reflux disease symptoms and poor adherence to inhaled therapy and outpatient visits;[124] whether modifying these would reduce exacerbation frequency is unclear.

Patients with undiagnosed COPD have a greater risk of hospital admission for AECOPD.[118] Protective factors include being offered influenza immunisation, patient-reported access to primary healthcare staff and the number of GPs and practice nurses per 1000 patients.[118]

The number of AECOPD requiring hospital admission peaks in the winter and is at its lowest during the summer.[125, 126] This may be due to low temperature, viruses, crowding of people indoors, a reduced immune system, or a combination of these factors.[110]

### *1.2.4 Impact of AECOPD on patients*

AECOPD have a marked impact on patients with COPD and are associated with worsening symptoms, lung function, health-related quality of life, and mortality risk.[26, 112, 127-129] AECOPD become more frequent with time, tend to occur in clusters,[130] and approximately one in three patients will be re-admitted within 90 days of discharge.[131] The severity of AECOPD tends to increase with subsequent exacerbations.[25]

#### *Symptoms and quality of life*

AECOPD are defined by worsening respiratory symptoms, notably breathlessness, and these symptoms have an important impact on health status. Improvements in health status following AECOPD may occur over a few weeks or many months, which may be due to several factors, including: a) individual variation in recovery; b) recurrent exacerbation (including both reported and unreported episodes); and c) a permanent decline in health status caused by exacerbation.

Individual variation in recovery of health status, as measured by the St George's Respiratory Questionnaire (SGRQ), has been shown in a number of studies.[127, 132] In one study, serial measures of health status following severe AECOPD showed an initial large mean improvement in the first four weeks.[133] In 51 patients hospitalised due to an AECOPD there were significant improvements in health status (using the SGRQ) over the entire nine month follow up period.[134] Measures of psychological distress (using the Hopkins Symptom Checklist) also improved, as did the physical domain of the World Health Organisation Quality of Life.

In 183 patients admitted to hospital with an AECOPD, health status was assessed over one year post discharge in ventilated (n=80) and non-ventilated patients (n=96); 7 patients failed to attend all assessments and were excluded. Most measures of quality of life peaked at 3 months, functional recovery peaked at six weeks, and most patients (70% and 76% in the ventilated and non-ventilated groups) did not experience a clinically important deterioration in St George's Respiratory Questionnaire total score.[105]

The changes in health status following AECOPD are different in those who do, and do not, have a further exacerbation. The non-exacerbator group tend to have a larger improvement in health status at 4 weeks and 12 weeks.[133]

Assessing the impact of AECOPD is problematic as patients commonly have episodes of worsening symptoms which fulfil the diagnosis of an AECOPD for which they do not seek medical help. This was observed in a study of 70 patients in the community with stable COPD, using daily diary cards.[112] Health status was strongly associated with exacerbation frequency, despite the fact that the mean time between administering the SGRQ and the previous exacerbation was 101 days. From this, the authors hypothesise that preventing AECOPD should be associated with a reduced decline in health status.

Several RCTs have shown an improvement in health status associated with a reduction in AECOPD frequency. Typically, COPD studies measure health status with the SGRQ. The minimum clinical important difference (MCID) is -4 in unselected patients with COPD, though in those with more severe COPD a difference of -8.3 at one month and -7.1 at six months has been suggested.[135]

The ISOLDE study [136] showed a lower rate of deterioration in health status in patients receiving inhaled corticosteroids, with a reduction in exacerbation frequency, but no impact in the decline in FEV1 compared to placebo. In a subsequent analysis of this study, a regression model showed that the effect of inhaled corticosteroids on health status was largely explained by their effect on exacerbation frequency.[137]

In the TORCH study [123] patients were randomised to treatment with salmeterol and fluticasone, fluticasone alone, salmeterol alone and placebo. There were significantly fewer moderate to severe exacerbation and better health status in the combined treatment group compared to the placebo group: the mean adjusted change in SGRQ over 3 years was -3.0 compared to +0.2, which falls short of the MCID.

Similarly, the UPLIFT study showed that treatment with tiotropium in comparison to placebo caused fewer exacerbations with an improvement in the mean change in the SGRQ up to 4 years which was below the MCID.[138] Whilst there was a reduction in exacerbation frequency requiring hospitalisation in TORCH, this was not the case in UPLIFT, though the annual rates of severe hospitalisation was low and similar in both arms and many patients in the UPLIFT study were already treated with LABA/ ICS.

The SUMMIT study [139] compared vilanterol and fluticasone, fluticasone alone, vilanterol alone and placebo. Combination therapy reduced the annual rate of moderate and severe exacerbations, but health status was only collected on a subset of 4443 (27%) patients and is not reported in the primary paper.

The FLAME study [140] compared two active dual therapies (LABA/ LAMA versus LABA/ICS) and showed a small improvement in exacerbation frequency and health status with LABA/ LAMA therapy.

*Lung function*

FEV1 deteriorates in adults as part of the normal ageing process, and a more rapid decline is seen in those who smoke.[141] AECOPD are associated with deterioration in lung function (measured by FEV1 or peak expiratory flow rate) which, in a minority, may not fully recover. This lack of recovery in lung function could be predominantly due to the background deterioration in FEV1 and independent of AECOPD, or occur as a direct consequence of AECOPD.

On average, small changes in lung function are observed with AECOPD, though it varies between individuals. In 101 patients with stable COPD at recruitment, patients recorded daily symptoms and peak expiratory flow rates, and a subpopulation of 34 performed daily spirometry over a two and a half year period.[23] Patients reported a deterioration in their symptoms prior to any deterioration in lung function. Median recovery time of peak expiratory flow rate was six days, with complete recovery in only 75% of exacerbations at 35 days, and 93% of exacerbations at 91 days, though changes in lung function were small. Those patients who did not recover lung function had a larger fall at the time of exacerbation. This shows that AECOPD worsen lung function in the acute period and that in some patients, resolution is slow or incomplete.

An association between AECOPD frequency and the annual rate of decline in FEV1 has been shown.[26, 142, 143] In a large cohort of 5887 smokers (The Lung Health Study), higher numbers of lower respiratory tract infection were associated with a higher annual rate of FEV1 decline in smokers.[142] In 109 patients with moderate to severe COPD daily diary cards were used to identify reported and unreported AECOPD. Compared to infrequent exacerbators, patients experiencing frequent exacerbations showed greater declines in peak expiratory flow rate and FEV1 (in the subset of 32 individuals who performed daily spirometry). Frequent exacerbators tended to be more likely to be current smokers (39.3% v 22.2%; $p = 0.056$).[26] Exacerbation frequency, rather than smoking status, was the main determinant of FEV1 decline; the small numbers in the FEV1 subgroup may bias the results. In a similar study of 102 patients who performed six-monthly spirometry, exacerbation frequency was associated with decline in FEV1 per cent predicted. Whilst smoking was the major determinant of lung function decline, exacerbation frequency was also a factor.[143]

Smoking has previously been shown to be the main determinant of FEV1 decline.[141] In contrast to more recent studies, Fletcher and colleagues found that decline in FEV1 occurred continuously and smoothly over a person's life, and that bronchial infections were not a factor. This was a large study assessing the effect of smoking status in working men in London, and not limited to those with confirmed COPD, which could partially account for the differences observed. A more recent study in 279 Japanese patients showed no relationship between AECOPD frequency and

decline in FEV1.[144] This study reported a lower AECOPD rate than other studies, though the authors observe that a lower frequency was also observed amongst Japanese patients in the UPLIFT study.

If AECOPD are responsible for a faster decline in FEV1, (rather than being associated with another cause, such as smoking) then preventing AECOPD should reduce this effect.

The TORCH study showed a reduction in exacerbation frequency and, in a subsequent analysis, a slower decline in FEV1 with combination ICS/LABA treatment compared to placebo.[123, 145] The rate of decline of FEV1 per year in mls was -39.0 compared to -55.3 (green line and black line on Figure 1.1). The annual rate of decline in the treatment arm was lower than historical controls.[145] This comparison accounted for other factors that may impact on lung function, such as differences in smoking. However, the difference in FEV1 decline between treatment and placebo was largest amongst those who reported no AECOPD, though treatment may have impacted on unreported events. As discussed, unreported events may account for 50% of AECOPD, and acutely worsen lung function.[23] It is now recommended that all AECOPD are captured in similar trials, including reported, self-managed and untreated events.[146]

Lung function decline was not a primary outcome of the TORCH study, and the observed difference in the annual rate of decline of FEV1 in TORCH may be inaccurate: the proportion of drop-outs and missing FEV1 data was higher in the placebo arm than the treatment arm. The real difference in FEV1 decline may have been larger; patients who withdrew from the placebo arm had higher rates of decline (blue line Figure 1.1). Conversely, higher rates of missing data at baseline (18% had missing baseline data compared to 9% in the combination treatment arm) would overestimate the initial FEV1 and exaggerate the difference in decline in the placebo arm (red line Figure 1.1).[147]

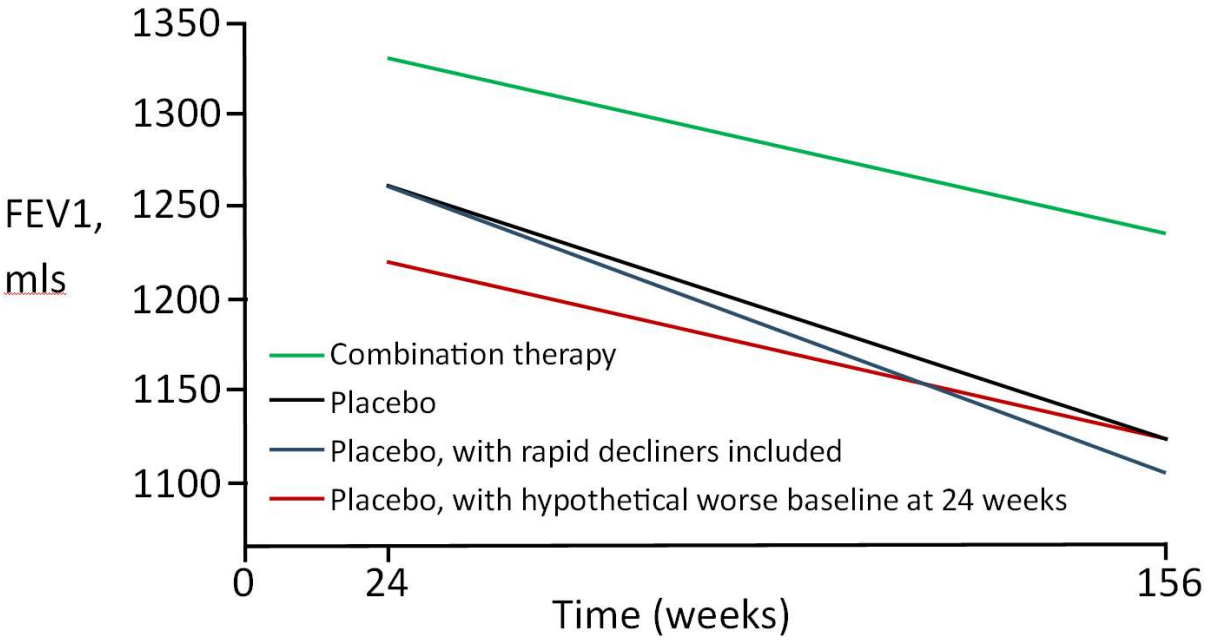


*Figure 1.1: Graph illustrating potential bias in FEV1 decline due to missing data*

- Green versus black line: The difference in rate of decline between combination therapy and placebo in the TORCH trial was 16mL per year.
- Green versus blue line: There were more patients with missing FEV1 values in the placebo arm, whose inclusion may have widened the difference in FEV1 decline.
- Green versus red line: Missing FEV1 data was higher in the placebo arm at baseline, whose exclusion could have resulted in no difference in the rate of FEV1 decline.

The UPLIFT trial showed that patients who were treated with tiotropium had significantly fewer exacerbations per patient year compared to the placebo group (0.85 versus 0.73).[138] Whilst there was no difference in the rate of decline of FEV1 (the primary outcome) between the two groups, the frequency of severe exacerbation was the same; milder exacerbations may have less impact on lung function decline.

The SUMMIT study [139] showed that combination therapy reduced the annual rate of moderate and severe exacerbations and led to a modest (12mls) annual improvement in the rate of decline of FEV1. As with the TORCH study, this value may have been under or over-estimated due to missing data. They report that the reduction in FEV1 should be placed in the context of the 25-30ml annual decline in FEV1 which occurs in the general population. Other sources suggest that the decline

in FEV1 may be higher in certain populations (including the study population- those with COPD, smokers and ex-smokers), and this higher rate may still be an underestimate due to participant drop out.[148] The absolute minimal clinical important difference for FEV1 in COPD is around 100mls, which is based on a volume that patients can perceive,[148] though the proportional difference based on baseline lung function is also important.[149]

RCTs of inhaler therapy in COPD generally report the mean annual difference in FEV1 between treatment groups. A more meaningful value to report would be the proportion of patients in each arm that reach the MCID: "the minimum worthwhile incremental advantage".[149] This would allow for the analysis of exacerbation frequency in responders to better understand the impact of exacerbation prevention on FEV1 decline.

*Mortality*

Inconsistency with terminology for COPD and AECOPD means mortality data may be inaccurate.[5] For AECOPD that require admission, in-hospital mortality is reported to be between 4.3% and 10.4%.[2, 11, 119, 125, 150-152] In a large inception cohort study, every new severe exacerbation increased the risk of death.[25] Mortality peaked in the first week after admission and stabilised after three months. There is substantial variation in an individual's risk of death, which can be calculated using the DECAF score and is discussed further in Chapter 6.[2]

In the UK national COPD audits, inpatient mortality was 7.7% in 2003, 7.8% in 2008 and 4.3% in 2014, though the reason for the drop in mortality in 2014 is unclear.[11] There have been no major developments in treatment that reduce mortality between 2008 and 2014; differences may be due to reporting practices. The DECAF deviation study and the 2008 UK national audit had an inpatient mortality of 10.4% and 7.7% (this fall is consistent with local audit data), despite the fact both studies were in the UK and were performed at a similar time.[2, 150] The higher mortality rate in the DECAF studies may reflect more complete case ascertainment; patients at risk of being missed are more likely to have died. A comparison of these studies provides insight into reported differences. Pneumonia is a strong, independent predictor of inpatient mortality in AECOPD,[1] and the rate of pneumonia in the DECAF study was double that of the equivalent national audit data (32.5% versus 16%). This largely accounts

for the observed differences in mortality. In the DECAF derivation study, all those with COPD and coexistent pneumonia received a diagnosis of pneumonic AECOPD and were included. Of note, most patients with pAECOPD had severe airflow obstruction when stable. This practice is not the same throughout the UK; in the national UK audit some patients who received a diagnosis of pneumonia rather than pneumonic AECOPD may have not been included. Furthermore, the 2009 influenza pandemic and high rates of comorbidity could have contributed to the high rates of pneumonia in the DECAF study.

Post discharge mortality was reported as 4.2%, 10.5%, and 17.4% at 30, 90 and 180 days in a large study from Northern Denmark.[125] As seen in previous studies,[25] mortality risk increased with each AECOPD hospitalisation. Ninety day mortality was 5.9% in the European COPD audit.[10] Again, this may be accounted for by differences in populations, as well as variations in healthcare systems.[153]

*Hospital admission*

Patients admitted for AECOPD have worse outcome than those that do not require admission. The need for hospital admission is used to define severe AECOPD.[52, 123, 138] Differences between the admitted and non-admitted population may explain the different outcome, for example COPD severity, comorbidity, and age.

Hospital admission is associated with poor nutrition, infection and deconditioning. In both stable and acute settings, COPD patients with a low BMI have a worse mortality,[2, 154] and poor exercise tolerance is a strong predictor of adverse outcome.[1] Whilst bed rest leads to physical deconditioning and muscle weakness, immobility is associated with many adverse outcomes, including increased risk of falls, delirium and venous thromboembolic disease.[155, 156] Conversely, pulmonary rehabilitation improves exercise capacity, health-related quality of life and reduces hospitalisation in patients with AECOPD.,[157] However, one large study of inpatients with AECOPD receiving an early, intensive rehabilitation programme compared to usual care failed to demonstrate a reduction in readmissions and showed increased mortality at one year. Falls and delirium are more likely in the unfamiliar hospital environment, the latter compounded by interruptions in the patient's usual routine and sleep patterns.

Advancing age and lung disease partly account for COPD patients' susceptibility to infection, the risk of which is increased by hospital admission. Viral and bacterial infections together account for 70-80% of exacerbations.[62]

RCTs of home treatment compared to hospital treatment for AECOPD have shown that home treatment may reduce readmission rates.[158] In one study, patients treated at home had fewer urinary tract infections.[159] Home treatment for AECOPD is the intervention in the DECAF implementation RCT and is discussed in more detail in a meta-analysis in Chapter 2

*Cost to society*

The annual healthcare cost of COPD has been estimated as 38.6 billion Euros and 49.4 billion dollars in the European Union and United States.[5] The majority of these costs are due to hospitalisation and the management of AECOPD.[152] In the UK, the cost of COPD care is between 817.5 million [160] and 982 million pounds,[29] of which 30 to 50 per cent is due to inpatient care. Costs of care dramatically increase with the severity of COPD, as hospitalisation and treatment with ambulatory or long-term oxygen is more common in severe disease.[5]

In the United States, the average cost of hospitalisation has been estimated at 9,545 dollars (plus or minus 12,700), with a total cost of 11.9 billion dollars.[152] In this study, costs were higher in patients with more comorbidity. In the UK, a hospital admission is estimated to cost 1,960 pounds.[161] A number of studies of Hospital at Home/ Early Supported Discharge (HAH/ESD) have calculated inpatient costs, though these were studies were performed in a subset of patients with milder disease. The cost of admission with regards to HAH/ESD are discussed in more depth in “2.3.6 Service costs”.

Patients with COPD may be unable to work, and family members may miss work to care for their relative.[5] In the late 1990s, the cost per year of lost productivity due to missed working days has been estimated at £2.7 billion.[161] Disability adjusted life years is a measure of disease burden, which is a composite of years lost due to illness, disability or early death. It is estimated that from 2002 to 2030, COPD will have moved from the eleventh to the seventh most common cause of disability adjusted life years.[27]

### *1.2.5 Management of AECOPD*

*Prevention*

Optimising the treatment of stable COPD is important to prevent AECOPD, and key treatments will be covered briefly.

Smoking causes COPD, and smoking cessation is the most effective treatment to modify disease progression. Stopping smoking is associated with a reduced risk of AECOPD [162] and smoke-free public policies are associated with a fall in COPD hospitalisation.[163]

In a randomised study of 60 patients, pulmonary rehabilitation was associated with a reduction in the number of AECOPD, but not admission to hospital.[164] In a meta-analysis of 432 patients, a reduction was seen in hospital readmission following AECOPD.[157] Subsequently, a large randomised controlled trial showed that early rehabilitation did not affect readmission rates, and that mortality was actually higher in the intervention group at one year.[165] In this study, patients were both recruited and rehabilitation initiated within 48 hours of admission to hospital for an AECOPD. Rehabilitation consisted of strength and anaerobic training, and neuromuscular electrical stimulation.

Long-acting muscarinic antagonists reduce AECOPD, but do not reduce AECOPD requiring hospitalisation or the number of days in hospital.[138] Treatment with long-acting beta-agonists (LABA) and/or inhaled corticosteroids (ICS) reduces the frequency of moderate or severe AECOPD, though the impact on AECOPD that require hospitalisation is more modest (annual 0.19 to 0.16, rate ratio 0.83, p = 0.03).[123] In this study most patients were already on treatment to reduce exacerbation frequency with 60.1% taking a LABA and 61.6% taking an ICS. In a large RCT, combined LAMA/LABA reduced the annual rate of all AECOPD by 11% compared to LABA/ICS (3.59 vs 4.03, p = 0.003). For severe exacerbations, there was no difference (0.15 vs 0.17, p = 0.231).[140]

Influenza and pneumonia vaccination should be offered to patients with COPD. A randomised controlled trial of 125 patients with COPD showed a 76% reduction in the incidence of influenza,[166] though in practice the effectiveness varies depending on the closeness of fit between the strains in the vaccine and the circulating viruses.

*Treatment for AECOPD*

## Oxygen and bronchodilators

Patients with AECOPD may require treatment with supplemental oxygen. Excess oxygen can cause hypercapnia, acidosis and death, and so oxygen should be given in a controlled manner and titrated based on the patients' oxygen saturations.[167] Venturi masks can deliver a precise fraction of inspired oxygen, whilst the delivery of oxygen with simple face masks and nasal cannulae is variable.

The dangers of excess oxygen in patients with AECOPD has been shown in a randomised controlled trial.[168] This study included patients with a suspected diagnosis of AECOPD who were transported to hospital by paramedics. Paramedics were randomised to treat patients with either high flow oxygen, or oxygen via nasal prongs with target oxygen saturations of 88 to 92%. In the intention to treat and per protocol analysis, death rates were higher in patients that received high flow oxygen.

Patients with AECOPD who are admitted to hospital receive nebulised short-acting beta-agonists (SABA) which can improve respiratory symptoms and improve airflow obstruction. There are no large randomised-controlled trials which demonstrate the clinical benefit of SABA in patients with AECOPD. In a randomised controlled trial of 86 patients, there was no difference found between those receiving 2.5 mg or 5 mg four-hourly salbutamol nebulisers in terms of lung function parameters or length of stay.[169] However, study numbers were small, and patients with more severe AECOPD were not included.

Short-acting muscarinic antagonists (SAMA) improve symptoms and airflow obstruction in patients with stable COPD who have received beta-agonists. However, in patients with AECOPD who have already received high doses of nebulised SABA there is a lack of evidence of added benefit. In one study, 70 patients with AECOPD were randomised to receive 5mg salbutamol nebulisers, or 5mg salbutamol nebulisers and ipratropium bromide 500 micrograms. There was no difference in length of stay or airflow obstruction.[170] A similar study recruited patients with asthma and COPD to receive 10 mg salbutamol or 10 mg salbutamol and 500 µg of ipratropium bromide.[171] Within the COPD group, the improvement in peak flow rate was the same in both treatment arms.

### Corticosteroid therapy

In 56 patients hospitalised with a non-acidotic AECOPD, 14 days of oral prednisolone 30 mg treatment was compared to placebo. Four in five patients were already receiving inhaled corticosteroids therapy. Corticosteroid therapy led to an early improvement in post-bronchodilation lung function (a daily increase of 90 ml versus 30 ml in the first five days), though there was no difference at six week's follow up.[172] Length of stay was seven days in the corticosteroid group compared to nine days in the placebo group. A greater improvement in symptoms was reported in the treatment arm. Five patients in the placebo arm withdrew, compared to one in the corticosteroid group which could have biased results. Compared to patients who completed the study, those who withdrew had greater improvements in their baseline post-bronchodilator percentage predicted FEV1 (withdrew = 14.1 to 31.4 compared to completed = 27.1 to 37.4).

In a study of 199 patients, patients hospitalised with an AECOPD were randomized to receive: a) nebulized budesonide 2 mg six hourly for 3 days followed by inhaled budesonide and placebo oral prednisolone; b) oral 60 mg daily prednisolone for three days, then 40 mg daily for seven days and placebo inhaled budesonide (nebulisers then inhaler); or c) placebo treatment (tablets and nebulisers then inhaler). Both treatment groups showed larger improvements in FEV1 over the first 72 hours of treatment (the primary outcome) compared to placebo, though there was no difference at two weeks (budesonide compared to placebo = 100 mls, prednisolone compared to placebo = 160 mls). There were fewer complications, such as hyperglycaemia, in the inhaled therapy group compared to the oral therapy group. There was no difference in the change in Borg breathlessness scale or length of stay across the three groups. The authors acknowledged that oral corticosteroids have multiple side-effects, and patients with AECOPD who are prone to the side-effects may receive multiple courses. Of importance, they concluded that the long-term risk/benefit of oral corticosteroids is probably not favourable, and that inhaled budesonide may be an alternative treatment.

In 261 patients hospitalised due to AECOPD,[173] patients were randomised to: a) an eight week course of corticosteroids; b) two week course of corticosteroids and six weeks of placebo; or c) eight weeks of placebo. Patients in both treatment arms

received 125 mg of intravenous methylprednisolone every six hours for three days, before switching to a tapering dose of oral prednisolone starting at 60 mg. In the eight week corticosteroid arm, patients remained on 20 mg of prednisolone whilst the two week group finished this therapy. There was a significant reduction in the primary endpoint of death, intubation, readmission for COPD, and intensification of therapy at 30 days and 90 days, but no difference at 182 days. The difference in the composite endpoint was due to intensification of therapy (mainly treatment with corticosteroids). The average length of stay in the glucocorticoid group was 8.5 versus 9.7 in the placebo arm. The absolute saving in bed days should not be generalised to current UK medical practice because length of stay has substantially reduced with time. Treatment with corticosteroids again led to an early improvement in FEV1 of approximately 100 mls, but there was no difference at or beyond two weeks. The high proportion of patients receiving corticosteroids in the placebo group could have diminished between-group differences. This may be unavoidable as: a) patients receiving placebo may be identifiable to clinicians (lower FEV1, potentially more symptoms and signs); and b) oral steroids treatment was part of usual care for AECOPD- receipt of systemic corticosteroids in the previous 30 days was the commonest reason for exclusion from the study (50% of those excluded).

In an open-label randomised study, 217 patients with AECOPD requiring ventilatory support were randomised to usual care or daily steroids (1 mg per kg) for up to 10 days.[174] Patients with evidence of pneumonia were not included. There was no difference in ICU mortality (the primary end-point), NIV failure, median mechanical ventilation time, or ICU length of stay, though the study was underpowered. The trial was ended before completion due to slow recruitment. At the time the study was stopped, ICU mortality was higher in the corticosteroid group (15.3%, n = 17/111 compared to 14.2%, n = 15/106). The authors state that the trial should not be regarded as negative, because the lower end of the CI meant that a 40% lowering in the risk of death with corticosteroids is possible. Similarly, the upper end of the CI means a 2-fold increase in death with corticosteroids is possible. At the end of the study, they had 70% power (as opposed to 80% power) to detect a 12% lowering the absolute risk of ICU mortality for an alpha of 0.05. As with previous trials, the main cause of non-inclusion was the receipt of corticosteroids within 30 days (n=160).

Hyperglycaemia requiring treatment occurred more frequently in the corticosteroid group (49.5% compared to 33%).

A more recent study assessed the non-inferiority of a short course of oral corticosteroid therapy (five days 40 mg prednisolone daily) compared to 40 mg prednisolone for 14 days (though all patients initially received 40 mg intravenous methylprednisolone on the first day).[175] The non-inferiority calculation was based on the judgement of 11 specialists who defined a 15% absolute difference in the percentage of patients suffering an AECOPD during six months of follow-up as the clinically tolerable upper-limit. Hospital readmission at six months is a more clinically relevant outcome to patients than changes in lung function within the first few days of treatment. A non-inferiority study, unlike a superiority study, is more likely to show a positive outcome if there is missing data so it may be appropriate to perform a per protocol analysis and intention to treat analysis. In both analyses, non-inferiority was demonstrated and the authors conclude that these findings support the use of five-day corticosteroids treatment in AECOPD. However, they did not include a placebo arm. In the study by Niewoehner et al., the previous largest study of steroids in patients hospitalised with an AECOPD, there was no difference in readmission rates at six months between treatment and placebo arms.[173] Both 14 days and 5 days of corticosteroids for AECOPD may have no impact on readmission rates at six months.

On review of the evidence, there are only marginal benefits of using oral corticosteroid in patients admitted with an AECOPD. The main reported benefit is in lung function in the early stages (days) of an AECOPD, though this difference may be lost after a few weeks. There is no RCT evidence to show that oral steroids for AECOPD impact on the rate of decline of FEV1. In terms of hard clinical outcome, such as death, a meta-analysis of 1,319 patients in 11 RCTs showed that there was no difference between treatment and placebo (OR 1.00, 95% CI 0.60 to 1.66).[176] This remained true when including studies with more unwell populations. Negative studies are less likely to be published, so the potential harm of steroids may be underestimated. The meta-analysis reported that there was no heterogeneity between studies, and that the funnel plot did not indicate a strong likelihood of publication bias. However, statistical tests for homogeneity lack power, and it is worth noting that the reported event rates in each arm varied substantially between studies,

although this may be due to the small number of events in smaller studies or differences in population.

Treatment with oral corticosteroid therapy is common in COPD. This is evident from several RCTs which excluded large proportions of patients due to recent use of oral corticosteroid therapy. Corticosteroids are known to cause serious side-effects, which may include osteoporosis and bone fractures, hyperglycaemia, weight gain and metabolic syndrome, gastric irritation/ulceration, cardiac disease, infection, muscle wasting and mood disturbance.[177] Inpatients with AECOPD have high rates of hypertension, IHD, and diabetes, and are elderly so are susceptible to the side-effects of cumulative courses of oral corticosteroids. Randomised controlled trials that look at the benefits and harms of corticosteroids in AECOPD have only looked at outcome following a single episode. Further research is required to: a) better understand the cumulative benefits and/or harms of corticosteroid use in this population; and b) identify which patients are at particular risk or benefit from treatment with corticosteroids. Eosinophil count is a simple biomarker which shows promise in identifying patients that may respond to corticosteroids.[73, 178]

### Antibiotics

In a retrospective cohort study of almost 70,000 patients admitted for AECOPD, 85% were treated with antibiotics.[179] Given the large numbers of patients that are treated with antibiotics, concerns have been raised regarding the overprescribing of antibiotics and of antibiotic resistance.[180] Whilst antibiotic therapy is used in the treatment of AECOPD, only some groups may benefit from this therapy. Guidelines on the assessment of patients with AECOPD are inconsistent in terms of the features that support antibiotic treatment.[181]

Characteristics associated with antibiotic response include: a) more severe stable state COPD; b) a more severe AECOPD; and c) new/increased purulent sputum. This section will consider these three aspects when reviewing RCTs of antibiotics compared to placebo. Studies that compare different types of antibiotic therapy will also be considered briefly. The effect of antibiotics on mortality will be considered first, followed by treatment failure.

There is a shortage of placebo-controlled randomised trials comparing antibiotics to placebo for AECOPD that have assessed important clinical outcome such as mortality. Those that have reported numbers of deaths were generally underpowered to assess this outcome. Meta-analysis can provide useful pooled estimates of mortality outcome, but results must be interpreted with caution given the heterogeneity of the trials, especially in terms of treatment (which assumes that antibiotic type and mode of delivery are equally efficacious) and variation in the diagnosis of an AECOPD.

A Cochrane meta-analysis from 2006 looked at three studies, and concluded that antibiotics improve survival [182] whilst a more recent Cochrane meta-analysis reported no such benefit based on five RCTs.[183] To understand the difference in conclusions between these meta-analyses, the three trials which appear in both meta-analyses will be considered first, then the two that are in the most recent meta-analysis.

Three trials are included in both mortality analyses; two by Pines et al. and one by Nouira et al..[184-186] Pines et al. performed a small pilot study of 30 patients with chronic bronchitis and an acute purulent exacerbation, half of whom received intravenous penicillin three million units (for 14 days) and intravenous streptomycin 0.5 g (for 7 days), and the other half received placebo.[184] This pilot study was stopped early due to high rates of deterioration in the placebo group. One patient died in the treatment group compared to three in the placebo group. Based on these results, the larger study that followed compared three active treatments, and did not incorporate a placebo group due to ethical concerns.[184]

Pines et al. compared chloramphenicol, tetracycline and placebo in an RCT, but excluded patients with a severe AECOPD in whom they thought there was sufficient evidence of benefit to warrant treatment.[185] In “moderately ill” patients with purulent exacerbations of chronic bronchitis 0 of 89 patients died in the treatment group compared to 1 of 86 in the placebo group.

Nouira 2001 [186] showed that in a trial of 93 who required mechanical ventilation on the intensive care unit there was a reduction in the primary outcome of inpatient mortality with oral ofloxacin 400mg for ten days (4% versus 22%). This is the only RCT to show a significant reduction in mortality. Patients appeared well matched for baseline characteristics including severity of AECOPD and a third of the placebo

group (compared to 6% of the antibiotic group) received “additional” antibiotic therapy, which may have improved outcome in the placebo group and underestimated the benefit of ofloxacin. The patients in this study had both: a) severe COPD when stable; and b) were suffering from a severe AECOPD. The mean FEV1 in the treatment and placebo groups was 0.79 L/s and 0.74 L/s with 1.7 and 1.6 exacerbations in the previous year. Even though the presence of infiltrate on chest radiograph was part of the exclusion criteria, these AECOPD were severe based on: a) the need for hospital admission; b) the mean pH (7.22 and 7.21 for treatment and placebo groups) and high proportion who required invasive mechanical ventilation; and c) high SAPSII scores (31 and 35 for treatment and placebo groups). Most patients were treated with invasive mechanical ventilation (IMV): one third of patients in each arm initially received IMV, and 80% of the remaining two thirds progressed from NIV to IMV. Rates of pneumonia were substantially higher in the placebo arm and death occurred after approximately seven days. Antibiotic use is strongly associated with a reduction in the risk of pneumonia.[187] Whilst antibiotics may prevent secondary infection in patients who have received IMV, these results cannot be generalised to the majority of patients with an AECOPD.

In both studies by Pines et al., all patients had purulent sputum. It is unclear if patients without purulent sputum were included in the Nouira study, though 61% of all patients had a positive sputum culture. Although these three trials were included in both Cochrane meta-analyses, the reported number of events from the Nouira study differ. In the Ram meta-analysis [188] all-cause mortality was reported as 4 of 47 for the antibiotic group compared to 18 of 46 for the placebo group, whilst the Vollenweider meta-analysis [183] quotes 2 of 47 and 10 of 46. This discrepancy appears to have arisen depending on whether or not the ICU and hospital deaths were considered to be mutually exclusive.

The Vollenweider meta-analysis includes two papers that do not appear in the earlier meta-analysis, one from 1967 by Petersen et al. (which included 19 patients and had only one death which occurred in the placebo arm)[189] and a more recent, larger study published by Daniels et al. in 2010.[190]

Daniels et al.[190] compared doxycyline 200 mg daily to placebo in addition to systemic corticosteroids in 223 patients hospitalised with an AECOPD. An AECOPD was

defined by Anthonisen criteria as a type one or type two exacerbation.[191] Type one exacerbations have all three cardinal symptoms of increased breathlessness, increased sputum volume and increased sputum purulence, whilst a type two exacerbations has two of these three cardinal symptoms. Patients with pneumonia and requiring mechanical ventilation were excluded (it is unclear if AECOPD newly treated with mechanical ventilation were included; no baseline pH levels are mentioned). There were seven deaths (7 of 107, 6.5%) in the treatment arm compared to three (3 of 116, 2.6%) in the placebo group. Compared to other studies reporting mortality outcome, this is perhaps most generalisable to the average inpatient with an AECOPD because: a) it uses a relatively modern definition of an AECOPD; b) treatment was more typical of current practices; and c) the study did not limit inclusion to patients with severe AECOPD. The study was underpowered to make any definite conclusions regarding mortality.

Since this meta-analysis, a further placebo-controlled study has been performed. In 100 outpatients with type one exacerbation of COPD, patients were randomised to antibiotics (a ten day course of a quinolone or amoxicillin). All patients received inhaled salbutamol, oral theophyllines and oral corticosteroids. Oral theophylline is not routinely recommended for the treatment of AECOPD. There are several significant limitations with this study. No primary outcome is provided, but rather a list of “main outcome measures”, no power calculation is provided, and neither the randomisation process or allocation concealment is adequately described. One patient died in the treatment arm (1 of 50) compared to three in the placebo arm (3 of 50).

There is a lack of evidence to determine the impact of antibiotics on mortality as studies are underpowered. A previous meta-analysis showing a mortality benefit was due to the inclusion of an ICU-based study [186] which is not generalisable to the majority of patients with AECOPD and may be due to the prevention of secondary pneumonia in invasively ventilated patients.

In common with most RCTs, the most recent Cochrane analysis [183] measured treatment success/ failure as the primary outcome, though trials varied in their definitions. In seven RCTs of outpatients with AECOPD, there was low quality evidence that antibiotics reduce treatment failure, but this benefit did not reach

statistical significant when restricted to five trials that used modern antibiotic therapies. In four RCTs of inpatients with AECOPD (and in three RCTs that used modern antibiotic therapies) there was a significant reduction in treatment failure, and this evidence was regarded as high quality; this did not include the Nouira ICU study. As with studies of corticosteroids, patients in placebo arms receiving treatment (for treatment failure of placebo) may reduce differences between groups.

There was no difference in length of hospital stay outside of the ICU setting in two trials that measured this outcome.[183] No studies report hospital admission rates following treatment, or antibiotic resistance rates, though adverse events, including diarrhoea, were higher in those that received antibiotic therapy.[192]

The largest single study in the meta-analysis is by Llor et al.[193] They randomised 310 patients with AECOPD to receive co-amoxiclav 625 mg three times a day or placebo for eight days. No data is provided on the number of patients that died, which is an important omission, especially given the conflicting data in previous, smaller studies. In common with other studies, the primary outcome was based on the short-term success or failure of treatment which was higher in the treatment group ("clinical cure at days nine to eleven", 74.1% n = 117 of 158 compared to 59.9% n = 91 of 152). Patients were followed up for a year, which is an important strength as most RCTs have too short a follow-up period. Time to next exacerbation in those that had had a clinical success measured at days nine to eleven was longer in the treatment group (median time 233 compared to 160 days). The median time to next exacerbation in each allocation group is not provided which is another limitation of the study. Patients requiring hospital admission were not included, and patients needed an FEV1 of greater than 50% predicted for inclusion. Therefore, compared to studies of inpatients with AECOPD, the selected cohort was lower risk. Little data is provided on the severity of the exacerbation and the rates of corticosteroids treatment were lower than expected at 16.5% and 17.8% in the co-amoxiclav arm and placebo arm.

In the study by Llor et al.[193] treatment failure was lowest in patients who produced purulent sputum and were treated with antibiotics. Treatment failure was highest amongst those with purulent sputum treated by placebo. A similar finding was seen in one of the earliest trials of antibiotic use [191] which looked at 173 patients over three and half years. Patients who had an increase in sputum purulence were more likely

to benefit from antibiotic therapy (co-trimoxazole, amoxicillin or doxycycline) and purulent sputum was a predictor of treatment failure. Such sub-analyses should be interpreted with some caution.

Given the uncertainty regarding the efficacy of antibiotic therapy and the problems of antibiotic resistance, further placebo control trials are appropriate in those patients with mild to moderate exacerbation of COPD. Rohde et al.[194] are undertaking a placebo controlled study and aim to recruit 980 patients with moderate AECOPD. The “ultimate goal (of the study) is to reduce unnecessary antibiotic prescription”. In the planned study, a “moderate” AECOPD is defined as one without respiratory failure or need for intermediate or intensive care. Patients will be excluded if they have: a) a PaCO2 greater than 45 mmHg and/or pH less than 7.35; b) pneumonia; or c) fever. These are not optimal criteria for assessing the severity of an AECOPD.

It is not clear which factors are most important in predicting response to antibiotics, though likely candidates include: severity of COPD, severity of AECOPD, and/or the presence of purulent sputum. In common with other studies, this study would benefit from a more discriminative measure of severity of AECOPD.

The primary outcome is clinical failure defined by the need for additional antibiotic treatment at 30 days; it is worth noting that the previous largest trial by Daniels et al. showed no difference in this outcome at 30 days. In the planned study, patients are receiving a short course of five days antibiotics. A strength of the study is that subsequent exacerbation rates will be recorded up to one year.

Observational data suggests antibiotic use in AECOPD may improve outcome. In a large, retrospective cohort study of 84,621, early antibiotic use was associated with improved outcome amongst inpatients with AECOPD.[195] Whilst the results were adjusted for confounding factors, unmeasured population differences could account for the difference.

A number of trials have been performed which compare different antibiotics in patients with AECOPD. These trials include far more patients and longer follow-up periods than the placebo controlled trials of antibiotics. Nine RCTs that report the long-term effect of treatment are summarised in a review by Wilson et al.[196] Measured outcome vary between studies. The primary outcome included clinical

response/success/cure/failure, time free of infection and time to re-exacerbation, and largely there is no difference between different agents. Recurrence/failure rates and bacterial eradication tend to be better with quinolones compared to clarithromycin or amoxicillin. One of the largest studies of 1,492 patients compared moxifloxacin 400 mg four times a day for five days to co-amoxiclav 975/125 mg twice a day for seven days.[59] The primary outcome of clinical failure was similar at eight weeks. Patients receiving moxifloxacin had higher bacterial eradication rates at the end of therapy, though this difference was not apparent at four and eight weeks post treatment.

Antibiotic resistance is a global crisis and the current evidence base supporting their use in AECOPD is poor. Further research is required to identify who benefits from antibiotics, and the size of the effect, with a view to limiting the inappropriate provision of antibiotics to low-risk AECOPD who have no evidence of bacterial infection.

## 1.3 Scores used to predict outcome following hospital admission with an AECOPD

The validation of the DECAF score, and the Hot DECAF RCT form the major part of this thesis. In “1.3.1 DECAF and background”, the DECAF score is considered in detail, followed in “1.3.2 Other prognostic scores used to predict acute mortality”.

No tool exists (prior to PEARL) that developed in patients with AECOPD to predict readmission/ death without readmission. “1.3.3 Scores that predict readmission and long term mortality in patients with an AECOPD following discharge” looks at the evidence base.

### *1.3.1 DECAF and background*

In-hospital mortality is between 4.3% and 10.4%.[2, 11, 119, 125, 150-152] Clinicians are unable accurately to estimate the risk of death in patients hospitalised with AECOPD.[197] A reliable prediction tool, which stratifies patients according to mortality risk, may help inform management. This could include the selection of low risk patients for Hospital at Home (HAH) or Early Supported Discharge (ESD), and the identification of high risk patients for early escalation or appropriate palliation.

The DECAF score was derived in a large cohort of consecutive unique patients hospitalised with AECOPD, is simple to apply at the bedside and predicts in-hospital

mortality using indices routinely available on admission.[2] To develop the score a wide range of clinical, physiological and demographic variables were collected in 920 consecutive patients admitted with AECOPD to either North Tyneside (NTGH) or Wansbeck (WGH) general hospitals between December 2008 and June 2010. Exclusion criteria were few and included the presence of co-morbidity likely to limit survival to less than one year or home ventilation. To ensure the maximal capture of patients and data, daily screening of patients' medical records, and review of hospital coding records was performed

The hospitals have diverse catchment areas and community support. One hospital covers a predominantly urban population, whilst the other serves a large rural area, supported by several community hospitals.

Patients with coexistent pulmonary consolidation were included, provided AECOPD was the primary diagnosis. This is consistent with the major UK audits of AECOPD [150] and non-invasive ventilation [198] which included patients with pneumonia AECOPD.

Patients with pneumonic AECOPD are treated similarly to those with non-pneumonic AECOPD, but differently to those with community acquired pneumonia and no underlying diagnosis of COPD. For example, patients with pAECOPD/ AECOPD are treated with corticosteroids, bronchodilators and, when appropriate, non-invasive ventilation. Compared to patients with non-pneumonic AECOPD, those with pneumonic AECOPD have similar sociodemographic details, severity of underlying COPD and range of organisms.[67] This justifies the classification of "pneumonic AECOPD" as opposed to community acquired pneumonia.

In the DECAF study, dyspnoea was assessed using both the traditional Medical Research Council Dyspnoea score and the extended MRCD (eMRCD) score. The eMRCD score divides the most severe category (MRCD 5 = housebound) into those who do not require assistance with washing and dressing (5a) and those who do (5b). This modification improves the discriminatory power for predicting mortality.[1] The eMRCD is described in more detail in section 1.1.5.

To ensure the prognostic tool was simple to administer, continuous variables were dichotomised. Independent predictors of in-hospital mortality were identified by

logistic regression analysis and the five strongest prognostic indices were selected to form the DECAF score, shown previously (Table 1.1). Zero, one or two points are scored for the eMRCD score, and one point is scored for the presence or absence of Eosinopenia, chest X-ray Consolidation, Acidaemia, or atrial Fibrillation.

Higher DECAF scores were associated with higher inpatient mortality, ranging from 0.5% in the DECAF 0 group to 70% in the DECAF 5 group. We assigned DECAF scores 0 and 1 as conferring low risk, 2 as moderate risk and 3 or more as high risk of mortality (Table 1.3). Compared to the British Thoracic Society audit in 2008,[150] mortality (after adjustment for the relative proportion of pneumonic exacerbations), length of stay and readmission rates were similar. In our study there was a higher proportion of patients requiring ventilation,[1] suggesting that our hospitals do not have a lower threshold for admission than other centres. Furthermore, a high percentage (86%) of patients with an eMRCD score 5b and acidaemia received non-invasive ventilation.

| Risk group | Score | n | % mortality |
|---|---|---|---|
| Low risk | 0 | 201 | 0.5 |
| | 1 | 291 | 2.1 |
| Intermediate risk | 2 | 226 | 8.4 |
| High risk | 3 | 125 | 24 |
| | 4 | 57 | 45.6 |
| | 5 | 20 | 70 |
| | 6 | 0 | N/A |

*Table 1.3: Percent inpatient mortality by DECAF score*

The predictive strength of the DECAF score was compared to other tools that have been used to predict mortality in AECOPD, though not all were developed for this purpose. Prognostic strength was assessed by measuring the area under the receiver operator characteristic (AUROC) curve, and were compared to other tools by the method of Delong et al.[199] DECAF was compared to the Acute Physiology And Chronic Health Evaluation (APACHE II) score,[200] the Blood urea nitrogen, Acute mental status change, Pulse rate and age 65 (BAP-65) score,[201] the COPD and

Asthma Physiology score (CAPS),[202] and the Confusion, Urea, Respiratory rate, Blood pressure and age 65 (CURB-65) score.[203]

DECAF was superior to APACHE II (AUROC = 0.78, p<0.0001), BAP-65 AUROC = 0.68, p<0.001), CAPS (AUROC = 0.71, p<0.0001) and CURB-65 for both patients with consolidation (AUROC = 0.77 vs. 0.66, p = 0.003, n = 299) and without consolidation (AUROC =0.87 vs. 0.72, p = 0.002, n = 621). It is important to note the developed score, in this instance DECAF, will be favoured when comparing it to other scores in its derivation cohort.

The 2014 UK National COPD audit recommended that the DECAF score be documented in all patients admitted with an AECOPD but noted that validation was required [11] which is essential to prove the generalisability of a prognostic score.[204] In chapter 7 we present the results of the validation of the DECAF score and compare its performance to other prognostic tools.

### *1.3.2 Other prognostic scores used to predict acute mortality*

There are a number of severity scores that have been assessed in patients with AECOPD.[205]

APACHE II [200] is a revised version of the APACHE score. It comprises of: a) 12 physiological measurements divided into up to eight categories; b) five categories of risk for age; and c) three categories for prior immunocompromised state and comorbidity. APACHE II was validated in many patients and hospitals, and demonstrated good performance in the prediction of in-hospital mortality in unselected patients admitted to an intensive care unit.

The performance of the APACHE score has been assessed in COPD patients admitted to a general medical ward.[206] ICD-9 codes were used to retrospectively identify 277 patients, of whom 101 met the their criteria for an AECOPD. Using coding to identify AECOPD is inaccurate,[207] and spirometric data was not available to confirm the diagnosis of COPD. The APACHE II score was combined with several covariates (smoking and pCO2) to predict death at three years; the AUROC curve was 0.76. Missing values were considered normal. The gold standard for missing data in this situation is multiple imputation (section 4.2.2). The original APACHE II score was developed using the most severe measure of individual indices in the

previous 24 hours, but in this study admission indices were used, which may have reduced prognostic power.

A study by Connors et al.[79] modified the APACHE II score and included other indices such as functional status and cor pulmonale, to predict mortality at six months. The cohort included 1,016 patients from five hospitals, all of whom had an AECOPD and a PaCO2 of 50mmHg or more. The AUROC was 0.73, but this has not been externally validated.

The BAP-65 score was developed in a retrospective study of 88,074 patients with an AECOPD between 2004 and 2006.[208] The four valuables used in the model are Blood urea nitrogen, Altered mental state, and Pulse rate greater than 109 per minute, and age greater than 65 years. The model was internally validated using bootstrapping. The AUROC for hospital mortality was 0.72 and 0.71 for the derivation and validation cohort (the need for mechanical ventilation at 48 hours was a secondary outcome). Patients were identified using coding which is inaccurate, and the diagnosis of COPD was not confirmed by spirometry. Those with acute respiratory failure and pneumonia were not included, which are two of the strongest predictors of death. It is unclear why pH was not included as a predictor. The raw data suggests that pH is a strong predictor, as those in the derivation and validation cohort had a mortality of 12.1% and 11.7% (10 fold higher than the baseline risk) if their pH was < 7.2, and 6.7% and 6.6% if the pH was > 7.21- 7.30.

The performance of the score was confirmed in a validation dataset of 34,699 admissions which showed an AUROC curve was 0.77 for in-hospital mortality.[209] Patients were identified using coding data which is unreliable, and smoking history and confirmation of airflow obstructive was not obtained. Subsequently, Tabet et al. have assessed the BAP-65 score to predict mortality and the need for mechanical ventilation in 980 patients admitted with an AECOPD to two Lebanese hospitals over an eight-year period.[210] There is no mention of missing data, the study was retrospective (and so accurate recording of the Glasgow Coma Score was relied upon as part of usual practice) and only 980 patients were identified over an eight year period, suggesting that consecutive recruitment of patients did not occur. There is no mention of smoking history or spirometric confirmation of COPD.

CAPS was developed in a retrospective cohort of 8,527 patients with obstructive airways disease who were admitted to intensive care units or high dependency units.[202] Consequently, it was not designed to be applied to general admissions of patients with AECOPD. Eight physiological variables were included in the final model using logistic regression to determine the optimum number and type of variable to predict in-hospital morality. The AUROC curve was 0.72 in the derivation and validation cohort showing consistent performance, though discrimination was lower in patients with COPD and no history of asthma in the validation cohort (0.70). Rates of missing data are clearly reported, with missing data between 1 and 32% for variables included in model development. Urea, glucose, albumin and bilirubin had the highest missing data rates, reported as being between 14 and 32%, however, bilirubin and glucose were not included in the final model. Data is not provided on missing data for the overall score. Missing data was assumed to be normal which may negatively impact on the accuracy of risk assessment. The model was superior to the APACHE II and APACHE III scores.

The CAPS score was expanded upon in a prospective cohort study looking at asthma and COPD exacerbations requiring admission to the intensive care unit or high dependency unit.[197] This added eight more variables to the score, including diagnosis (COPD, asthma or both), gender, level of physical function, age and GCS (Glasgow Coma Score). The outcome was 6 month mortality with a AUROC curve of 0.75. A key strength of the research is that they measured the ability of clinicians to predict outcome, which is the default approach in the absence of a prognostic score. Clinicians had worse discrimination and markedly worse calibration than the model (see “4.2.11 Model assessment” for explanation of terms). The diagnosis of COPD was not confirmed by preadmission spirometry results, and smoking history is not reported. The performance of the model requires external validation to demonstrate the generalisability of the results. The complexity of the score may limit its use outside of the high dependency unit / intensive care unit.

The CURB-65 score is a retrospective study first developed and validated in patients with pneumonia. Data from three large prospective studies were combined, in which pneumonia had been confirmed with chest x-ray. Overall, patients with chronic lung disease comprised 35% of the entire cohort of 1,068 patients. The CURB-65 score has been assessed in patients with non-pneumonic AECOPD.[211] The study was

performed prospectively, which allowed for the collection of complete CURB-65 data in 252 consecutive admissions. Only 3 of 252 patients did not have outcome data, and were not included in the analysis. CURB-65 was a good predictor of 30 day mortality with a AUROC curve of 0.73, but was not a predictor of one year mortality. Most patients (74%) had COPD confirmed with preadmission spirometry, but the need for obstructive spirometry was not part of the eligibility criteria. A small number of patients had abnormal spirometry on follow up, but analyses with and without these patients were no different.

Roche et al. developed and validated a tool to predict in-hospital death.[43] All patients were reviewed by respiratory physicians to confirm the diagnosis of COPD. Patients requiring ICU monitoring and/or NIV were not included. The score included several clinical signs, including use of inspiratory accessory muscles and expiratory use of abdominal muscles. Such signs are subjective, and may require specialist expertise. The seniority and specialty of the clinician who assessed these signs is not provided. Despite this, the score showed good discrimination across 103 emergency departments in both validation and derivation cohorts, which shows that these signs can be reliably assessed. The population sample was randomly split into derivation and validation cohorts. This approach will tend to give over-optimistic results as the two datasets are very similar; non-random splitting is preferable to random splitting (though neither demonstrate external validity which requires an external validation cohort).[212] The score has not undergone external validation.

Stiell et al.[213] conducted a prospective cohort study in six emergency departments. Using multivariate analysis, high risk indices were identified which included acute ECG features of ischaemia and radiographic pulmonary congestion. It is questionable if such patients had a primary AECOPD, as these features suggest an alternate diagnosis. No validation study has been performed.

Quintana et al. performed a prospective study in 16 hospitals.[214] The derived score showed good discrimination, but no validation study has been performed. The score included subjective recognition of “use of inspiratory accessory muscles or paradoxical breathing”, so may be less universally applicable, especially in healthcare settings which lack specialist review within 24 hours of admission.[11, 151] Recruitment was lower than equivalent audit data [151] due to the need for written

patient consent which disproportionately excludes the lowest and highest risk patients.

### *1.3.3 Scores that predict readmission and long term mortality in patients with an AECOPD following discharge*

Clinicians are unable accurately to identify patients at particular risk of readmission.[215] A simple and accurate prognostic tool would help identify those who may benefit most from additional health and social care services, and this hopefully would translate into improved outcomes for patients and more efficient use of scarce resources. A condition-specific score to predict this outcome following hospitalisation for AECOPD has not been developed.

In this section, studies will be reviewed that aimed to predict readmission or death (or readmission alone) in patients following hospitalisation for AECOPD. Inclusion of studies that look for "death without readmission" as a combined outcome with "readmission" is appropriate because, in patients who die outside hospital, earlier recognition of deterioration is likely to have led to readmission.

Within the CODEX study,[216] the ADO, BODEX, CODEX and DOSE scores were all assessed for their performance at predicting the combined outcome of readmission or death without readmission in patients with COPD (Table 1.4). However, most were originally developed to predict death (ADO [217] and BODEX [218]) or health status (DOSE [219]) and all offer only modest prediction of readmission/ death without readmission. The performance of CODEX was superior to the updated ADO and BODEX score, with a trend towards better performance than DOSE, but this comparison was in the CODEX derivation population.[216] Derivation studies bias results in favour of the derived tool, in this instance CODEX, and so comparison in an external validation cohort is required.

ADO was developed to predict death in two cohorts: a group of patients post rehabilitation in secondary care, and a group of patients admitted to hospital due to an AECOPD.[217] It requires only three indices to score: age, breathlessness, and the degree of airflow obstruction. Obtaining recent data on FEV1 to score ADO may be challenging. In the 2015 British Thoracic Society (BTS) national audit, only 46% of patients had spirometry recorded in the notes in the last five years.[11] This score was

subsequently validated, and adjusted, in a large international study of 10 cohorts in primary, secondary and tertiary care looking at three year mortality.[220] Its performance at predicting 90 day readmission or death was assessed in the CODEX study. It performed poorly, though it is worth reiterating that it was not designed to predict readmission.

The BODEX score was developed in a prospective study of 185 patients who were followed up, on average, for 36 months.[218] It measures BMI, airflow obstructive, the degree of breathlessness and exacerbation frequency and has been adapted from the BODE index. The BODEX had an AUROC curve of 0.74 for predicting all-cause mortality, and showed similar prognostic power to the BODE index. BODEX may be easier to calculate than the BODE index; the latter requires measurement of exercise capacity which may be difficult to assess whilst a patient is exacerbating. The number of patients in this study was relatively small, and no power calculation was provided; the study may have been underpowered to look at all-cause mortality, though this is less of an issue for readmission which is a more frequently occurring outcome.

| | Measured indices | | | | | | | | | | | Study population and primary outcome | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | BMI | Comorbidity* | Dyspnoea † | Airflow obstruction ‡ | Exacerbations x | Severe exacerbations § | Smoking status | Length of stay | Acuity ‖ | ED visits last 6 months | COPD specific? | Stable-state or exacerbating at inclusion | Outpatients or admitted patients | Primary outcome | AUROC for death or readmission[216, 221] |
| ADO[217] | √ | | | √ | √ | | | | | | | √ | Both | Both | Death | 0.58 |
| BODEX[218] | | √ | | √ | √ | | √ | | | | | √ | Stable | Outpatients | Death | 0.61 |
| CODEX[216]# | √ | | √ | √ | √ | | √ | | | | | √ | AECOPD | Mostly admitted | Death or readmission | 0.67 |
| DOSE[219] | | | | √ | √ | √ | | √ | | | | √ | Unclear | Outpatients | Health status¶ | 0.64 |
| LACE[221] | | | √ | | | | | | √ | √ | √ | X | n/a | Admitted | Death or readmission | 0.68◊ |

*Charlson comorbidity index, †mMRC dyspnoea score, ‡Forced expiratory volume in one second per cent predicted, xPatient reported AECOPD in previous year, §AECOPD in previous year requiring admission or ED attendance, ‖Elective or emergency admission, #uses age adjusted Charlson index, ¶measured by the clinical COPD questionnaire, ◊30 day death or readmission. ED= Emergency Department

*Table 1.4: Tools that have been used to predict readmission in AECOPD*

The AUROC curve for BODEX in predicting 90 day readmission or death was 0.61 in the CODEX study.

The CODEX study was developed in several hospitals, the population is clearly described, and it is superior to ADO and BODEX, with a higher AUROC than DOSE, for 90-day readmission or death. CODEX was developed and validated in previous cohort studies, but the gold standard for derivation studies is prospective cohort studies. The validation cohort comprises a single hospital, and it is unclear if this site was included in the derivation study. Only geographical validation (validation at sites not included in model development) demonstrates the generalisability of a score.[212]

The aim of the CODEX study was to create a tool for patients discharged from hospital, but 11.5% were not admitted. In the derivation study, only 91.9% had death data at 3 months, and the original ESMI paper (from which the model was created)[222] reports readmission data in “484 surviving patients” (84% of survivors). It is unclear how missing data was handled. Information is lacking on model development and the selection of indices. The predictors of death reported on multivariate regression from the original ESMI study do not include all CODEX indices, and no multivariate analysis is reported related to readmission.[216, 222] Model performance is appropriately assessed, but there is no mention of calibration, and, as with the LACE index, CODEX required patient consent, and included the Charlson index, compromising ease of use at the bedside. For 90 day readmission or death, the performance of CODEX in its derivation cohort was superior to the updated ADO and BODEX, with a trend towards better performance than DOSE amongst inpatients with AECOPD.

The DOSE index was derived in 375 patients with COPD in primary care to predict health status. It comprises of four indices: Dyspnoea, airflow obstruction, smoking status and exacerbation frequency. Exacerbations were reported by patients, and confirmed from primacy care records. This differs from the BODEX and CODEX score that only score for exacerbations that require hospital admission. The tool was validated in datasets from Holland, London and Tokyo. In this study, there was no relationship between the DOSE index and hospital admission, though data was only available in 175 patients. In the CODEX study, DOSE was shown to be a modest predictor or readmission or death.

LACE was developed in all emergency and elective admissions [223] and was developed for 30-day (and not 90-day) outcome. There are several generic tools to predict readmission, most of which are not considered here. The LACE score was selected as it showed better discrimination than other generic tools that can be used in the acute setting, and is used in some UK hospitals. In principle, a generic tool is preferable to a specific tool if it offers equal performance.

The study population is adequately described, follow-up was good (95.6% population), model development robust and validation was performed in a separate, large cohort. The main limitations of the LACE index are: a) that readmission is self-reported; b) it requires the full Charlson index to be calculated (which includes many indices and is complex to calculate at the bedside); and c) the analysis was performed in a previous multicentre prospective cohort study for which patients had to give informed consent, have a telephone, be cognitively intact and not be a nursing home resident, reducing the generalisability of the results.

# Chapter 2 Review and meta-analysis of Hospital at Home compared to usual hospital care.

## Chapter introduction

The DECAF implementation study undertaken as part of this thesis compared Hospital at Home (HAH) to usual care for patients with low risk AECOPD (Chapter 7). Prior to the initiation of this study, we performed a systematic review and meta-analysis to assess the safety, efficacy and cost of Early Supported Discharge (ESD) and HAH which forms this chapter.

## 2.1 Background

Hospital at Home (HAH) "provides active treatment by health care professionals in the patient's home for a condition that would require acute hospital inpatient care." [224] Early Supported Discharge (ESD) [225-227] aims to shorten length of stay. However, the definition of HAH and ESD varies across healthcare systems; in some settings HAH refers exclusively to admission avoidance,[228] whilst elsewhere HAH simply implies a higher level of care than ESD.[229] In published RCTs in COPD, the terms HAH and ESD are variably used to refer to similar services, and individual studies often include schemes aimed at both admission avoidance and shortening length of stay. Such schemes also vary substantially in the level of clinical and social support provided. Loan equipment, such as oxygen concentrators and nebulisers, is typically available and patients are supported by visiting respiratory specialist nurses, with medical supervision. Some services will provide intravenous therapy and short-term social services input.

ESD/HAH may encourage greater mobility and independence, and should include education on self-management, which may improve outcomes. Contrary to national guidelines, the 2008 UK national audit showed that most hospitals in the UK do not offer ESD/HAH.[150] The 2015 UK national audit did not report the proportion of patients receiving ESD, and only presented the proportion discharged under the care of COPD / ESD or equivalent scheme.[11] In AECOPD, previous meta-analyses concluded that ESD/HAH is safe.[158, 188, 230] Two recent meta-analyses were published at similar times, but differed in their conclusions in regard to readmission risk,

reflecting differences in trial selection and interpretation of the event rates and risk of bias.[158, 231]

It is advised that treatment reviews and meta-analyses are updated bi-annually.[232] Our meta-analysis includes an RCT published subsequent to earlier reports and compares the efficacy of ESD/HAH to usual care with respect to mortality, readmission and cost. We describe how the benefit of ESD/HAH depends on whether return to hospital during the period of acute care is considered a readmission. In contrast to other studies, in our primary analysis we excluded patients lost to follow up. Including such patients assumes their event rate is zero and introduces bias, particularly when there are substantial differences in the proportion lost to follow up between arms. Some RCTs included patients who did not present through accident and emergency (A&E) departments (or equivalent) [233] or were not triaged for admission at the time of randomisation (i.e. patients in UC were discharged directly from A&E).[234] Such patients are likely to be experiencing milder exacerbations and may have been well enough for immediate discharge from A&E; to ensure consistency and avoid bias they have been excluded.

We also review the structure of ESD/HAH schemes, and assess costs, whilst recognising the problems of comparing cost across different countries and healthcare structures.

## 2.2 Methods

### *2.2.1 Selection criteria and outcome measures*

RCTs of ESD/HAH compared to UC in patients with a primary diagnosis of AECOPD, presenting to A/E or equivalent and triaged for admission, were considered for inclusion. Studies were only included if, without ESD/HAH, all patients would have been admitted; patients could receive ESD/HAH directly from A&E provided this criterion was met. The reported outcomes are: number of patients experiencing one or more readmissions, mortality and cost.

### *2.2.2 Search strategy and selection of studies*

The pre-planned search strategy included combining search terms COPD, pulmonary disease, lung disease, respiratory disease, airway disease, airway obstruction,

airflow obstructive, hospital at home, home care, home base, home support, early supported discharge, early discharge, hospitalisation, hospital base, hospital care, usual care and acute care. Searches using all available date ranges were conducted on databases including Medline, Embase, Amed, Cinahl and HMIC and in web-based libraries (e.g. British Library, United States National Library of Medicine and Institute of Health Economics), relevant national organisations (e.g. NICE), BTS, Global Initiative for Chronic Obstructive Lung Disease) and current research registers (e.g. Clinical Trials Register, Current Controlled Trials Register, Centre for Health Economics). Hand-searching of relevant journals was performed to ensure abstracts and conference proceedings were retrieved and the bibliography of each trial was screened to identify any additional RCTs not retrieved in the initial search. All searches were completed by November 2014. Abstracts were screened and, if potentially eligible, full papers reviewed. All reports identified were independently assessed by three reviewers. Disagreements were resolved with discussion.

### *2.2.3 Methodological quality assessment (Risk of bias)*

Bias was assessed and reported using The Cochrane Collaboration six core risks of bias [235]. Bias was assessed independently by at least 2 reviewers for all trials.

### *2.2.4 Data extraction*

Data were extracted onto a data abstraction table. When available, characteristics of the trial (e.g. author, year of publication and journal citation, country, setting, design, methodology), study population (e.g. total number enrolled, patient characteristics, age, other important baseline characteristics), interventions (ESD/HAH and UC details), risk of bias in trials, duration of follow-up and outcomes (including outcome definition, unit of measurement) were recorded. Where possible, all data extracted were those relevant to an intention-to-treat analysis. The time points at which outcomes were collected and reported were noted. All authors were contacted to clarify reported data.

### *2.2.5 Statistical analysis*

Trials with similar outcome measures were pooled in meta-analyses. For time to event (hospital readmission) data, it was not possible to extract the log of the hazard ratio [log(HR)] and its standard error from trial reports or approximate using the

methods of Parmar et al.[236] Consequently, we analysed readmission outcomes at the specific time points reported to estimate the risk ratio (RR). A fixed effect risk ratio was calculated for each trial using the Mantel-Haenszel approach ($RR_{MH}$) and these were pooled in sub-groups of trials with similar durations of follow up. Fixed effect models were chosen (unless otherwise stated) as most trials were similar in methodology, setting and population.

Ninety-five percent confidence intervals (CI) were calculated for the summary effect size and $p<0.05$ was deemed statistically significant. Heterogeneity between trials was assessed by visual inspection of forest plots and estimation of the percentage heterogeneity between trials that cannot be ascribed to sampling variation.[237] If there was evidence of substantial heterogeneity, potential reasons for this were assessed.

### 2.3 Results

From the literature search, 1,689 references were screened. Including hand-searching, we identified 52 unique references that were retrieved in full. Eight RCTs were included, all published within the last fifteen years. The majority of excluded studies were not RCTs or did not involve a comparison of ESD/HAH and usual care. Seven RCTs [159, 225-227, 229, 238, 239] were included in the mortality and readmissions review. Four trials included a cost analysis.[159, 226, 240, 241] One RCT published separate clinical [227] and cost [241] analyses. The process of trial selection is shown in the Figure 2.1.

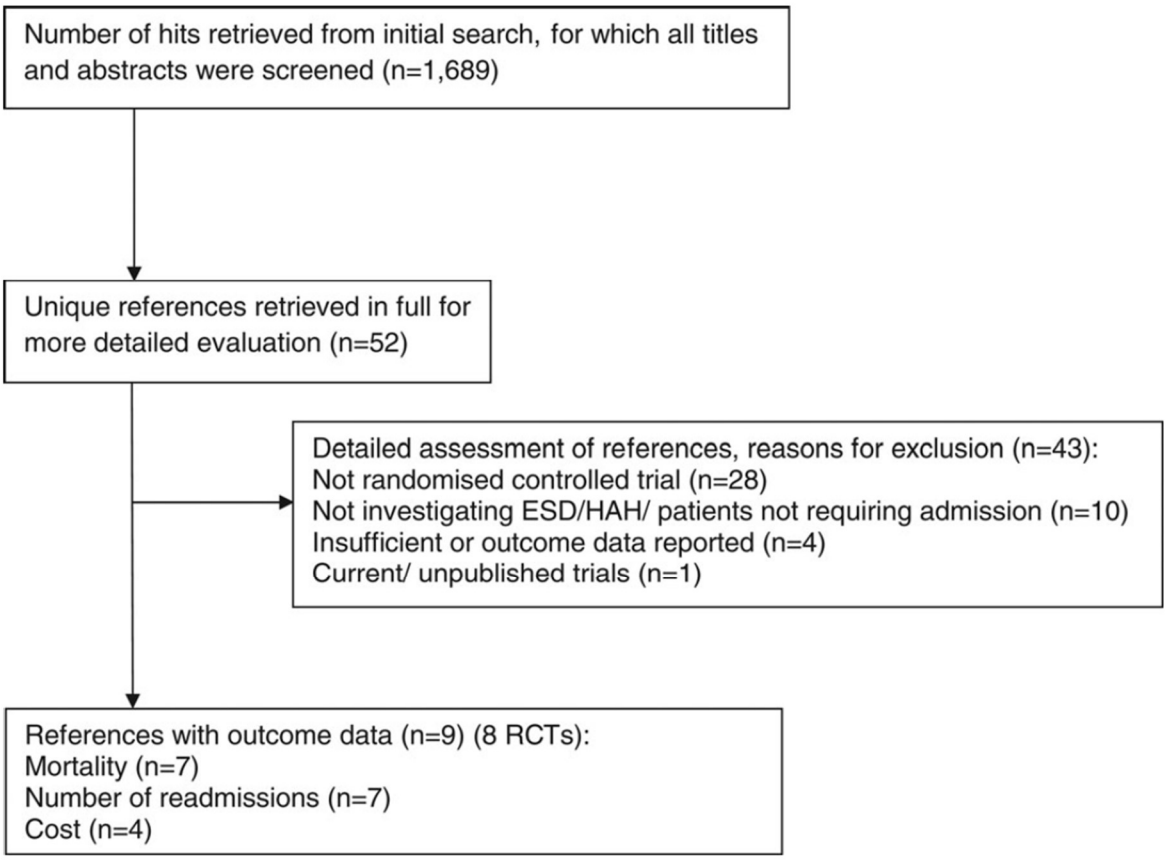


*Figure 2.1: Results of the search strategy and reasons for excluding trials form the review*

### *2.3.1 Description of selected studies*

Four RCTs were conducted in the UK,[225, 226, 229, 238] two in the Netherlands,[227, 239, 241] one in Australia [240] and one in Italy.[159] The inclusion and exclusion criteria are summarised in Table 2.1. All trials randomised patients to ESD/HAH or UC and provided some description of the ESD/HAH service offered. Clinical responsibility for patients in the ESD/HAH arm remained with the hospital team until discharge from the scheme, with the exception of one trial in which the General Practitioner provided care out-of-hours and for "other medical problems".[225] Reported outcomes include mortality,[159, 225-227, 229, 238, 239] readmissions,[159, 225-227, 229, 238, 239] cost,[159, 226, 240, 241] length of in-hospital stay for UC [225, 226, 229, 238, 239] and ESD/HAH,[159, 225, 239] total length of care (in hospital and at home) for ESD/HAH,[159, 225, 226, 229, 239] patient preference,[226, 229] and service satisfaction.[159, 226, 229, 240]

### *2.3.2 Methodological quality of included studies*

Seven trials [159, 225-227, 229, 238, 239] reported the method of randomisation. Two trials [226, 227] employed computer-generated random numbers and three trials used random numbers.[159, 225, 239] Four trials reported allocation concealment using sealed envelopes.[227, 229, 238, 239]

Blinding of participants and treating clinicians is not possible. Only one RCT was single blind (Ricauda et al.);[159] clinicians who performed baseline assessments and the researcher assessing outcomes were unaware of allocation. For subjective outcomes (e.g. quality of life) the risk of bias was considered moderate for Ricauda et al., and high in the remaining trials. Mortality is an objective outcome with low risk of bias regardless of blinding.[235] Readmission was regarded as objective in the Cochrane 2012 meta-analysis.[158] On balance, we agree, although subjective influences may affect patient behaviour.

Six trials [159, 225-227, 229, 238] included patients who were lost to follow up, withdrew consent or were excluded from analysis (e.g. due to incorrect diagnosis). In total, 726 and 688 patients were included in the mortality and readmission analyses respectively.

The baseline characteristics of patients and risk of bias, other than blinding, in the included trials are shown in Table 2.2. The recruitment process and structure of ESD/HAH services is outlined in Table 2.3.

| Study | Additional AECOPD inclusion criteria | Exclusion criteria | | |
|---|---|---|---|---|
| | | Clinical indices | Co-morbidities | Demographic and social |
| Cotton 2000 | Not reported | Acidaemia ($H^+$>45 nM)<br>Pneumonia or lung cancer on CXR | Other medical conditions, including: Chest pain suggesting MI or PE<br>Anaemia<br>Gastrointestinal or endocrine disorders<br>Musculoskeletal disease<br>Nausea, vomiting and dehydration | Non-Glasgow resident<br>Homeless or Hostel dwellers<br>Unable to consent<br>No telephone<br>Discharge already planned<br>Primary social admission |
| Davies 2000 | $FEV_1$<80% predicted<br>$FEV_1$/FVC<70%<br>HR<100, SBP>100<br>pH>7.35, $PaO_2$>7.3, $PaCO_2$<8<br>WCC 4-20x10g/l<br>MMSS>7 | Marked use of accessory muscles Uncontrolled LVF<br>Acute changes on echocardiogram<br>Need for intravenous therapy<br>Suspected malignancy, pneumothorax, or pneumonia on CXR | Asthma | Require full-time nursing care |
| Skwarska 2000 | Not reported | Impaired LOC or acute confusion<br>pH<7.35<br>Acute changes on CXR | Other serious medical conditions, e.g.:<br>Ischaemic cardiac pain<br>Cardiac failure | Social reasons |
| Ojoo 2002 | $FEV_1$/FVC<70%<br>Previous $FEV_1$ reversibility to salbutamol<15%. | Acidosis or new type 2 respiratory failure<br>Cor pulmonale<br>Acute changes on CXR | Concomitant medical conditions requiring medical admission. | Age >18; no telephone<br>Resident >15 miles from hospital Poor home support or lives alone |
| Nissen 2007 | $FEV_1$<80%<br>$FEV_1$/FVC<70% with lack of reversibility 30 mins after bronchodilator therapy $PaO_2$>7.3 | Need for intravenous therapy<br>Need for NIV or ventilation<br>ECG changes<br>Pneumonia on CXR | Unstable heart failure<br>Confusion<br>Other severe medical disorder | Inadequate social conditions<br>No telephone<br>Lives outside the hospital area<br>Previously participated in the study<br>Participant in another study |
| Ricauda 2008 | Not reported | $PaO_2$<6.7; pH<7.35 or >7.55<br>Suspected PE or MI<br>MMSS<14 (severe dementia) | Severe renal impairment<br>Cancer (not skin)<br>Hepatic failure | No family or social support<br>Age<75; no telephone<br>Living outside catchment area |
| Utens 2012 | 10 pack years of smoking | Impaired LOC or acute confusion<br>Indication for admission to ICU or NIV<br>Acute ECG changes; pneumonia on CXR<br>By day 3: no decrease in physical complaints<br>IV therapy or newly prescribed oxygen therapy<br>BM ≥15 mmol/l (and unable to self-regulate) | Major uncontrolled co-morbidity including heart failure and malignancy<br>Mental disability including dementia<br>Active alcohol and/or drug abuse | Age <40<br>Lives outside care region<br>Inability to understand<br>Lack of home care<br>By day 3, independent toileting |

Key: AECOPD – Acute exacerbation of COPD; $FEV_1$ – forced expiratory volume in 1 second; MMSS – Mini mental state score; $FEV_1$/FVC – $FEV_1$/forced vital capacity; HR – heart rate; SBP – systolic blood pressure; $PaO_2$ - partial pressure of oxygen in arterial blood; $PaCO_2$ – partial pressure of carbon dioxide in arterial blood; WCC – white cell count; LOC – level of consciousness; LVF – left ventricular failure; CXR – chest x-ray; MI – myocardial infarction; PE – pulmonary embolus; ICU – intensive care unit; NIV – non-invasive ventilation.

*Table 2.1: Inclusion and exclusion criteria for trials included in the mortality and readmission analysis*

| Study | | Number of patients | Age | $FEV_1$ | $PaO_2$ | $PaCO_2$ | Risks of bias |
|---|---|---|---|---|---|---|---|
| Cotton 2000 | ESD/HAH | 41 | 65.7 (1.6)* | 0.95(0.08) 41 (3)*% | 8.5 (0.4)* | 6.0 (0.3)* | Follow up method varied. Some patients had face-to-face contact, others did not. More withdrawals in ESD/HAH. |
| | UC | 40 | 68.0 (1.2)* | 0.94(0.06) 44 (3)*% | 9.2 (0.4)* | 5.5 (0.2)* | |
| Davies 2000 | ESD/HAH | 100 | 70(8) | 0.82(0.37) 36.1(17.2)% | 9.7 (2.9) | 5.2 (1.0) | Methods of sequence generation and follow up not reported. Higher rate lost to follow up in usual care group. |
| | UC | 50 | 70(8) | 0.76(0.28) 35.1(14.7)% post bd | 9.0 (1.2) | 5.2 (0.8) | |
| Skwarska 2000 | ESD/HAH | 122 | 68.5 | 0.77 | >7 (91.6%) | Not reported | Allocation concealment unclear. Unequal proportions lost to follow-up. |
| | UC | 62 | 69.9 | 0.66 | >7 (90%) | Not reported | |
| Ojoo 2002 | ESD/HAH | 30 | 69.7 | 1.0 (0.38) | Not reported | Not reported | Random sequence generation method not reported. |
| | UC | 30 | 70.1 | 0.85 (0.34) | Not reported | Not reported | |
| Nissen 2007 | ESD/HAH | 22 | 69 (10.3) | 1.5 at admission 40.1 (17.7)% | 9.2 (1.4) | 5.5 (0.7) | Sequence generation not described in article; author confirmed sealed envelopes were used. |
| | UC | 22 | 69 (10.1) | 1.4 at admission 33.7 (10.0)% | 8.9 (1.3) | 5.5 (0.81) | |
| Ricauda 2008 | ESD/HAH | 52 | 80.1 (3.2) | 0.92(0.4) | 9.2 (2.5) | 5.9 (1.6) | Education only provided within the ESD/HAH arm. |
| | UC | 52 | 79.2 (3.1) | 1.04(0.5) | 8.7 (1.9) | 6.1 (1.6) | |
| Utens 2012 | ESD/HAH | 70 | 68.3 (10.3) | Not reported | 9.0 (1.1) | 5.2 (0.7) | Unequal proportions of patients lost to follow up. |
| | UC | 69 | 67.8 (11.3) | Not reported | 9.4 (1.8) | 5.0 (0.8) | |

Values are given as means (standard deviations). Key: * – standard error; † – 8 weeks post discharge; $FEV_1$ – forced expiratory volume in 1 second; $PaO_2$ – partial pressure of oxygen in arterial blood; $PaCO_2$ – partial pressure of carbon dioxide in arterial blood; ESD/HAH – early supported discharge/ hospital at home; UC – usual care; bd – bronchodilator.

*Table 2.2: Baseline characteristics of patients and risks of bias in trials included in the mortality and readmission analysis*

| Study | ESD/ HAH recruitment structure | | | Structure of ESD/ HAH services | |
|---|---|---|---|---|---|
| | When? | Where from? | Who by? | Intervention | Additional services provided |
| Cotton 2000 | Monday to Friday mornings Discharge next working day after recruitment | Medical Wards | Respiratory specialist nurse, respiratory middle grade doctor | Nurse visited morning after discharge and then as required: median 11 visits over median 24 days.<br>GP out of hours care. | Nebulised bronchodilators, oxygen cylinders.<br>(Additional social support or community physiotherapy not provided). |
| Davies 2000 | Monday to Sunday 08.00 to 18.00 | Accident and Emergency | Respiratory specialist nurse;<br>Respiratory Doctor | Nurse escorted home, visited mornings and evenings for first 3 days, then as required: mean (SD) 11 (3) home visits.<br>District nurse cover evenings and overnight. | Social support (cleaning, shopping, W&D, MOW, day and night-sitters). Nebulised bronchodilators, oxygen concentrator. |
| Skwarska 2000 | Monday to Friday 09.00 to 17.00 | Accident and Emergency; Medical Admissions Unit | Medical Registrar; Acute Respiratory Assessment Service; Respiratory Consultant | Nurse visited next day and then 2–3 day intervals: mean 3.8 nurse visits. Weekly meeting with consultant. Medical advice available daily from on-call respiratory team | Nebulised bronchodilators, oxygen concentrator. |
| Ojoo 2002 | Monday to Thursday 09.00 to 17.00 Discharge within 48hrs | Medical Chest Unit | Respiratory outreach nurses | Nurses complete daily progress and symptoms score charts. The medical chest unit were available out of hours by phone. | Oxygen therapy and nebulised bronchodilators. |
| Nissen 2007 | Discharged from hospital within 48 hours of admission | Not reported | Project nurses | Chest physiotherapy (assumed provided in hospital). Mean 2.6 (1-6) home visits; mean 1.5 hours nurse visit; mean 2.1 (0-6) phone contacts; mean phone time 15 mins; average time per patient= 4 hours 15 mins. | Oxygen therapy. No additional social support. |
| Ricauda 2008 | Monday to Sunday. Mean time in emergency department=15.5 hrs | Emergency department | Not reported | 3 Geriatricians, 13 nurses, 3 physiotherapists, 1 social worker, 1 counsellor. Daily meetings. 7 day service. Physician and nurse visit day after discharge, then daily nurse visit (mean=14.1) and physician visit every 2–3 days (mean=9.9). | Oxygen therapy, nebulised bronchodilators, intravenous antibiotics and steroids. |
| Utens 2012 | Screened for inclusion day 1. Randomised day 3 of admission, home on day 4 | Not reported | Community nurses; Respiratory Physician | Community nurses visited or contacted patient at least once daily on day of discharge and for 3 consecutive days. | 24 hour telephone access to hospital respiratory ward for emergencies. |

Key: GP – General Practitioner; W&D – washing and dressing; MOW – meals on wheels.

*Table 2.3: Recruitment process and structure of care for ESD/ HAH services in trials*

### *2.3.3 Organisational structure of ESD/HAH schemes*

Two trials offered ESD/HAH from Monday to Friday only [225, 226] and two trials provided a seven day service.[159, 238] Utens et al.,[227] Nicholson et al.[240] and Ojoo et al.[229] provided telephone support seven days a week, but it is unclear if patients were visited at the weekends. Patients were recruited from the A&E department,[159, 238, 240] or from general or speciality wards.[225-227, 229, 239]

In most trials, patients returned home within 24 [159, 226, 238] to 48 [229, 239] hours of hospital admission. Patients were usually visited at home within 24 hours of discharge,[159, 225-227, 238] though Nicholson et al.[240] and Nissen et al.[239] were unclear in this regard.

Most ESD/HAH services involved home visits from hospital-based nurses with respiratory experience, but not physicians.[225, 226, 229, 238] In one trial of patients aged 75 years and over, home visits were performed by both geriatricians and nurses; although not respiratory specialists, they are experienced in delivering HAH treatment.[159] In other trials, visits were performed by "generic community nurses"[227] or community based nurses and General Practitioners.[240] Within most ESD/HAH services, the nurses could obtain medical advice from respiratory physicians.[225, 226, 238, 240] Out of hours support varied, and included district nurses,[238] out of hours GP,[225] the on call respiratory team / medical chest unit / respiratory ward,[226, 229, 242] or the HAH team (which included nurses and physicians);[159] in one study this information was unclear.[239] Five trials [159, 225, 226, 238, 239] reported the number of home visits, which ranged from a mean of 2.6 visits,[239] to 14.1 visits from nurses and 9.9 visits from geriatricians.[159] The trial with the least number of nurse home visits also offered a telephone support service. The mean (SD) number of telephone calls from patient to nurse was 0.76 (1.34) and from nurse to patient was 1.56 (1.31).

Two trials offered patient and carer education.[159, 229] including recognition and management of AECOPD, to the ESD/HAH group only. Other support offered includes social support,[159, 238] physiotherapy,[159, 239] and counselling and occupational therapy.[159]

### *2.3.4 Mortality*

Meta-analysis of seven RCTs,[159, 225-227, 229, 238, 239] assessing 726 participants showed a trend towards lower risk of death within 2 to 6 months favouring ESD/HAH ($RR_{MH}$ = 0.66, 95% CI: 0.40-1.09, p = 0.10; Figure 2.2). The percentage of the variability in effect estimates due to heterogeneity rather than sampling error (chance) was not important ($I^2$ = 0%).

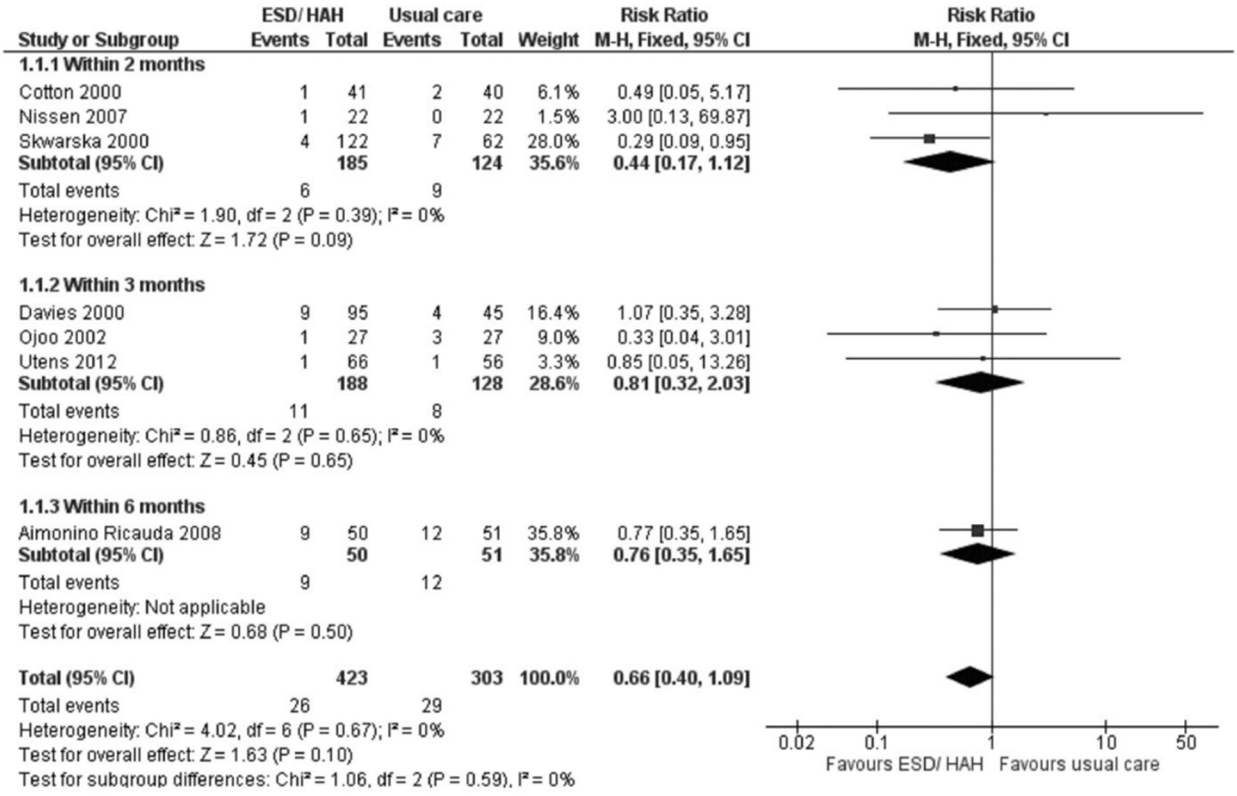


*Figure 2.2: Forest plot comparing ESD/HAH to usual care for mortality*

The results using a random effects model were similar ($RR_{MH}$ = 0.67, 95% CI: 0.40-1.11, p = 0.12), which suggests a small amount of between trial variation. To investigate the possibility of publication bias, the analysis was performed only including the largest trials, which did not reduce the treatment effect but widened the confidence interval (0.60, 95% CI: 0.28-1.25, p = 0.29).[226, 227, 238] We performed a sensitivity analysis excluding the trial with the most select population (patients aged 75 and over) ($RR_{MH}$ = 0.60, 95% CI: 0.32-1.16, p = 0.13).[159] Finally, the analysis was repeated including all patients lost to follow-up (assuming zero event rate) to allow comparison to previous meta-analyses which adopted this approach ($RR_{MH}$ = 0.67, 95% CI: 0.41-1.10, p = 0.11).[158, 231]

### *2.3.5 Readmissions*

Meta-analysis of seven RCTs,[159, 225-227, 229, 238, 239] assessing 688 participants, assuming return to hospital during ESD/HAH was not a readmission, showed ESD/HAH was associated with a lower risk of readmission within 2 to 6 months than UC ($RR_{MH}$ = 0.74, 95% CI: 0.60-0.90, p = 0.003). This, and the time periods for readmission, are shown in Figure 2.3.

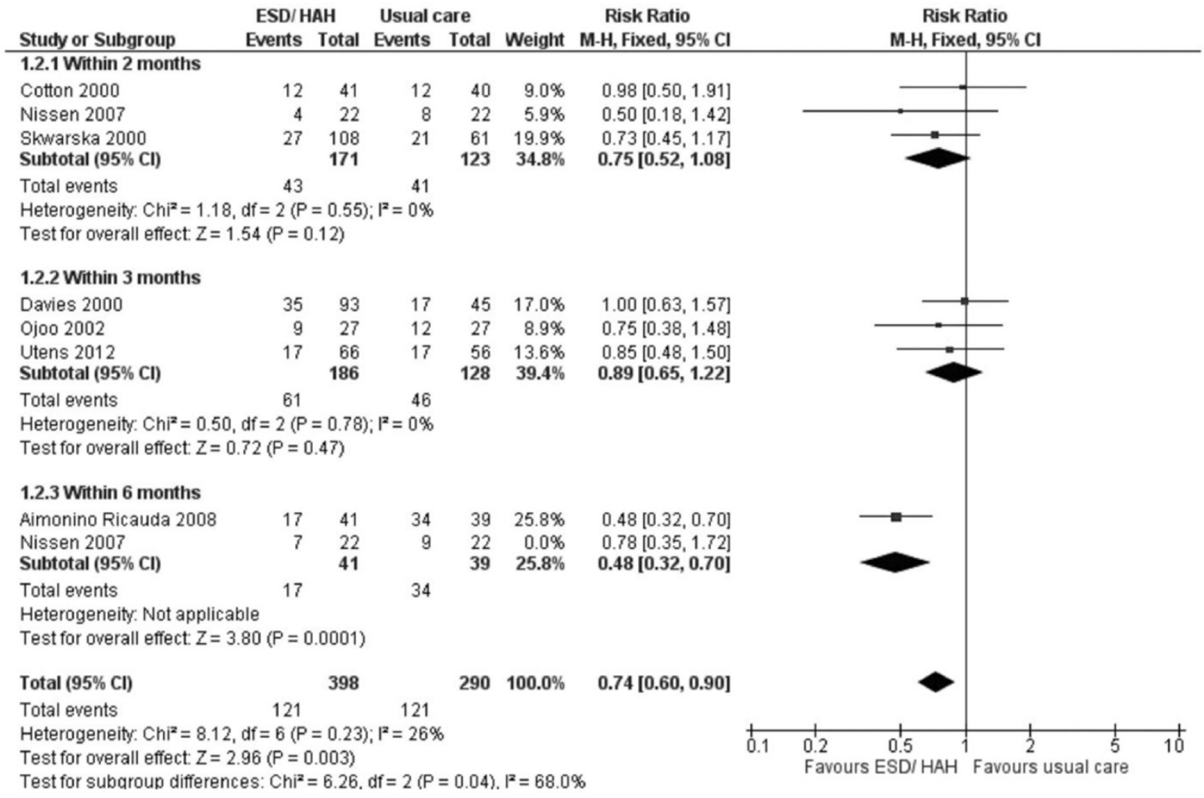


*Figure 2.3: Forest plot comparing ESD/HAH to usual care for proportion of admissions with return to hospital not classed as a readmission*

The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was $I^2$ = 26%. An analysis with random effects was similar ($RR_{MH}$ = 0.72, 95% CI: 0.57-0.92, p = 0.010).

The results were not robust to a sensitivity analysis that excluded the trial of Aimonino Ricauda et al.[159] in which patients were limited by age (greater or equal to 75 years) ($RR_{MH}$ = 0.83, 95% CI: 0.65-1.05, p = 0.11, $I^2$ = 0%).

The benefit was also not seen when including all trials with return to hospital during the period care within ESD/HAH classed as a readmission ($RR_{MH}$ = 0.84; 95% CI 0.69-1.01, p = 0.07; Figure 2.4).

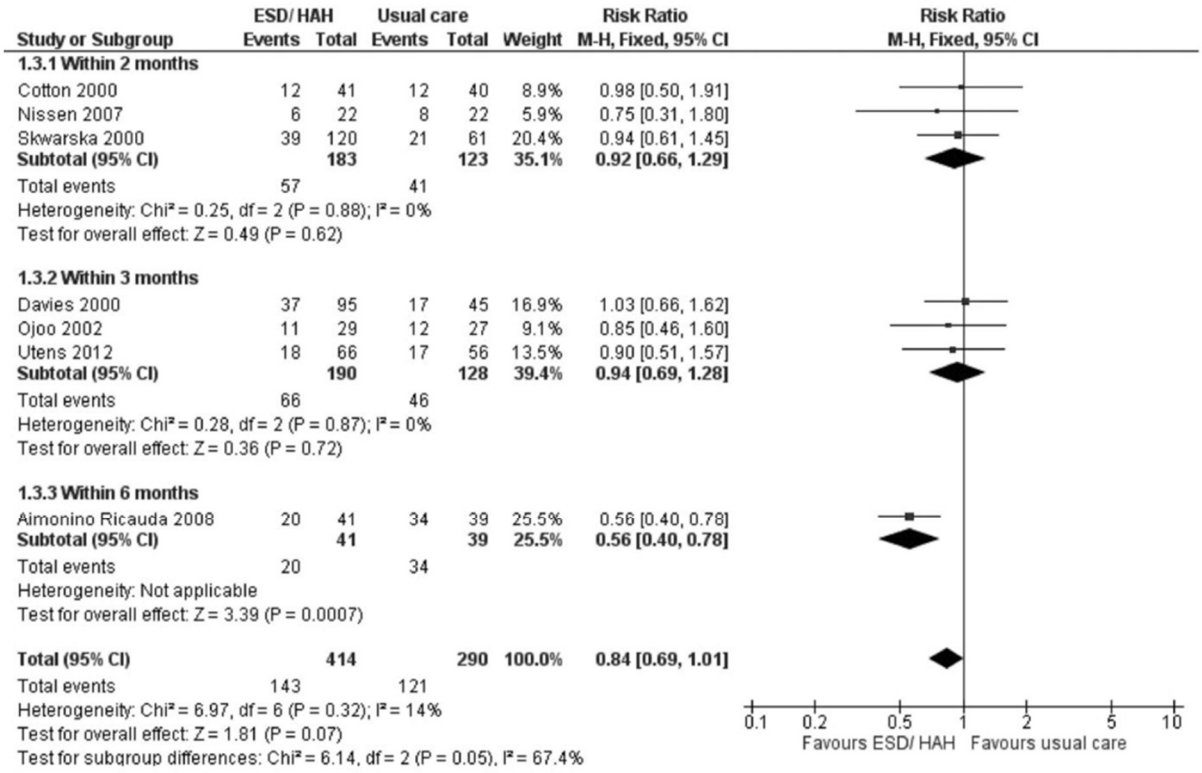


*Figure 2.4: Forest plot comparing ESD/HAH to usual care for proportion of readmissions including return to hospital as a readmission*

Finally, the analysis was repeated including patients lost to follow up. Once again ESD/HAH was associated with fewer readmissions ($RR_{MH}$ = 0.75, 95% CI: 0.61-0.93, p = 0.007), but not if return to hospital during ESD/HAH was considered a readmission ($RR_{MH}$ = 0.88 95% CI: 0.72-1.07, p = 0.21).

A detailed description of the numerator and denominator used for the readmission and mortality risk is shown in Table 2.4.

| Study | Readmitted / at risk patients | | Died / at risk patients | | Notes | Further information provided by author? | Lost to follow up? |
|---|---|---|---|---|---|---|---|
| | ESD/ HAH | UC | ESD/ HAH | UC | | | |
| Cotton 2000 | 12 / 41 **12 / 41** | 12 / 40 | 1 / 41 | 2 / 40 | Readmission and mortality data analysis as reported in study. | Clarification on definition of readmission, and exclusions and withdrawals. | Nil reported |
| Davies 2000 | 35 / 93 **37 / 95** | 17/ 45 | 9 / 95 | 4 / 45 | Two patients died within 14 days in ESD/HAH, both developed pneumonia, not visible on admission CXR, and returned to hospital before death. Denominator reduced in ESD/HAH and UC for patients with missing data for readmission and mortality. | Confirmed 14 day period defined as the period of acute care and additional details regarding mortality. | 5 in ESD/HAH 5 in UC |
| Skwarska 2000 | 27 / 108 **39 / 120** | 21 / 61 | 4 / 122 | 7 / 62 | In UC one patient died in acute period so removed from denominator for readmission. In ESD/HAH, twelve patients readmitted during hospital at home period, who were not analysed as readmissions so subtracted. | Mortality and readmission data confirmed with author. On review of the data, author confirmed that two patients in ESD/HAH were not included in the readmission analysis (subtracted from denominator). | Nil reported |
| Ojoo 2002 | 9 / 27 **11 / 29** | 12 / 27 | 1 / 27 | 3 / 27 | In UC readmission rate reported as 44.4% (12/27). ESD/HAH readmission rate 33.3%. As 27 followed up, number of events= 9. Of three patients excluded from ESD/HAH analysis, authors report two patients returned to hospital during ESD/HAH. | No. | 3 in ESD/HAH 3 in UC |
| Nissen 2007 | 4 / 22 **6 / 22** | 8 / 22 | 1 / 22 | 0 / 22 | No deaths during the acute period. No patients lost to follow up. | Detailed information provided on readmission and return to hospital data. Two patients who were admitted during ESD/HAH were included in the analysis, and were not readmitted during follow up, so denominator not adjusted. | Nil reported |
| Ricauda 2008 | 17 / 41 **20 / 41** | 34 / 39 | 9 / 50 | 12 / 51 | Three patients returned to hospital during ESD/HAH, not termed readmissions. Unable to clarify if these 3 patients were readmitted during follow up period. | No. | 2 in ESD/HAH 1 in UC. |
| Utens 2012 | 17 / 66 **18 / 66** | 17 / 56 | 1 / 66 | 1 / 56 | Patients died during the follow up period, not acute period, so denominator not adjusted. | Detailed information provided on follow up. UC- of 16 lost to follow, 3 known to be readmitted. ESD/HAH- of 6 lost to follow up, 2 known to be readmitted prior to being "lost". | 4 in ESD/HAH 13 in UC |

In some instances, patients who returned to hospital during EDS/HAH were not included in the authors' analysis, so they have been removed from both the numerator and denominator. Patients who died during the acute period are not at risk of readmission and have been removed. The numbers in bold (readmission column) describe readmissions including return to hospital during ESD/HAH. Patients who were lost to follow up have been removed.

*Table 2.4: Readmission and mortality rate in trials*

### *2.3.6 Service costs*

Three trials performed cost analyses,[159, 226, 240] and one trial performed cost-effectiveness and cost utility analysis.[241] There is substantial variation in the costs that were included in the analyses, and how these costs were assessed.

Although the trials were conducted in different countries with different healthcare systems, the cost per episode of healthcare associated with ESD/HAH was consistently lower than UC (UK ESD/HAH = £877, UC = £1753;[226] Italy ESD/HAH = $1,175.9, UC = $1,390.9;[159] Netherlands ESD/HAH = €1,219, UC = €1,463;[241] and Australia ESD/HAH = Aus$745, UC = Aus$2543).[240]

Only one trial assessed costs beyond the acute event; both healthcare and societal costs were reported over three months [241]. Healthcare costs for the acute period (the period receiving in hospital or home treatment)) and the acute and follow up periods combined (ESD/HAH = €4,129, UC = €4,297) marginally favoured ESD/HAH. However, during the follow up period alone, usual care was less expensive (ESD/HAH = €2,910, UC = €2,834). The largest costs during the follow up period were due to community nursing and readmissions. Readmission costs were equal in both arms (€941), however in the usual care arm a larger proportion of patients were lost to follow up. This may have underestimated the readmission cost in UC by underestimating the readmission rate. UC patients had a marginally lower mean change in their Clinical COPD questionnaire, reflecting a smaller deterioration in symptoms. The UC group had marginally higher QALYs, though the difference was small and statistically non-significant. Therefore, from a healthcare perspective HAH was associated with a savings per QALY lost of €31,111. This is not consistent with other studies which tend to show improved quality of life with ESD/HAH though do not report in-depth economic evaluations. When costs from a societal perspective were also considered, including formal and informal carer costs and production losses for the patient, over the acute and follow up periods combined, ESD/HAH was more expensive than UC (ESD/HAH = €6,304, UC = €5,395).

## 2.4 Discussion

### *2.4.1 Principal findings*

Compared to UC, ESD/HAH was associated with a trend towards lower mortality in trials reporting outcome between two and sixth months after discharge from hospital or ESD/HAH.

ESD/HAH was associated with a lower rate of all-cause readmission than UC at two to six months provided all trials were included and that return to hospital during the period of acute care within ESD/HAH was not considered a readmission. Of importance, the trial by Ricauda et al.[159] was age restrictive, education was only routinely provided in the ESD/HAH arm and there was a high event rate in the UC arm (after correction for age and co-morbidity). If this trial is excluded from the analysis, the difference in readmission rates is no longer significant. However, this trial [159] provides strong evidence that patients aged 75 and over may be safely included in ESD/HAH schemes. Most patients hospitalised with AECOPD are elderly [150] and older patients are most at risk of readmission,[243] and death.[43, 243, 244]

Conceptually, if patients receiving ESD/HAH remain fully under the care of the specialist hospital based team, return to hospital during the period of acute care may be regarded as a transfer to a higher level of care within the same episode, rather than a readmission. This may also be of interest to commissioners and inform service tariffs. Whilst the distinction between HAH and ESD is blurred, return to hospital during a period of ESD is more typically regarded as a readmission. Regardless of the service description and level of care provided, the patient and their carers may regard return to hospital as a failure of ESD/HAH and the event as a readmission, which may have a negative impact on quality of life and service satisfaction. If this approach is adopted, readmission rates were similar for ESD/HAH and UC.

Compared to UC, ESD/HAH is associated with a shorter in-hospital stay, although the total period of care tends to be longer. This does not necessarily mean that patients receiving ESD/HAH are kept under review unnecessarily. Pressures to reduce length of stay in hospital may have led to patients being discharged earlier than is optimal. If return to hospital is regarded as a readmission, this favours UC because UC patients cannot be ‘readmitted’ during their inpatient stay. Conversely, as the total period of care is longer in ESD/HAH, and the risk of readmission is

highest in the early discharge period, not defining return to hospital as a readmission may favour ESD/HAH. In common with earlier reviews,[158, 231] we estimate that 23% of patients could be safely treated at home. Service costs relating to health during the initial treatment phase favour ESD/HAH over UC. For most studies, a description and breakdown of the cost calculations are not provided. Due to this, and heterogeneity of studies, identifying the most cost-effective model is not possible. Goossens et al.[241] provide a detailed cost analysis, and when considering health and social costs combined, ESD/HAH was more expensive. In this study all patients spent three days in hospital, and so this model is closer to ESD than HAH, and the results may have been different if the patients had returned home soon after admission or hospital admission was avoided.

Patient preference favours ESD/HAH over UC, whilst service satisfaction appears to be similar although further robust trials are required.

### *2.4.2 Strengths and weaknesses of meta-analysis and comparison of included studies*

This review and meta-analysis has provided an up-to-date analysis of ESD/HAH compared to UC for AECOPD prior to our RCT of HAH selected by low risk DECAF score. It includes a trial [227] not published at the time of previous reviews.[158, 231] We employed a comprehensive search strategy and contacted the corresponding authors to verify data when necessary.

The included trials were conducted in different countries with different healthcare systems. The diagnostic criteria for AECOPD were similar, but there were important variations in inclusion criteria and the structure and organisation of ESD/HAH services. Some trials did not offer enrolment at the weekends,[225, 226, 229] reducing both the cost of, and the number of patients who could access, ESD/HAH. In two trials [159, 238] patients were recruited directly from A&E or the Emergency Department, facilitating quicker discharge home, whilst in other trials [225-227, 229, 239] patients were recruited from wards, allowing a period of stabilisation and observation as an inpatient. It is likely that offering both pathways, tailored to the individual patient, would optimise costs and the proportion of patients suitable to access the service.

The structure of ESD/HAH services varied, including the healthcare professionals involved, the number of home visits, telephone support, access to medical services

such as home oxygen, and provision of temporary social support. Differences in selection criteria and service structure may, in part, explain the striking variation in the level of support provided in the ESD/HAH arm; the mean number of home visits ranged from 2.6 nurse visits [239] to 14.1 nurse and 9.9 physician home visits.[159]

Amongst patients with AECOPD who require in-hospital or ESD/HAH treatment, those with more severe exacerbations and/or poor performance status may require greater clinical and social support at home. A more comprehensive service, offering frequent visits from professionals, home oxygen therapy and temporary social services if required, will allow inclusion of a broader spectrum of patients. Although this will increase the cost of ESD/HAH, it may still be less expensive than UC.

In some trials there were differences in the elements of care provided in each arm. For example, in one trial, education, including exacerbation self-management, was provided to patients and carers in the ESD/HAH group, but not to the UC group.[159]

The period of follow up varied; this influenced the event rate. To address this, we initially planned to analyse results using hazard ratios, but the data required were not available and could not be estimated using Parmar's methods,[236] therefore risk ratios were calculated.

Differentiating between ESD and HAH is challenging, and in this review we have considered both together. HAH is an appropriate term for patients that have their entire episode treated at home, without admission. The term HAH is also used in some healthcare systems for patients who are assessed in the medical admission unit and return home for treatment the same day or the following morning if admitted overnight. For patients who deteriorate at home, during the period of care under ESD/HAH, an overnight stay in hospital is often defined as a readmission. However, equally this may be considered an escalation in level care within a single acute episode, and alternatively defined as "return to hospital". We have analysed the data separately, where possible, to reflect this variation. Some patients may have a brief assessment in an emergency department or ambulatory setting without an overnight stay; this would typically not be considered a readmission, and we consider that the RCTs described were consistent in this respect.

### *2.4.3 Comparison with previous meta-analyses*

*Trial selection*

Two meta-analyses comparing ESD/HAH and UC published in 2012 came to different conclusions with regards to outcome. Cochrane [158] reported moderate quality evidence that ESD/HAH was associated with lower readmission risk than UC (RR 0.65, 95% CI 0.59-0.99, p = 0.04),[158] which was further strengthened following exclusion of the trial deemed to have the highest risk of bias (CI 0.58 to 0.91; p = 0.006), and moderate evidence of a trend towards a reduction in mortality. In contrast, McCurdy [231] found no significant difference in readmission and mortality rates. The evidence was regarded as low to very low in quality, with a need for further research.

Two trials included by Cochrane failed to meet our selection criteria. We did not include the study by Nicholson et al.,[240] which primarily compares costs, in our meta-analysis of readmission. This RCT included patients referred by the outpatient department. No information was provided on baseline function, the randomisation process, allocation concealment, mortality or readmissions. Data on readmissions was obtained at the time of the Cochrane review, but the period of follow up is unclear. In the ESD/HAH arm the risk ratio for readmission was high compared to other trials,[225, 226, 229, 234, 238] however due to the small number of subjects, the confidence intervals are wide (RR = 2.77, 95% CI 0.69 to 11.17). Cochrane also raised concerns and excluded this paper in a sensitivity analysis.

We excluded Hernandez et al.,[234] which was included by Cochrane, because patients attending A&E with an AECOPD without the need for admission were considered eligible; 38.6% of the patients in the UC arm were discharged directly from A&E. A similar proportion of those treated within ESD/HAH would be expected to not otherwise require admission, thus this structure of care does not meet the definition of ESD/HAH for all included patients. Whether or not this group of patients benefit from home support is of importance, but is not the subject of this review.

*Patient events*

McCurdy differs from Cochrane in the number of events because McCurdy classes return to hospital during ESD/HAH as a readmission. Neither adjusted their analyses

for patients who die prior to discharge, yet such patients are not at risk of readmission.

McCurdy discusses the issues surrounding missing data, but, like Cochrane, did not make any adjustment in the analysis. Both performed an intention to treat analysis, but included those patients lost to follow up in whom outcome data was not available. This assumes their event rate is zero, though other RCTs suggest that patients with missing data have a higher event rate than the population with complete data [245]. The ideal approach to missing data is multiple imputation, but this requires raw trial data.

We analysed readmission rates with and without return to hospital counting as a readmission and with and without patients lost to follow up. We are grateful to all authors who clarified data.

### *2.4.4 Implications for clinicians and policymakers*

AECOPD are associated with substantial morbidity, mortality and healthcare costs. It is imperative that clinically and cost effective methods to reduce admissions and readmissions are considered and implemented. In selected patients presenting with AECOPD, ESD/HAH schemes substantially reduce length of stay, with similar or lower mortality and readmission rates compared to conventional inpatient care. Despite this, many Trusts currently do not offer such services.

### *2.4.5 Future research*

We recommend that future RCTs of ESD/HAH clearly define readmission, and provide data on patients who return to hospital during ESD/HAH and whether these same patients are readmitted during the follow up period.

The optimal selection criteria and structure of care for ESD/HAH services are unclear. Selection of patients should be based on their chance of surviving the acute episode, among other factors. The application of a robust prognostic tool for use in AECOPD would potentially be very useful in this respect.[2] It is likely that a tailored approach to ESD/HAH, depending on the clinical and social dependency and performance status of each patient would be most efficient. Compared to basic ESD/HAH schemes primarily reliant on specialist respiratory nurses, multi-disciplinary interventions including higher levels of clinical support, temporary social support and

input from occupational therapists and physiotherapists may allow a broader spectrum of patients to access ESD/HAH.

Incorporating services such as early pulmonary rehabilitation and education for both patients and carers within ESD/HAH is likely to confer additional benefits. The clinical outcomes and costs associated with different models of ESD/HAH warrant further study. A better understanding of patients', carers' and clinicians' views of ESD/HAH may help inform the refinement and expansion of these services. Cost analyses should be based on actual costs rather than tariff and include all direct and indirect costs, including temporary social care, primary care and readmission costs. ESD/HAH schemes may foster greater independence and reduce the risk of subsequent readmission, particularly if combined with education, including self-management. Consequently, ESD/HAH could be provided for readmissions as well as the index admission, and costs analysed across all episodes.

# RESEARCH AIMS AND METHODS

# Chapter 3 Aims and objectives

## 3.1 Validation of the DECAF and eMRCD scores

1. To validate the DECAF prognostic tool internally in a cohort of patients admitted consecutively with an AECOPD over a different time period to the derivation cohort.

2. To validate the DECAF prognostic tool externally in other UK NHS trusts.

3. To validate the eMRCD score in an internal and external validation cohort

The DECAF score was developed in 920 consecutive admissions of patients with an AECOPD to two UK hospitals, and was an excellent predictor of inpatient mortality with an AUROC curve of 0.86.[2] Prior to wider implementation of clinical prediction tools, validation and implementation studies should be performed. We aimed to validate the DECAF score at a different time point, but in the same population (also known as internal validation or temporal validation) and to validate DECAF in a separate population in the derivation and internal validation study (also known as external validation, or geographical validation; this study also took place at a different time from the derivation study).

The eMRCD score [1] was developed from the same cohort [2] in which the DECAF score was derived. Of the DECAF indices, the eMRCD score was the strongest predictor of inpatient death on multivariate analysis. We aimed to reassess the prognostic strength of the eMRCD score for inpatient mortality, as well as in predicting long-term mortality and readmission risk.

## 3.2 Hospital at Home in patients with a low DECAF risk, implementation and impact assessment

1. To assess the cost and clinical outcome of treating patients admitted with low-risk DECAF AECOPD with Hospital at Home compared to usual care.

AECOPD are one of the commonest reasons for hospital admission, and in the DECAF derivation study, over half of the admitted population had a low risk DECAF score and a median length of stay of 4-5 days. Such patients could return home with Hospital at Home within 24 hours, potentially reducing length of stay, costs and avoiding complications associated with inpatient stay. We intend to perform an RCT of HAH versus standard inpatient care for patients with AECOPD and at low risk of

death by DECAF score, assessing clinical outcomes, patient preference and health and social care costs. We will also evaluate barriers to HAH as directed by DECAF using semi-structured interviews of patients, carers and health professionals. These interviews will inform future implementation of HAH in the event of a successful trial.

### 3.3 Readmission prediction in AECOPD, the PEARL score

1. To develop and validate a score to predict 90 day readmission or death in the DECAF derivation, internal validation and external validation cohorts in survivors to discharge.

Patients admitted with AECOPD have high readmission rates. Risk stratification may allow allocation of resources to at risk patients. There are a number of tools that have been assessed with regards to the risk of readmission or death in either unselected patients or those admitted with AECOPD. However, these tools only offer modest performance, which is unsurprising as they were either not derived in the COPD population (LACE [221]), or were primarily developed to predict death (ADO,[217] BODEX,[218] CODEX [216]) or health status (DOSE [219]). In other words, there was no method such as multivariate regression analysis performed to identify the strongest independent predictors.

# Chapter 4 The derivation and validation of prognostic models

## Chapter introduction

Methods which are common to different studies are included here. The specific statistical tests used to compare data are included in tables in the results section.

To identify the appropriate statistical test, the distribution of data was assessed by visual inspection of the histogram. Further assessment of normal distribution was performed by analysing the mean, standard deviation, kurtosis and skewness and the median and interquartile range.

Data were analysed using IBM SPSS statistics 22, SigmaPlot 12.3 and Microsoft excel. All reported p values are two-sided and confidence intervals are at 95% unless stated otherwise.

This work belongs to a larger programme of research, which included the derivation of the DECAF score. The following section describes methods used to validate the DECAF score, and to derive and validate the PEARL score. For simplicity, in this section the terms “derivation cohort”, “internal validation cohort” and “external validation cohort are used”. For the DECAF internal and external validation study, this includes all patients, and for the PEARL study this includes all patients that survived to discharge; the methods are the same for each study, unless stated otherwise.

Methods related to the DECAF derivation study are not described here, as this was part of a previous study.[2] Data from the DECAF derivation study was used to develop the PEARL score.

## 4.1 Ethical considerations and ethical approval

In the original DECAF study, and in the internal and external validation studies, the ethics committee agreed that written patient consent was not required. Without this decision, the methodological rigour of the study would have been detrimentally affected. The need for consent would have resulted in the loss of patients that were admitted to hospital, and discharged shortly afterwards, or those that were too unwell (or died prior to) giving patient consent. This is analogous to trying to assess the fairness of a die without being able to roll a one or a six.

According to the Mental Health Act, 2005, adults are presumed to have capacity unless it can be established to the contrary. MCA 2005 s30 relates to capacity and research; research is intrusive “if it is of a kind that would be unlawful if it was carried out: a) in or in relation to a person who had capacity to consent to it; but b) without consent”. Accessing patients’ medical records usually requires consent, without which there is a breach of confidentiality, unless the person accessing the notes is part of the care team. BMA Medical Ethics today says, “Some record based research is carried out in parallel with the provision of treatment by health professional who already have access to the records as part of their duty of care. In such cases, where researchers are working on data form their own patients, there is no breach of confidentiality, as only those who already have access to the information use it for research.” This is the same principle that is used to justify accessing patients’ notes to collect data for national audit.

The indices proposed for collection in the validation study are routinely measured in normal clinical practice, and it was planned that the patients would not undergo any extra investigations. Data would be collected, and anonymised, by the usual care team. The definition of “usual care team” is broad, and it can include staff such as radiologists and pathologists that may never see the patient, and the respiratory team meet this definition.

In ensuring only the usual care team access patient notes, and that data extracted was anonymised, the validation study posed minimal risk to individual patients. There are a number of potential benefits. In AECOPD, HAH and ESD services have been shown to be safe and effective, with endorsement by the National institute of Clinical Excellence (NICE). As described in Chapter 2, these may reduce healthcare costs, and improve patient care. NICE recognise that patients should be considered for such services, but acknowledged the (previous) lack of a prognostic tool.

Ethics approval was awarded by NRES committed North East- Sunderland on 3rd December 2012.

## 4.2 Developing and validating a prognostic Tool

There has been a marked increase in the number of published prediction models. For example, the TRIPOD statement [246] and CHARMS checklist,[204] are guides for assessing the quality of such studies. The latter reports that there are over 100 models for outcome following brain trauma, 60 for breast cancer prognosis, and 45 for cardiovascular outcome in diabetics. Systematic reviews of prognostic scores often conclude that there is widespread use of poor methods.[247] The following section discusses the rationale for the selected methods, including the strengths and weaknesses of alternative approaches.

### *4.2.1 Power calculation*

*DECAF*

Based on an expected sensitivity of 70%, a standard error of the estimate of sensitivity of 5% required a minimum of 840 patients in both the internal and external validation cohorts.[248]

*PEARL*

The derivation cohort was adequately powered based on the minimum expected events per index.[249] For the internal and external validation cohorts, the sample size required was 227 for an expected sensitivity of 70%, a standard error for this estimate of 5% and an event rate of 37%.[248]

### *4.2.2 Dealing with missing data*

Missing data is unavoidable, and may bias the results of clinical and epidemiological research.[250] The consequence of missing data depends on the pattern of missing data. Missing data is described as: a) missing completely at random (MCAR); b) missing at random (MAR); and c) missing not at random (MNAR).

For data MCAR, there is no difference between the missing values and the observed values. For example, the mean and standard deviation would have been the same if the values had been included. The assumption that data is MCAR can be tested and if the assumption is fulfilled, complete case analysis can be performed. In practice, data is almost never MCAR.

It is more likely that data is MAR or MNAR, though proving that data are missing at random (MAR), as opposed to missing not at random (MNAR), is generally impossible.[246]

If data is MAR or MNAR, complete case analysis can lead to biased results depending on the rate of missing data. If missing data is less than 5%, it is generally agreed that estimates using complete case analysis may not be biased. Complete case analysis refers to analyses that only use available data- cases with missing data are removed. This is a problem in prognostic research, as even a small amount of missing data per index can result in the exclusion of a large number of participants. The rate of missing data per index and per patient needs to be considered.

Steyerberg [251] gives an example in which a model is being developed using five predictors, in 500 patients 20% of whom experience the outcome of interest. If each predictor has 10% missing data, the complete case analysis may result in the exclusion of 50% of the participants. Not only is this inefficient, but estimates will be biased; if large numbers of patients are excluded, it is not possible to establish if any resultant association is due to correlation between the predictor and the outcome, or due to patient selection. Furthermore, missing data may prevent the meaningful comparison of models, as the populations with complete data for each model may be different.

Simple measures to account for missing data may result in biased estimates. For example, imputing the mean as the missing value is unlikely to be correct. This assumes that the characteristics of patients with missing data are the same as those without missing data. Also, this will lead to a narrowing of the standard error of the mean, which may result in false positive results when comparing data.

“Missing at random” does not mean that values are “randomly missing” (which describes data missing completely at random) but rather that systematic differences between missing data and observed data can be explained by observed data. For example, haemoglobin and haematocrit measurements correlate well with each other.[252] If haemoglobin data were missing for a patient, but the haematocrit were available, then the missing haemoglobin value could be calculated.

For data MNAR the missing data depends on the missing value or on other predictors that have not been measured (in other words, we have not measured

haematocrit). Patients not attending clinic due to the severity of their illness may be an example of data missing not at random.

There may be multiple indices that have been measured that predict the missing data index. Regression models can be used to calculate missing data points from other indices. As with mean imputation, this can result in a reduction in the standard error, which may bias results.[253]

Multiple imputation is a method that uses linear and logistic regression to calculate the value of missing data points for data that is MAR. To prevent the reduction in the standard error, multiple data sets are created, with multiple imputed values. Table 4.1 is a hypothetical example to illustrate the principle. Patient C has missing data for haematocrit. Based on the relationship between haemoglobin and haematocrit for patient A and B, three values have been created for patient C. This value is a more accurate result than the mean of the other haematocrit values.

| Patient | Haemoglobin (g/dl) | Haematocrit |
|---|---|---|
| A | 12.3 | 0.372 |
| B | 11.1 | 0.340 |
| C | 14.4 | Missing |
| Patient imputed values: | | |
| C1 | 14.4 | 0.427 |
| C2 | 14.4 | 0.431 |
| C3 | 14.4 | 0.436 |

*Table 4.1: Hypothetical values to illustrate data Missing at Random*

Actual datasets would require far more patients, and at least five or more datasets, depending on the rate of missing data. In order to use this data in analysis, the values in the dataset are pooled by Rubin's method.[254]

### *Multiple imputation by Rubin's method*

To explain this approach, a specific example from the DECAF validation study is used in which the AUROC curve for the APACHE II score is calculated and compared to the AUROC for the DECAF score. The comparison of AUROC curves in multiple datasets cannot be done in SPSS nor SigmaPlot. Therefore, the latter stages of Rubin's approach was calculated manually in Microsoft Excel. This required a detailed knowledge of the process and is therefore described here in detail. The

described approach was used for all AUROC comparison in the internal and external validation analyses.

It is unlikely that missing data rates of only a few percent will bias results. In this situation, complete case analysis may be used. However, missing data rates of 1 to 2% per index can result in large overall missing data rates for a score such as the APACHE II which measures 12 physiological variables, age and comorbidity. In the validation study overall missing data were 26.8%; multiple imputation is not reliable for indices with more than 20% missing values. Therefore, multiple imputation was used for individual indices rather than prognostic tools.

Data were imputed using the Markov Chain Monte Carlo method on IBM SPSS Statistics 22, with linear and logistic regression for continuous and categorical variables.[254] Multivariate regression is discussed later in this chapter.

As many indices as possible should be included in multiple imputation,[254] though there may be computational limitations to the number of indices. A large number of variables (n = 67) were used as predictors for variables with missing data. Before the first imputation, 10,000 iterations were performed which converge to a stationary distribution. Following this, five datasets were imputed and the AUROC curve for the APACHE II score was calculated for each dataset as well as the mean (Table 4.2).

To compare the APACHE II score to DECAF the 1) between imputation variance and 2) within imputation variance must be calculated to find 3) the total variance. The 4) overall standard error, 5) degrees of freedom and 6) t statistic can then be calculated to provide a p value using the t distribution.

1) To calculate the between imputation variation †:

a) The mean of the five ROC curve areas (*) is subtracted from the individual ROC curve areas (“AUROC area A to E”), which is squared “(AUROC area minus Mean)$^2$ A to E”.

b) The five results “(AUROC area minus Mean)$^2$ A to E” are divided by the number of datasets (five) minus one.

Mathematically stated, the between imputation variation is (where m is the number of datasets):

$$B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}_i - \overline{Q})^2$$

| | AUROC area A to E | (AUROC area minus Mean)$^2$ A to E | |
|---|---|---|---|
| APACHE II ROC curve A | 0.785 | 4.09^-06 | |
| APACHE II ROC curve B | 0.786 | 8.24^-06 | |
| APACHE II ROC curve C | 0.779 | 2.26^-05 | |
| APACHE II ROC curve D | 0.783 | 1.55^-08 | |
| APACHE II ROC curve E | 0.783 | 6.83^-08 | |
| Mean | 0.783 * | 8.76^-06 † | Between imputation variance |

*Table 4.2: AUROC and imputation variance for APACHE II imputed datasets*

2) To calculate the within imputation variation ‡:

Using SigmaPlot 12.3, the AUROC curve for all five APACHE II curves were compared to the DECAF score (which had complete data and did not require imputation) to provide the standard error for the difference in the areas (Table 4.3). The mean of the square of the standard error gives the within imputation variance.

Mathematically stated, the within imputation variation is:

$$\overline{U} = \frac{1}{m}\sum_{i=1}^{m}\hat{U}_i$$

| | Standard error APACHE II versus DECAF A to E | standard error^2 | |
|---|---|---|---|
| APACHE II ROC curve A | 0.020 | 0.000417 | |
| APACHE II ROC curve B | 0.020 | 0.000415 | |
| APACHE II ROC curve C | 0.021 | 0.000450 | |
| APACHE II ROC curve D | 0.021 | 0.000429 | |
| APACHE II ROC curve E | 0.020 | 0.000417 | |
| Mean | 0.021 | 0.000426 ‡ | Within imputation variance |

*Table 4.3: Standard error and calculation of within imputation variance for APACHE II imputed datasets*

3) To calculate the total variance:

The total variance is calculated by the within imputation variance ‡, plus 1.2 multiplied by the between imputation variance †.

0.000426+((1+1/5)*(8.76x10-6)) = 0.000436

Mathematically stated, the total variance is:

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

4) The overall standard error is the square of the total variance:

0.000436^-1/2 = 0.021

5) To calculate the degrees of freedom:

Four, multiplied by one plus the within imputation variance divided by 1.2 multiplied by the between imputation variance squared.

Mathematically stated, the degrees of freedom is:

$$v_m = (m-1)\left[1 + \frac{\overline{U}}{(1+m^{-1})B}\right]^2$$

6) The t statistic is calculated by the mean of the AUROC curves divided by the overall standard error. The t statistic and the degrees of freedom can then be used to calculate the p value using the t distribution, which in this example is $p < 0.0001$.

### *4.2.3 Comparison of patient characteristics*

Baseline population characteristics were described using proportions, means with standard deviations (SD) or medians with inter-quartile ranges (IQR), and compared using Fisher's exact test, analysis of variance or Welch, and Kruskal-Wallis's test.

### *4.2.4 Study design*

Prospective cohort studies are regarded as the gold standard for diagnostic modelling studies.[204] This ensures that data on predictors and outcome are reliable. Retrospective studies are conceived after some participants have had the outcome under investigation. Data may be collected prospectively, but this does not mean the

study is prospective. This is an important distinction, as the increased use of technology in healthcare has resulted in increasing volumes of routinely stored data. This makes retrospective studies easier and cheaper, but retrospective cohorts tend to have poorer data quality, and some important predictors may be missed. Some types of data may be accurate when collected retrospectively, such as the recording of blood tests at admission, although data such as patient-reported symptoms may be very unreliable.

Retrospective study designs are regarded as acceptable in validation studies.[212] However, there is still a risk of bias depending how accurately and consistently the predictor indices were collected and whether the identified population is representative of the population of interest.

For these reasons, the derivation and external validation study were performed prospectively. The internal validation study was conceived prior to any outcome, though the majority of patients were identified retrospectively. The derivation study was performed in the same hospitals as the validation study, in which usual care included the recording of key data, such as the eMRCD score, which minimises bias. At all sites in the internal and external validation studies, the eMRCD score was accompanied by clear guidance notes for consistent scoring, which have also been published so that it can be replicated in clinical practice.[255] All sites had data collection guides which included clear definitions for collected indices. Furthermore, outcome data, such as death and readmission, are objective and are reliably recorded on NHS computer systems and in patient's medical notes.

Six UK hospitals participated between January 2012 and May 2014. Sites A and B formed the internal validation cohort and C to F formed the external validation cohort. The latter were selected to ensure wide variation in structures of care and population characteristics (COPD prevalence, socioeconomic factors and rurality). In participating hospitals, consecutive patients admitted with AECOPD were identified. In the internal validation cohort hospitals, the DECAF indices are recorded as part of routine practice. This allowed the period of the study to be extended retrospectively to enhance recruitment; patients were primarily identified from a broad coding records search (discharge codes). However, this was cross-referenced with existing records of patients identified by respiratory specialist nursing and physiotherapy teams. In the external validation cohort to identify consecutive admissions of patients

with AECOPD, all medical admissions were screened prospectively. This involved dedicated staff attending the medical admissions unit and base wards. Coding records were also reviewed to maximise patient capture.

### *4.2.5 Population*

The study population should be representative of the population of interest to ensure that the score can be used in practice.[256] To achieve this, consecutive admissions should be identified, though this is seldom performed and results in potential bias due to selective sampling.[204] As with missing data, missed patients are not missed completely at random. The following are examples of methods which risk missing patients: a) not confirming the diagnosis of AECOPD and/or COPD; b) broad exclusion criteria; c) relying solely on coding records to identify patients; d) relying solely on the usual care team to identify patients; e) the need for consent; and f) the exclusion of patients without complete data.

In the validation studies, patients were required to have a primary diagnosis of an AECOPD for inclusion. This was defined as symptoms of an AECOPD in a patient with proven airflow obstruction in whom an alternative diagnosis was not more likely. This included patients with COPD who for example received diagnoses such as lower respiratory tract infection or pneumonia, but met the criteria for an AECOPD. Preadmission spirometry from any time period was included. The difficulty of finding spirometry in medical notes is highlighted by the 2015 UK COPD audit, which showed that only 46% of patients admitted with an AECOPD had obstructive spirometry documented. In the validation studies, all paper and electronic records (including old volumes or notes, lung function databases, and GP records) were searched for spirometry records. Obstructive spirometry was defined as an FEV1 / VC of less than 0.7. The vital capacity was used rather than the FVC because some patients with severe COPD may have spirometry that is consistent with a restrictive pattern on a forced manoeuvre, but have severe airflow obstructive based on a relaxed VC.

Eligibility criteria were few, to maximise inclusion of patients:

*Inclusion criteria*

1. Age greater than or equal to 35 years
2. Smoking history greater than or equal to 10 pack years

3. Obstructive spirometry (FEV1 / VC < 70%)
4. Primary diagnosis of AECOPD (nonpneumonic or pneumonic)

*Exclusion criteria*

1. Previous inclusion in the study
2. Other illness likely to limit survival to less than one year

These criteria were the same for the DECAF score and the PEARL score, except that the PEARL score cohort did not include those patients that died as an inpatient.

Patients needed to be 35 years or older and have a smoking history of 10 cigarette pack years of more. This was to ensure that patients with a diagnosis of COPD were included; younger age and a relatively low cigarette pack year history may favour a diagnosis of asthma.

Patients could only be included within the study once, usually for their first admission. If patients were admitted with suspected COPD, they could be included for a future admission due to an AECOPD once they had COPD confirmed by spirometric testing: to achieve this, all patients admitted with a provisional diagnosis of an AECOPD had all future admissions reviewed within the research time-frame for each site. A potential criticism of this approach is that it does not include patients with a new diagnosis of COPD, and therefore may reduce the generalisability of the results. However, this may lead to the inclusion of patients who turn out not to have COPD. Also, the inclusion of such patients will introduce immortal time bias as survivors to discharge and patients sufficiently well to perform spirometry during their exacerbation will be included whilst those that are very unwell or die during their admission will be missed.

Patients with a survival of less than one year for a reason other than COPD were excluded.

Relying on coding searches alone to identify patients coded with AECOPD is unreliable. There is no single code for AECOPD, and AECOPD are both over- and under-diagnosed by the current ICD-10 classification. Over-diagnosis of AECOPD is less of a concern than under-diagnosis, as the former can be identified by reviewing patient's medical records. The "under-diagnosed" group are at risk of being missed completely. To avoid this, a broad coding search was developed and refined.

There were 24 codes identified which could be considered an AECOPD, or could represent the miscoding of an AECOPD. An initial search was performed for any diagnosis using the terms J10 to J18 (influenza and pneumonia), J20 to 22 (other acute lower respiratory infections), J40 to J47 (chronic lower respiratory diseases), J96.0, J96.1, J96.9 and/or J98.2 (acute and chronic respiratory failure not elsewhere classified and interstitial emphysema) over an eight month period.

The search retrieved over 11,000 patient episodes. For this group, discharge letters were reviewed and patients classified into definite, probable or no AECOPD for one month of data. This was then compared to medical notes which showed that for this time-period, discharge letters were 100% accurate at excluding an AECOPD (no AECOPD classification based on the discharge letters), but could not be relied upon to confirm an AECOPD without looking at the medical notes.

Patients were also categorised into their primary diagnosis (asthma, bronchiectasis, pneumonia, COPD, etc.) to establish how often patients with AECOPD receive these as their primary diagnosis and how often COPD is included as a non-primary code. The search was subsequently refined to: patients aged 35 and over, with a primary diagnosis of J10 to J18, J20 to 22, J40 to J47, J96.0, J96.1, J96.9 or J98.2, and a secondary diagnosis of any J44 code.

In the external validation cohort, consecutive patients with AECOPD were identified prospectively. This involved a dedicated research person or team visiting admission units and wards Monday to Friday to screen all admissions (screening on Monday included identifying patients admitted over the weekend). Coding records were also reviewed to ensure all consecutive patients were identified. Prospective identification of patients at sites captured approximately 90-95% of patients with AECOPD. Those that were missed and identified by coding were more likely to have been discharged sooner (the most well) or died soon after admission (higher DECAF scores are associated with a shorter time to death).[3] Similarly, for patients whose medical records were difficult to obtain, death rates were higher. Missing these patients would narrow the risk range and bias results: it would be analogous to trying to assess the fairness of a die without being able to roll a one or a six on some occasions.

In the internal validation study, most patients were identified retrospectively. However, the usual care team routinely aims to review all patients with an AECOPD, which when combined with a broad coding search allowed for the identification of

consecutive patients. This was confirmed by comparing two months of dedicated prospective identification of patients by two members of the research team, compared to using the coding search and information from the clinical team. The research team identified patients missed by the usual care team, which shows that having staff solely dedicated to identify patients improves recruitment. Furthermore, only one patient was missed by the coding search that was identified prospectively over a two month period (by the research and clinical teams). Recruitment rates in the internal validation study were similar to the original prospective DECAF study, which supports complete capture of patients.

In the validation study, patient consent was deemed unnecessary by the ethics committee. Studies that require patient consent risk excluding large numbers of patients who are too unwell to provide consent, and subsequently die. As such patients are not MCAR this introduces bias affecting the assessment of the tool performance in the whole population. For example, in a study by Quintana et al.,[214] recruitment was substantially lower than in equivalent audit data.

Patients who did not survive to discharge were appropriately excluded from analyses that looked at readmission risk. In the validation cohort, those that did not have complete data for all DECAF indices were not included in the analysis, to allow assessment of how the score would perform in clinical practice. This is a potential source of bias, as study data are often missed in a selective and biased way. This pragmatic approach was supported by measures to ensure that missing data would be at a minimum: only 1% of the population were not included, mainly patients that had oxygen saturations sufficiently low to warrant arterial blood gas analysis but that declined this investigation.

### *4.2.6 Study sites*

Six UK hospitals were included in the study. North Tyneside General Hospital (NTGH) and Wansbeck General Hospital (WGH) were the sites of the internal validation study, and the same sites at which the decaf derivation study was performed. The external validation study was performed at the Royal Victoria Infirmary (RVI) in Newcastle, the University hospital of North Tees (UHNT), the Royal Cornwall Hospital (RCH), and the Northern General Hospital (NGH) in Sheffield.

Study sites were selected for the variation in the hospitals and in the population that they serve to maximise the generalisability of the results.

### *4.2.7 Outcome*

*DECAF validation*

The primary outcome was in-hospital mortality prediction, with comparison of DECAF risk groups between the derivation and validation cohorts. Secondary outcomes included assessment of the optimal thresholds for pH and eosinopenia, prediction of 30-day mortality by DECAF, and comparison to other prognostic scores (APACHE II,[200] BAP-65,[209] CAPS,[202] and CURB-65 [203]). Length of stay was compared across DECAF scores.

*PEARL*

The primary outcome was prediction of 90 day readmission or death without readmission in patients discharged from hospital following admission with AECOPD. Secondary outcome included assessment of other prognostic scores with comparison to the newly developed tool (PEARL), 30 day readmission or death without readmission, prediction of readmission alone, time to death or readmission and readmission frequency.

In common with previous studies (Table 1.4), we selected “death without readmission” as a combined primary outcome with “readmission”. This is justified as patients who die without readmission are likely to have been readmitted had the clinical deterioration been recognised in time, and death without readmission and readmission share similar predictors. Furthermore, readmission alone as the outcome would mean that those who die without readmission appear in the “favourable” outcome group.

We selected a 90 day timeframe for our primary outcome as this covers the high risk period. In patients hospitalised due to AECOPD who survive to discharge, one third are re-admitted within 90 days[131] and the risk of further exacerbation and readmission over the 8-12 weeks post-discharge outweighs the risk over the subsequent year.[25, 130] Such events are associated with substantial risk of death, adverse qualify of life[112, 127-129] and high healthcare costs.[5]

### *4.2.8 Data collection*

Data collection of the derivation cohort was collected as part of a separate thesis, and is described in detail elsewhere.[2]

For the validation cohorts, data collection guides were provided to all sites and included information on sources of data, the definitions of diseases and terms, and time-points for collection. This allowed for precise and consistent data collection. Socio-demographic and clinical data were collected on admission. The eMRCD scale was provided with written instructions on scoring.[255] The presence of consolidation on x-ray was based on the consultant's ward round review (or most senior doctor review). Atrial fibrillation was diagnosed by the admission electrocardiogram or known history. A diagnosis of left ventricular failure and cor pulmonale was based on clinical findings or echocardiogram: reliance on echocardiography alone would limit the real-life application of the score. All blood tests (including eosinophil count and arterial blood gas results) were from admission.

Ninety day readmission and mortality data were collected from medical records. Admission and readmission were defined as an admission to a hospital ward outwith the emergency department. Clinical assessments and care was not influenced by the research team, and no additional tests were performed.

Data was only deemed to be missing once all data sources were exhausted, to minimise missing data. The data collection form included a checklist to search the patient's clerking, GP letters, full medical notes (all volumes if required) and nursing notes.

Clinical indices on admission, and demographic, survival and readmission data that were collected are shown in Table 4.4.

In the DECAF derivation cohort,[2] 118 patients had oxygen saturation ($SpO_2$) greater than 92% while breathing room air, of whom none had an arterial pH of less than 7.30 (DECAF Acidaemia score = 1). In the internal and external validation cohorts, therefore, if the attending physician deemed that arterial blood gas (ABG) sampling was unnecessary and $SpO_2$ was greater than 92%, it was presumed that the arterial pH was greater than or equal to 7.30 and therefore the patient did not score for the pH component of the DECAF score.[167]

| Type | Data point |
|---|---|
| Demographics and admission information | Admission age, gender, hospital site, social care prior to admission (nursing home, residential home, sheltered accommodation, need for carers), date and time of admission |
| Inclusion criteria | Primary diagnosis of AECOPD (nonpneumonic or pneumonic), age greater than or equal to 35 years, Smoking history greater than or equal to 10 pack years, Obstructive spirometry (FEV1 / VC < 70%) |
| Exclusion criteria | Previous inclusion in the validation study, Other illness likely to limit survival to less than one year |
| Population descriptor | Number of respiratory, non-respiratory and total admissions in past 6 and 12 months, Number of respiratory, non-respiratory and total A&E visits in past 6 and 12 months, exacerbation frequency past 12 months, smoking status, number of pack years and year quit smoking, previous pulmonary rehabilitation, previous treatment with NIV, NIV during admission, resuscitation status. |
| Spirometry | FEV1, FVC and ratio and date (preadmission, discharge and follow-up) |
| Admission information | CXR consolidation, eMRCD (independent in washing, dressing or feeding), effectiveness of cough, height, weight (measured weight on admission and 3 to 6 months ago, reported and calculated weight loss, intentional or unintentional weight loss), BMI, nutritional intake preadmission, pulse rate, blood pressure, respiratory rate, temperate, confusion, GCS scale and pedal oedema. |
| Co-morbidity | Cor pulmonale (clinical or echo diagnosis), cognitive impairment, anxiety, depression, left ventricular dysfunction, aids, cerebrovascular disease, chronic pulmonary disease, asthma, congestive heart failure, connective tissue disease, dementia, hemiplegia, solid tumour, leukaemia, malignant lymphoma, myocardial infarction, ischaemic heart disease, atrial fibrillation, peripheral vascular disease, gastrointestinal ulcer disease, diabetes with or without end organ damage, liver disease (and severity), renal disease (and severity), |
| Medication | Long term prednisolone and dose, beta-blocker, long-term oxygen therapy, diuretic, statin, ACE inhibitor, ARB inhibitor |
| Bloods (all admission) | ABG (Fi02 on admission ABGs, pO2, pCO2, pH, bicarbonate, base excess), sodium, potassium, urea, bilirubin, creatinine, albumin, serum glucose and BM, troponin, CRP, haemoglobin, haematocrit, red cell distribution width, platelets, white cell count, neutrophil count, eosinophil count |
| Outcome | Death (date, place and cause up to one year), length of stay, readmission (and reason for readmission up to one year in the internal validation study and 90 days in the external validation). |

*Table 4.4: Collected indices*

### *4.2.9 Predictors for 90 day readmission of death*

Indices that are known to predict death or readmission were selected by performing a systematic review of the literature and by clinical plausibility.[257] Those predictors that are not routinely assessed or available at admission were not included for ease of use of the final tool. Predictors and outcome were clearly defined prior to data

collection. A potential limitation of the internal validation cohort is the retrospective identification of most patients. However, the risk of any consequent bias is low as the relevant indices had been recorded prospectively, and the researchers were blind to outcome at the time of data acquisition. This was not a risk in the derivation and external validation cohorts which were prospective.

A complete list of indices included in the development of a tool to predict 90-day readmission or death (the PEARL score) are shown in Table 4.5.

| |
|---|
| Sociodemographic details |
| Female |
| Age |
| Institutional care |
| Cigarette pack years |
| Preadmission details |
| eMRCD |
| Admissions in previous year |
| Weight loss >5% |
| FEV1 % predicted |
| Long term oxygen |
| Long term prednisolone |
| Left ventricular failure |
| Cor pulmonale |
| Diabetes |
| Chronic Kidney Disease |
| Cerebrovascular Disease |
| Atrial Fibrillation |
| Asthma |
| Cognitive impairment |
| Admission details |
| Length of stay |
| Radiographic consolidation |
| Ineffective cough |

*Table 4.5: Candidate predictors of readmission or death without readmission*

It is important to ensure that indices are not included which strongly correlate with each other to ensure stability in a prognostic model.[258, 259] Predictors that are closely related do not offer independent information.[256] This can be suspected in instances where indices measure similar phenomenon, such as haematocrit and haemoglobin. This can be quantified by paring all indices and measuring the correlation coefficient. If the correlation coefficient is greater than 0.7 this would support excluded one of the two indices.

All indices were dichotomised or categorised by visual inspection of the ROC curve, a clinically relevant cut-off, or a median split.[2] Where multiple appropriate cut-offs were apparent, the prognostic power of each cut-off was compared.

It is recognised that for ordered categorical indices, such as the eMRCD, collapsing categories may be required.[256] Generally speaking, transforming continuous indices into dichotomous indices is not advised, as it may result in a loss of predictive information. However, simplifying indices in this way allows a score to be remembered and easily calculated at the bedside without the aid of a computer or calculator. It is possible to compare models with a continuous index in the same index dichotomised to look for any loss of prognostic information.

In the development of the PEARL score, the above indices were categorised: age <80 or 80+; cigarette pack years <45 or 45+; eMRCD score 1-3, 4, 5a or 5b; forced expiratory volume in one second (FEV1) %predicted <50 or 50+; previous admissions <2 or 2+; and length of stay as per the LACE study (0, 1, 2, 3 ,4-6, 7-13, or 14+ days).[221]

### *4.2.10 Model development*

Logistic regression is a commonly used statistical technique for binary outcome in prognostic research in medicine. The model can include different types of predictors, such as continuous, categorical and binary indices. To understand the principles of logistic regression, it is useful to first consider the linear regression model.

Linear regression models take the form:

$$Y = \beta_0 + \beta_i * x_i$$

$\beta_0$ refers to the intercept on the y axis, $\beta_i$ represents the regression coefficients for one or more predictors ($x_i$). A model with two predictors would look like the following:

$$Y = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2$$

Where $x_1$ and $x_2$ are the first and second predictor. If $x_1$ were a continuous index, such as age, then $\beta_1$ represents the difference in Y for each unit of $x_1$. As a hypothetical example, a one year increase in age ($x_1$) might be associated with a one mmHg increase in systolic blood pressure (Y). A linear regression line can be fitted to these indices (Figure 4.1, “A”). If $x_2$ were a binary predictor, such as diabetes, then

only a one unit change is possible from 0 to 1, where 0 represents no diabetes (and acts as the reference group), and 1 represents diabetes (and is the comparison group). $\beta_2$ is then the risk associated with diabetes in addition to age. The exponent ($e^{\beta}$) provides the odds ratio, which is perhaps a more easily understood measure of risk than the beta-coefficient. The beta-coefficient associated with age alone will be different if diabetes or other indices are included in the model. When only one predictor is included in a regression model it is an unadjusted or univariate model.

It is not possible to fit a linear regression line to the data points if the outcome is binary (such as death) rather than continuous (Figure 4.1, "B"). In this situation, logistic regression can be used. The outcome is considered in terms of the probability of its occurrence (P(y=1)). For example, the relationship between age and the probability of death (Figure 4.1, "C") follows an S shaped curve: using the exponential function, the intercept, regression coefficients and predictors can be log transformed to provide a linear function (Figure 4.1, "D"):

$$\text{Logit}(P(y=1)) = \beta_0 + \beta_i * x_i$$

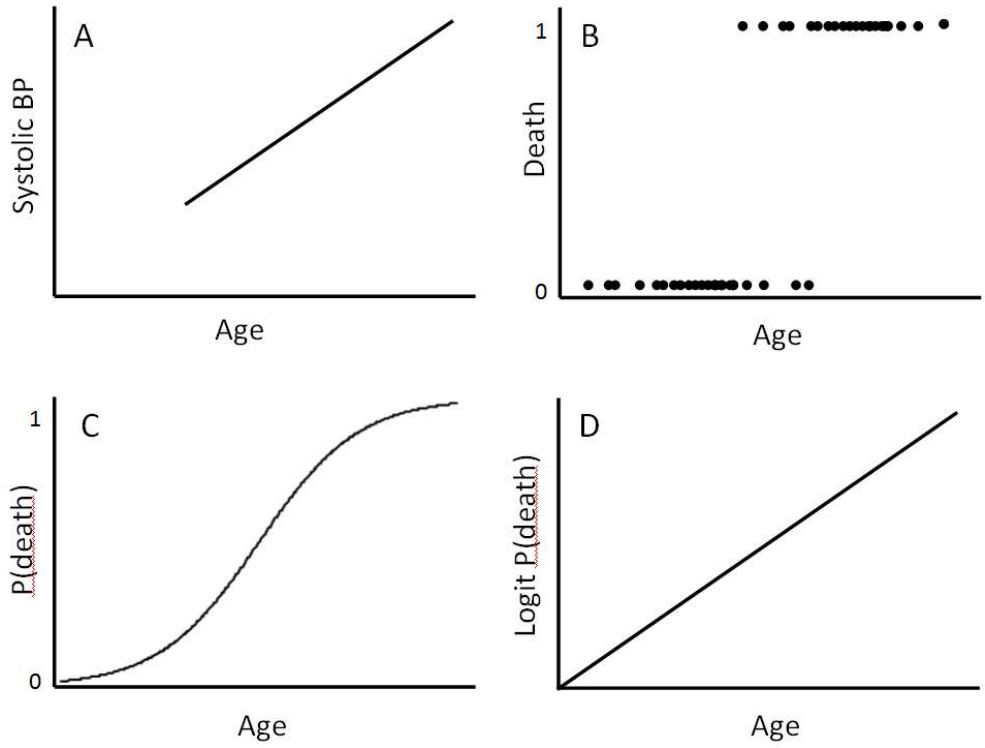


*Figure 4.1: Illustrative figure of A) a linear regression line, B) a continuous index and binary index, C) an S shaped curve for the probability of death and age, and D) the logit of the probability of death which transforms the curve into a straight line.*

There is no agreed single approach for the development of a prognostic tool. In this study, binary logistic regression is used to develop predictive models. There are two common approaches: a) reducing the number of candidate indices by using univariate analysis prior to multivariate analysis; and b) including all indices in multivariate analysis.

In the first approach, univariate analysis (such as univariate logistic regression, or the chi squared test) is used to look for associations between predictors and the outcome. To explain this approach and a potential weakness, the following hypothetical example is used.

In an observational study, a group of adults of 65 or over are monitored over a ten year period. Over this period, 200 of the 500 men and 200 of the 500 women die (t, “A”). On univariate analysis gender is not a predictor of death (“A” odds ratio 1, 95% CI 0.78-0.129, p = 1), but smoking is strongly related (“B”; odds ratio 11.40, 95% CI 7.50 to 17.34, p < 0.0001). The rates of death in male and female smokers are the same (“C”).

| | | Died | Survived | Died / total % |
|---|---|---|---|---|
| A | Female | 200 | 300 | 200 / 500 (20%) |
| | Male | 200 | 300 | 200 / 500 (20%) |
| B | Smokers | 150 | 30 | 150 / 180 (83.3%) |
| | Non-smokers | 250 | 570 | 250 / 820 (30.5%) |
| C | Men who smoked | 50 | 10 | 50 / 60 (83.3%) |
| | Woman who smoked | 100 | 20 | 100 / 120 (83.3) |

*Table 4.6: Illustrative data to show limitations of using univariate analysis to exclude indices*

However, the overall rates of smoking were twofold higher in women than men, and so a higher death rate would be expected in women. As this did not occur, it suggests that being male is associated with death. This is confirmed when performing multivariate analysis, which shows both smoking and male gender are independent predictors of death: smoking odds ratio = 12.35, 95% CI 8.05 to 18.94, p < 0.0001; male gender odds ratio = 1.39, 95% CI 1.05 to 1.85).

In order not to reduce the chances of missing important predictors on univariate analysis, a p value of 0.1 or 0.2 may be selected, rather than 0.05. However, the above example shows that it is still possible to miss predictors with this approach.

To avoid this problem, all variables can be included in model development.[256] There are various ways this can be performed, and the approach taken in this study for the development of the PEARL score is described.

All candidate indices shown in Table 4.5, except for weight loss, were included in the initial model and the removal criteria were set (p = 0.1). There is no requirement to use a p value of 0.05, which is the case in hypothesis testing and estimation. The strength of the association with the outcome is of more relevance in prognostic research and it may be appropriate to include an index with a p value higher than 0.05. This is described by Steyerberg [251] who explains that non-significance is not evidence for a zero effect of a predictor; indices that occur infrequently may not meet statistical significance without a very large sample size. Furthermore, the inclusion of indices in a model that have no association with the outcome lead to a minimal decrease in prognostic power within simulation studies.

Weight loss was not entered into the model due to the relatively high rate of missing data and labour intensity in collection, a problem which would likely recur in clinical practice.[256] The index with the highest p values was removed, and the model was then re-fitted to the remaining indices. This process, known as backwards elimination, is repeated until only indices with a p value of less than 0.1 remain.

Previous studies have demonstrated a relationship between both anxiety and depression and readmission.[260, 261] Methods of recording anxiety and depression vary substantially between clinicians and across healthcare settings. Due to the lack of objective data regarding these variables, they were not included in model development.

Once all of the independent predictors of outcome have been identified on multivariate logistic regression, the final indices need to be selected. The number of indices in a model follows the law of diminishing returns, in that additional indices have less impact on prognostic power. For example, in the DECAF derivation study, the full model of ten indices had an AUROC of 0.89 compared to 0.86 for the five strongest indices which appear in the DECAF score. The removal of independent predictors is a pragmatic decision: smaller models are easier to interpret and use in practice, and the loss of prognostic power may be minimal. The coefficients of the remaining predictors will be different once other indices are removed, and should be re-estimated.

This selection of fewer prognostic indices is a pragmatic decision as such scores are easier to calculate at the bedside. Similarly, converting beta coefficients into weightings allows for bedside calculations without the aid of a computer.[262] This is the approach we followed in the development of all scores.

*Overfitting in regression models*

In developing a model, there is an assumption that the derivation population are representative of the underlying population (all patients admitted with an AECOPD). This should allow for accurate predictions in a new population based on the analysis in the derivation cohort. However, even if a derivation study is robustly performed, and data collection is accurate and complete, the predictors may not apply to new subjects due to "idiosyncrasies of the sample".[251] If a developed model includes such idiosyncrasies then the model may be overfitted. A model that is overfitted will not perform well in a separate validation cohort.

One reason for this difference in performance is regression to the mean.[251] In a derivation study, many indices are included, and the best performing candidates may be selected. There is a greater likelihood of selecting indices which are performing at their best. The model may therefore include indices in which the strength of the association (beta coefficient) has been over-estimated. The more indices included in the original model, the greater the risk of overfitting. It is even possible for indices to be selected by chance that have no true association with the outcome. This risk can be reduced by having a larger sample size and by only including indices with relatively large effects.

Predictions for future subjects can be improved by adjusting regression coefficients. In a linear regression model, this involves reducing the mean squared error, which will slightly increase bias but increase precision (by reducing variance). A similar approach may improve prediction within logistic regression models too.

Shrinkage after estimation is a method that reduces regression coefficients towards zero. The shrinkage factor is based on the likelihood ratio for the model and the degrees of freedom (the number of indices in the model). A model can also be re-adjusted based on analysis in new cohorts; in this situation the beta coefficients can be adjusted towards the new estimate, rather than towards zero.

### *4.2.11 Model assessment*

In linear regression models, the variation between predicted values and observed values can be measured with $R^2$. This is a measure of the distance between predictions and observed outcome, with a score of 1 indicating that the model is a perfect fit to the data. Whilst $R^2$ is a useful measure for linear regression models, it cannot be performed for binary logistic regression models

We report the Nagelkerke's $R^2$, which can be used in logistic regression models. This measure is severe for instances in which a patient with the outcome has a very low prediction, and Nagelkerke's $R^2$ values tend to be lower than are seen with $R^2$ values in linear models.[263]

There are two key aspects to measuring overall performance of a clinical score: discrimination and calibration. Discrimination is a measure of how accurately predictions discriminate between those patients with the outcome compared to those without the outcome. Calibration is a measure of the agreement between predicted outcomes and the actual (observed) outcomes across the full range of predicted outcomes (risk groups).

*Sensitivity, specificity and discrimination*

The c statistic is a measure of concordance used to assess the discrimination of a generalised linear model.[263] For a binary logistic regression model, the c statistic is identical to the area under the receiver operating characteristic (AUROC) curve.

The AUROC curve plots the sensitivity (the true positive rate) against 1 – specificity (false positive rate). In order to do this, patients need to be classified as positive or negative based on different cut-offs. The following example uses the DECAF score.[2] The starting point assumes that all patients are classified as positive. This means that the false positive rate is zero, and represents the farthest top right point on the curve with a sensitivity of 1 and specificity of 0 (Figure 4.2). The curve then shifts though different cut offs (which in this example are based on the DECAF scores of patients) towards the bottom left hand corner of the curve which represents a sensitivity of 0 and specificity of 1.

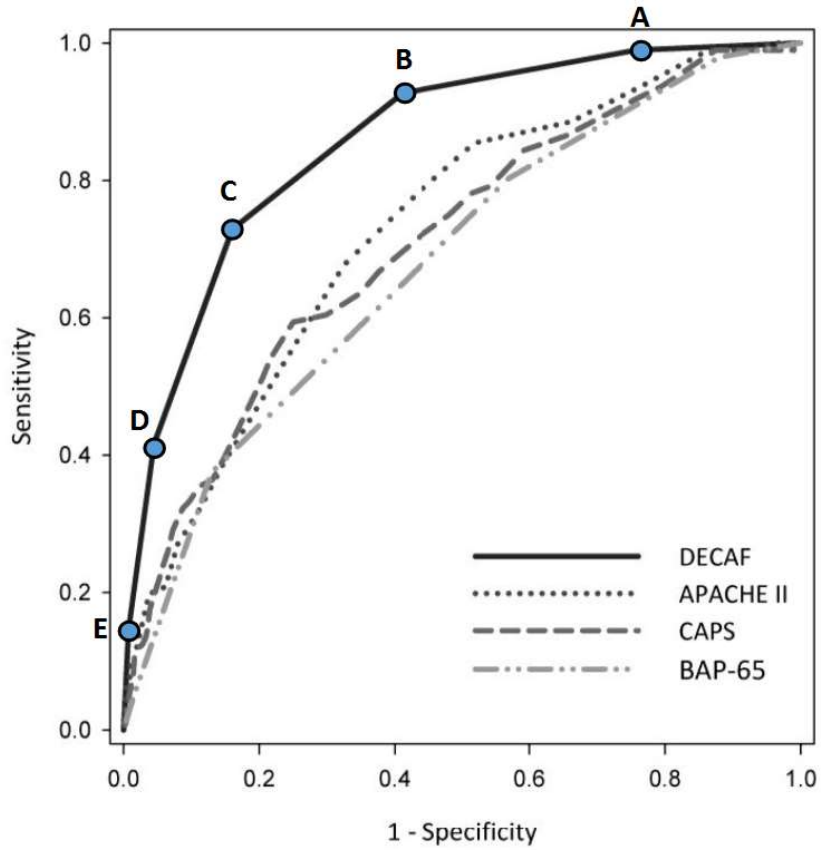


*Figure 4.2: DECAF, APACHE II, CAPS and CAP-65 ROC curves from DECAF derivation study*

Sensitivity= true positive / (true positive + false negative). This calculation is performed for all DECAF cut-offs, with all patients that died above the cut-off labelled as true positives and all those that died below the cut-off labelled as false negatives. For example, for a DECAF score of 3 (which represents a cut-off of 3.5) the sensitivity is calculated as follows. All those patients with a DECAF score of 4 or more who died are labelled as true positive (n = 70, Table 4.7). The false negative value is those who died who had a DECAF score of 3 or less (n = 26). 70/(70+24) = 0.73.

Specificity= true negative / (true negative + false positive). This calculation is performed for all DECAF cut-offs, with all patients that survived above the cut-off labelled as true negatives and all those that survived below the cut-off labelled as false positives.

For example, there were 132 patients who survived with a DECAF score of 4 or more, and 692 with a DECAF score of 3 or less. 132 / (132+162) = 0.16. This value is subtracted from one to give the 1 – specificity which is plotted on the graph with the

corresponding sensitivity (point C, Figure 4.2). Table 4.7 shows the different values which are calculated to plot the AUROC curve for the DECAF score.

| DECAF | Group, n | Died, n | True +ve | False -ve | Sensitivity | True -ve | False +ve | Specificity | 1 - specificity | Point on graph |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 201 | 1 | | | 1 | | | 0 | 1 | Top right |
| 1 | 291 | 6 | 95 | 1 | 0.99 | 624 | 200 | 0.76 | 0.24 | A |
| 2 | 226 | 19 | 89 | 7 | 0.93 | 339 | 485 | 0.41 | 0.59 | B |
| 3 | 125 | 30 | 70 | 26 | 0.73 | 132 | 692 | 0.16 | 0.84 | C |
| 4 | 57 | 26 | 40 | 56 | 0.42 | 37 | 787 | 0.04 | 0.96 | D |
| 5 | 20 | 14 | 14 | 82 | 0.15 | 6 | 818 | 0.01 | 0.99 | E |
| 6 | 0 | n/a | | | 0.00 | | | 0 | 1 | Bottom left |

*Table 4.7: Example tables showing how to calculate sensitivity and 1-specificity for ROC curve analysis*

Once these points have been plotted, the area under the curve can be calculated. The area under the curve is the probability that a patient with the outcome, in this example death, is given a higher probability by the score than a randomly chosen patient without the outcome. The nearer the AUROC curve area is to 1, the better the prognostic score (Figure 4.3). A perfect predictive score will have a AUROC of 1, whilst a score with no predictive power- such as the toss of a coin- would score zero.

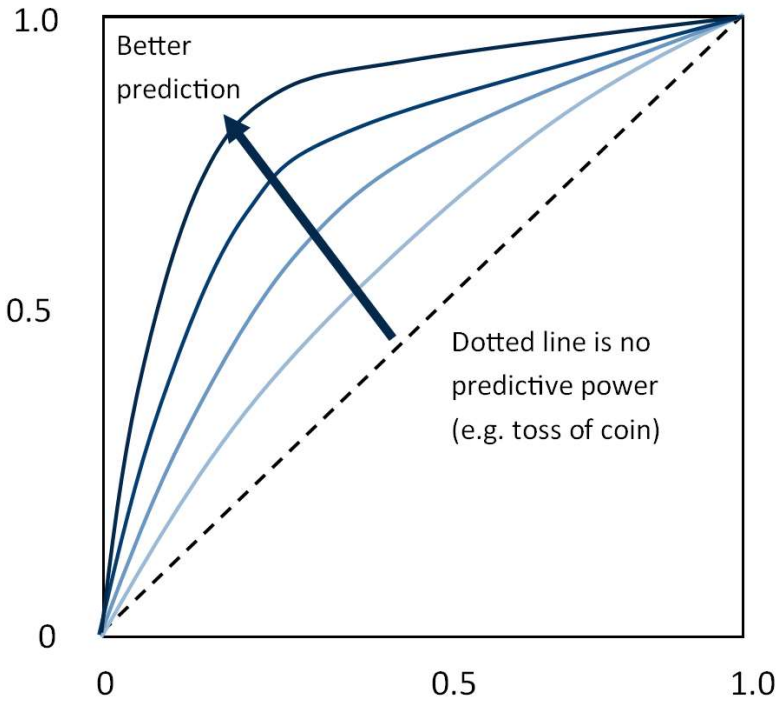


*Figure 4.3: Graph showing better prediction with higher AUROC values*

The usefulness of a clinical score in practice depends on more than discrimination and calibration. To establish clinical usefulness, a cut-off is required which can be termed the “decision threshold”. The choice of cut-off depends on the context of the medical decision. For example, in identifying patients with an AECOPD who are suitable for home treatment, a DECAF score of 0-1 would be appropriate, as only 7 in 492 patients died. The low number of false negatives is reflected in the high sensitivity. A prognostic score could show good discrimination, but be unsuitable at identifying low risk patients. This can be seen with the CURB-65 score in patients with pneumonic AECOPD (6.3 Validation of the DECAF score). Though the discrimination of CURB-65 was good, there was a high risk of death in the low risk group. This illustrates the importance of showing measures such as the sensitivity and specificity for each cut off, as well as calculating discrimination and calibration.

*Calibration*

There are several different ways of assessing the agreement between observed outcomes and predictions, also known as calibration. For a logistic regression model, the Hosmer-Lemeshow goodness-of-fit test [264] divides patients into risk groups. Hosmer and Lemeshow recommended that the number of risk groups selected should be one or more than the number of covariate in the model, though typically ten groups are used. Too few groups may not detect mis-calibration. The test calculates the observed number of outcomes (the proportion of patients in that group experiencing the outcome) to the predicted number of outcomes (the mean risk of all patients in that risk group). The null hypothesis for the test is that the model is fit to the data. A Hosmer-Lemeshow goodness-of-fit test less than $p = 0.05$ rejects the null hypothesis that the model does not fit the data well. However, it does not show that the model is a good fit to the data.

Calibration can be displayed visually on a calibration plot, which graphs the predicted risk on the x axis and the observed risk on the y axis (Figure 4.4). This again divides patients into risk groups based on observed and predicted outcomes. One approach is to plot the observed outcome into deciles of prediction, which is a graphical representation of the Hosmer-Lemeshow test.[251]

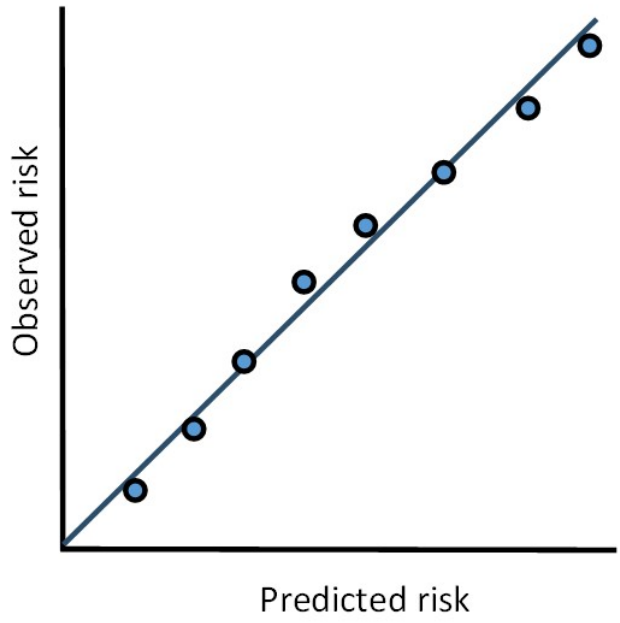


*Figure 4.4: Graph showing excellent calibration with measures of observed and predicted risk (dots) close to perfect (blue line)*

Rather than use deciles of risk, for a weighted model with a binary outcome, the observed and predicted risks can be calculated based on the weighted scores.[221] To explain this approach, Table 4.8 shows the results for a hypothetical readmission score from a derivation cohort. Only patients that scored a 2 have been included, and their individual risk calculated ("Patient risk of admission") from a regression equation. The mean risk is then calculated, which is 0.2, and can be plotted against the observed risk, which is the proportion of patients that were actually admitted ("Readmitted"- also 0.2). This can be repeated for each score, and the predicted and observed risks can be plotted.

| Patient | Patient risk of admission (predicted risk) | Readmitted (observed risk) |
|---|---|---|
| 1 | 0.18 | No |
| 2 | 0.19 | No |
| 3 | 0.2 | No |
| 4 | 0.21 | Yes |
| 5 | 0.22 | No |

*Table 4.8: Predicted risk and observed risk for patients scoring 2 for a hypothetical readmission score*

The predicted risk for the derivation cohort can be plotted against the observed risk by PEARL score for the derivation cohort, internal validation cohort and external validation cohort. For a well calibrated score, the observed risk should be close to the predicted risk, and lie near the 45 degree line (Figure 4.4).

Another form of calibration compares the observed risk by risk score across each cohort. The proportions of patients (with the outcome / total) can be compared across all cohorts by risk score using Fisher's exact test. A p value greater than 0.05 would show that there is no significant difference in the observed proportions.

*Comparing prognostic tools*

It is possible to compare prognostic tools using the method of DeLong.[199] This is a nonparametric approach to compare the AUROC curve between two models within the same data set. It is a paired comparison, so it is important that missing data has been dealt with appropriately prior to analysis, for example using multiple imputation.

Novel prognostic indices can be added to pre-existing tools. Using binary logistic regression, the additional prognostic benefit of a new index in an existing model can be assessed. In this situation it is inappropriate to use the DeLong method to compare the old model to the new model, which tends to provide conservative estimates. A preferred approach in this situation is to compare the Akaike Information Criterion (AIC).[204] The AIC is based on the -2 log likelihood calculated for the model from the regression analysis, with an adjustment for the number of indices in the model.

### *4.2.12 Model implementation*

The gold standard in creating a prognostic score involves three steps: 1) development, 2) validation and 3) assessment of its impact on patients with respect to health and cost outcomes when used in practice.[265] The deficits in prognostic studies are well described. There are many models that have been developed, but fewer that have been validated. Most of these studies that have been validated are done so in the same (split) cohort of patients, which does not assess the external validity of the derived model. Furthermore, published analyses of the impact of a prognostic model are rare: a recent review only identified two published analyses of the impact of a prognostic model.[265]

In order to assess the impact of a model an intervention and control arm is required. For the DECAF implementation study, we performed a randomised controlled trial of usual care compared to Hospital at Home in patients with a low risk DECAF score (0-1).

# Chapter 5 DECAF implementation study. Randomised Controlled Trial of Hospital at Home compared to usual care for patients admitted with a low risk AECOPD

## Chapter introduction

This chapter focusses on the research aims and methods of our RCT which compared HAH to standard inpatient care in patients admitted to hospital with a low risk (DECAF 0 or 1) AECOPD. Throughout this chapter, standard inpatient care will be described as usual care or abbreviated to UC.

## 5.1 Ethical approval

Eligible patients were approached in the admission units by a member of the respiratory team. Patients provided written consent for inclusion in the trial: patients who had diminished capacity were not approached. It was made clear to patients that non-participation in the trial would not affect their care. The existing literature shows that HAH/ESD is a safe intervention, and, in some instances, superior and preferable to standard inpatient care. Previous studies did not have the benefit of an accurate prognostic score to aid patient selection, which we used to identify low risk patients. Conversely: a) many of the previous studies were of ESD (rather than true HAH), in which patients are sufficiently well to return home; b) the DECAF score identifies a larger proportion of patients as low risk then were included in previous ESD/HAH studies; and c) a low risk DECAF score can include those with coexistent pneumonia who were typically excluded from previous studies.[2, 3, 255]

Written patient consent was obtained in all patients. Ethics approval was awarded by NRES committee North East- Sunderland on 22nd October 2013.

## 5.2 Study monitoring and safety

An independent data monitoring committee reviewed data on serious adverse events with the authority to stop the trial, but no interim efficacy analysis was planned.

Previous research showed that patients with a DECAF score of 0 or 1 have an in-hospital mortality of approximately 1.4%.[255] Based on this figure, one or two deaths in the acute period (14 days from admission) is expected. Given that the death rate in the acute period was expected to be low, the data monitoring group examined the

details of any deaths in this time period. Three or more deaths in the HAH was regarded as sufficiently high to trigger a review of the procedures around HAH, with four grounds for recommending discontinuation of this arm.

| Number of deaths | Probability of death |
|---|---|
| One or more | 0.39 |
| Two or more | 0.086 |
| Three or more | 0.013 |
| Four or more | 0.0014 |
| Five of more | 0.00012 |
| Six or more | 0.0000086 |

*Table 5.1: Number and probability of expected deaths at 14 days (provided to the data monitoring group)*

## 5.2 Study design and participation

The study took place at Northumbria NHS healthcare trust and the surrounding community as part of the HAH arm. The target population was consecutive patients triaged for admission with a primary diagnosis of AECOPD.

*Inclusion criteria*

1. Age ≥35 years
2. Smoking history ≥10 pack years
3. Obstructive spirometry (FEV1/VC <70%)
4. Primary diagnosis of AECOPD
5. DECAF score 0 or 1
6. Lack of ability to give informed consent.

*Exclusion criteria*

1. Other illness likely to limit survival to <1 year
2. Long term ventilation
3. Coexistent secondary diagnosis which necessitates admission
4. Acute confusion precluding discharge
5. Assessment more than one overnight stay after admission

We planned to recruit 140 patients over 20 months. Eligible patients were provided with verbal and written study information, and those that consented were randomised to HAH or standard inpatient care and followed-up for 90 days. The estimated recruitment period was based on recruitment to, and outcome of, the DECAF derivation study, which was conducted in the same hospitals as the RCT. We

allowed for acceptance and attrition rates of 60% and 15% respectively. We estimated that 585 patients would be assessed for eligibility, 445 of whom would be excluded for the following reasons:

- DECAF score >1, n=293
- Failure to meet remaining inclusion and exclusion criteria: n=59
- Decline to participate: n=93 (40%)

140 patients were to be randomised to HAH (n=70) or standard inpatient care (n=70). It was estimated that 12 patients per group would withdraw consent or be lost to follow-up resulting in 58 in each arm. All analyses were conducted on an intention to treat basis.

Risk stratification was performed by the DECAF score. Those admitted with a DECAF score of 0-1 (low risk) were eligible. All patients with an AECOPD who are low risk and meet the eligibility criteria were offered inclusion in the trial. If a patient was judged as “unsafe” for home treatment by any member of the healthcare team, but met all study entry criteria (which included having a low risk of acute death by the DECAF score), the patient was still offered inclusion. However, the final decision to allow the patient to return home with Hospital at Home was with the respiratory consultant in charge of the patient’s care; they could decide to keep the patient in hospital and treat them with usual care. Such patients were analysed in their allocated group (Hospital at Home) and all protocol violations were reported in the published study.

Patients remained in their allocated group for 90 days following the index admission. Those that received HAH for their index admission could also receive HAH for any future admissions with AECOPD within 90 days, provided the further AECOPD was low risk by DECAF score. Patients and healthcare professionals were not be blinded to the treatment.

### 5.3 Our model of Hospital at Home

HAH is the provision of care to support a patient at home during an illness normally requiring hospital admission. HAH as described here differs from supported discharge schemes, which are a part of standard usual care in some hospitals:

Patients will typically be discharged sooner, and will have access to more intensive treatment and clinical and social support in HAH.

HAH may help to maintain normal activities, foster greater independence and avoid hospital acquired infections. Education, including self-management, may be more successful if delivered in the home to the patient and their primary carer, rather than in the busy ward environment. Eligibility for HAH and the degree of support was assessed in hospital; whilst receiving HAH, the patient remained under the care of the hospital team. In our RCT, HAH treatment comprised once to twice daily respiratory specialist nurse visits supervised by a respiratory consultant, with additional input from physiotherapy, occupational therapy and formal social care as required. Telephone support was available with an on-call RSN 24 hours a day, seven days a week. Routine phone calls took take place every evening, with other extra calls on an ad hoc basis. Telephone calls were in addition to, and not a replacement for, home visits. Patients' observations, such as respiratory rate and pulse oximetry, were recorded. Other equipment, such as nebulisers and oxygen concentrators, were provided as needed. In those patients who had high care needs, a pendant alarm was available via social services which allowed direct contact to a named individual. One of the aims of this model of care was to allow patients to gain confidence managing their AECOPD at home, in a supported environment. The range of healthcare disciplines and level of support available were greater than many other services, reflecting the inclusive selection criteria, but tailored to the patient to ensure use of resource is appropriate.

Those randomised to HAH returned home with support from the specialist team as soon as possible, provided that the initial arterial pH ≥7.35 and $PaCO_2$ ≤6kPa. Patients with $PaCO_2$ >6 kPa without acidaemia returned home, provided they were improving, at 24 hours and patients with acidaemia were considered for transfer to HAH 24 hours after the acidaemia had resolved (Figure 5.1).

All patients, had an assess of their mobility, home circumstances and any additional social care needs (help with shopping, cleaning, personal care, meals on wheels), and transfer to HAH was dependent on adequate social support being in place. Urgent additional, same-day social input was available.

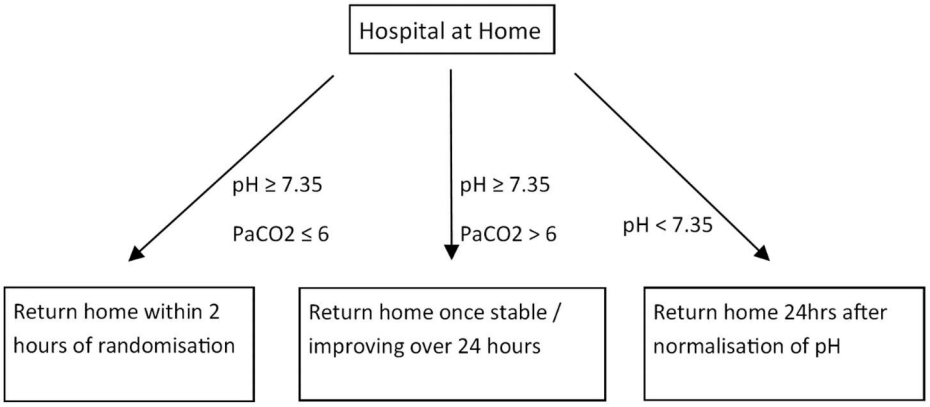


*Figure 5.1: Flowchart showing planned timings to return home based on arterial blood gas sampling*

## 5.4 Standard inpatient care

It is important to emphasise that standard inpatient care included the usual measures which are taken to ensure prompt discharge of patients with AECOPD, including supported discharge by specialist respiratory nurses. For the standard treatment group we anticipated that median stay would be similar to UK audit data and our previous local figures (median ~5 days).[150] The decision to discharge patients in the standard care group was made by the attending clinician, and not influenced by the research team.

## 5.5 Statistical methods

### *5.5.1 Randomisation and minimisation*

One to one randomisation was performed by minimisation, with a 30% chance of randomisation by random number sequence. This was provided by an external, independent agency. To allocate patients to groups, the researcher entered minimisation criteria into a web-based system. This ensured that the allocation sequence was unpredictable and blinded to the entire research team, including the person enrolling patients into the study. Baseline data, including quality of life scores, were collected prior to allocating patients to treatment groups. This was done to avoid the risk of bias which can result when collecting baseline health related quality of life scores in patients who have just been told that they are not receiving their preferred treatment. The minimisation criteria were selected based on their association with readmission and/or death (using a logistic regression model on DECAF 0 or 1 patients from previous DECAF studies) which are the major determinants of cost (Table 5.2).

| | | | |
|---|---|---|---|
| ABG (Management pathway) | CO2≤6 pH ≥7.35 | pCO2>6 pH ≥7.35 | pH < 7.35 |
| Hospital admissions previous year | 0 | 1 | 2 or more |
| Prior social care (private or social services) | | None | Social care |
| eMRCD score | | 1-4 | 5a |
| Cerebrovascular disease | | Yes | No |

*Table 5.2: Minimisation criteria*

### *5.5.2 Power calculation*

The estimated standard deviation of costs was £1,143, based on tariff costs received by the trust for 373 patients admitted with DECAF 0-1 AECOPD. This was based on the best available data, which was limited to health costs for the index admission. Based on tariff costs received by the trust for 373 patients admitted with DECAF 0-1 AECOPD, the estimated standard deviation of costs was £1,143, and a non-inferiority limit of £150 was chosen. We estimated that Hospital at Home would be £-470 per patient cheaper than usual care. If the true difference between groups was £-470, 118 patients would be required to be 90% sure that the lower limit of a one sided 95% confidence interval was above the non-inferiority limit of £150. This calculation was based on the standard approach described by Chow, Shao and Wang.[266] All participants provided consent for their data to be monitored electronically in the event that they withdraw from the study. This allowed for complete collection of data for health and social costs.

Bed days were analysed over the acute period (defined as the first 14 days from admission), follow up (end of acute period to 90 days) and the whole 90 day period. For hospital bed days over 90 days, including readmissions, in the standard care arm the estimated mean bed days as 7.8 days and for HAH 3.1 days, with a standard deviation of 7.8 days. We needed two groups of 58 patients to detect a difference in mean scores of 4.7 (7.8 days v 3.1 days) with 90% power assuming a type 1 error rate of 5%.

### *5.5.3 Missing data*

Data completion rates will be provided for outcome and the number of patients lost to follow up will be reported.

Patients who die in a study may have lower costs than those that survive. In the event that equal numbers of patients die, costs were to be included up to the point at which they died. We planned a sensitivity analysis excluding those that die in the event that death rates were different between arms.

Multiple imputation was used on missing data as described by Rubin (as described in 4.2.2 Dealing with missing data).[254]

### *5.5.4 Populations analysis*

Baseline characteristics, including severity of COPD and minimisation criteria are shown by treatment group and overall. This included: age, gender, minimisation indices (Table 5.2), markers of AECOPD severity (including DECAF indices, such as CXR consolidation), social circumstances, income, academic qualifications, smoking history, FEV1 per cent predicted and co-morbidity.

The inclusion or exclusion of patients in the final analysis who were randomised in error was, where possible, decided without knowledge of their allocated group and prior to any outcome.

The main two study populations compared were: 1) patients allocated to Hospital at Home treatment, and 2) patients allocated to usual care. Analyses were intention to treat, and in a sensitivity analysis multiple imputation was used for missing data to allow the inclusion of all patients.

A third patient group, those that declined to take part in the study, will be described. Descriptive data will be shown on patient age, gender, severity of AECOPD ad co-morbidity. This helps with the generalisability of the results to clinical practice by indicating if patients who declined were more or less well than included patients.

## 5.6 Treatments received

All patients with an AECOPD who were low risk and met the eligibility criteria were offered inclusion in the trial. If a patient was judged as “unsafe” for home treatment by any member of the healthcare team, but met all study entry criteria (which included having a low risk of acute death by the DECAF score), the patient was still offered inclusion. However, the final decision to allow the patient to return home with Hospital at Home was with the respiratory consultant in charge of the patients’ care, who could decide to keep the patient in hospital and treat them with usual care. Such patients were analysed in their allocated group (Hospital at Home).

Patients remained in their allocated group for 90 days following their index admission. Those that received HAH for their index admission could also receive HAH for any future admissions with AECOPD within 90 days, provided the further

AECOPD was low risk. Patients and healthcare professionals were not blinded to the treatment.

### 5.7 Overview of outcomes

The primary outcome was the total cost of health and formal social care over 90 days from presentation (informal carer costs are not shown). Secondary outcomes were cost-effectiveness, survival, readmission rates, bed days, patient preference, COPD exacerbations, hospital anxiety and depression scores (HADS), COPD assessment tool (CAT) scores and the EQ-5D-5L score[44] measured at 14 and 90 days.

Resource use and associated costs were calculated at the patient level and average costs per treatment arm and variance were estimated. Data collection was the same in both arms, except for resource collection during HAH treatment. All visiting health and social care staff recorded time spent with the patient and travel time.

Over 90 days, patients in both arms maintained a diary of all health and social care visits, and attendances (such as accident and emergency, GP, and outpatient appointments). Patients were phoned every two weeks to prompt completion and obtain a back-up record of activity. These data were cross-referenced with primary, secondary and social care records, and were reviewed at the 90 day home visit. To ensure complete capture of information for the primary outcome, additional consent was sought for remote monitoring of health and social records if the patient withdrew from the trial.

For primary care, resource use included all medications, GP appointments, and home visits by doctors and allied healthcare professionals. Secondary care inpatient resource was recorded for the index admission and for all readmissions (including return to hospital) and included staff time, diagnostic and laboratory tests, medication, and length of stay. Hospital costs and capital costs were obtained from NHS trust finance department, and the cost of a day on a ward was micro-costed. All outpatient visits and accident and emergency attendances were recorded.

Social care resource use, including formal social care and equipment costs, were obtained from individual social care records.

Unit costs were obtained from a variety of national and local sources and are reported in Chapter 7 for the financial year 2015 (pounds sterling). Average costs per patient were calculated by multiplying unit cost by resource use.

For secondary health-related quality of life measured by the EQ-5D-5L instrument, data were recorded in hospital at baseline and at home visits at 14 and 90 days.

### *5.7.1 Primary cost analysis*

All costs were calculated at the patient level, unless stated otherwise. The study was costed from an NHS and personal social services perspective.

The data collection method or tool are listed below:

1) staff resource use questionnaires (data from medical and electronic records);
2) time and motion questionnaires for Respiratory Specialist Nurses;
3) a baseline health and resource use proforma;
4) post-discharge health economics questionnaires completed by patients; and
5) post-discharge social services costs spreadsheet.

*NHS - Primary care and community care costs*

Following discharge from their index episode, patients recorded all health and social care costs and were phoned on a two weekly basis to ensure data were completed. Data were reviewed at the 90-day visit and triangulated with data from medical records which included GP records.

*NHS - Secondary care costs*

Some patients with AECOPD have all of their investigations and initial treatments in accident and emergency, whilst others have some of these performed in the admissions unit. If all aspects of care were costed from admission, patients who had identical investigations and treatments could be costed differently. Therefore, for consistency, all investigations and treatments in accident and emergency were included in the cost of admission. This is appropriate, as in many hospitals the main route of admission for GP admissions is direct to the admissions unit. All other costs were calculated from the time of admission.

| NHS costs | Data collection method |
|---|---|
| Primary care | |
| GP visits- surgery | 1 and 4 |
| GP visits- home | 1 and 4 |
| GP telephone calls | 1 and 4 |
| Practice nurse visits | 1 and 4 |
| Medications | 1 and 4 |
| Investigations | 1 and 4 |
| **Community care** | |
| District nurse | 1 and 4 |
| Physiotherapy | 1 and 4 |
| Occupational therapy | 1 and 4 |
| Dietician | 1 and 4 |
| Psychology | 1 and 4 |
| Investigations | 1 and 4 |
| **Secondary care** | |
| A + E attendances | 1 |
| Length of stay by ward | 1 |
| Medications | 1 and 3 |
| Investigations | 1 |
| Physician time | 1 |
| Respiratory Nurse time | 2 (and 1) |
| Physiotherapy | 1 |
| Occupational therapy | 1 |
| Dietician | 1 |
| Psychology | 1 |
| **Social care resource use** | |
| Social worker | 3, 4 and 5 |
| Home help | 3, 4 and 5 |
| Adaptations | 3, 4 and 5 |

*Table 5.3: Resource use and data collection (numbers correspond to list p113)*

The cost of the time on a ward was micro-costed to give a cost per day. This was used to calculate the hospital bed stay and staffing costs associated with the patients' in-hospital stay. This approach was used for HAH and usual care patients for the time spent in hospital.

All patient reviews by healthcare staff such as doctors (including level of seniority), pharmacist and physiotherapy was recorded.

During Hospital at Home episodes, the Respiratory Specialist Nurses completed time and motion forms on a selection of patients. This included the collection of data on all aspects of care related to the patient, including administration duties. For all patients in the Hospital at Home arm, visits and travel time undertaken by health and social care staff were recorded.

The cost of all inpatient medication was calculated from the patients' medication chart. The cost of medication supplied as an inpatient was based on the tariff costs from the British National Formulary. The costs of all investigations was calculated, and included add-on costs.

*Social care resource use*

Patients and their carers kept a record of all social services resources use. Records of social service resource use was triangulated with social services social records at the patient level.

*Valuation of NHS and informal care giving resource use*

For each trial participant, all components of treatment costs stratified by category of resource use were computed by multiplying units of resource use by their unit costs. These were then summed over all resource use categories to obtain a total cost for each participant both from an NHS and personal social services perspective. This was then used to generate the average cost per patient in each arm of the trial.

The unit costs for resources used for the costs of the HAH intervention includes short term in-hospital costs, staff time, medications and costs of investigations. The cost of the ward stay was micro-costed from the Trusts finance department and included nursing staff costs and hospital bed stay costs and was presented as an average cost per day. With the exception of the costs of a respiratory ward stay, all unit costs were derived from multiple sources including NHS Reference Costs (2015) (Department of Health 2015)[267] and the Personal Social Services Research Unit's Unit Costs of Health and Social Care 2015 cost compendium.[268] All unit costs are expressed in GBP (£) and valued at 2015-16 prices.

*Cost analysis*

The primary outcome was the difference in health and social costs between both treatment groups at 90 days. Our null hypothesis is that Hospital at Home treatment

is inferior to usual care treatment for health and social costs at 90 days. For the primary analysis, a one sided 95% confidence interval was used to calculate the inferiority analysis. For all other comparisons, a two-sided significance level of $p<0.05$ was be used.

A bootstrap approach was used to compare the mean difference in costs between the groups and estimate the one sided 95% confidence interval for the non-inferiority analysis. In non-inferiority studies, it is considered good practice to show a graph of the confidence interval and the non-inferiority limit to explain the results.[269] If the confidence interval lies entirely above the inferiority margin, then the null hypothesis can be rejected (lines A and B, Figure 5.2). If the confidence interval crosses the non-inferiority margin (line C, Figure 5.2) or lies entirely below it, then the null hypothesis has not been rejected. The non-inferiority limit is £150 (Δ, Figure 5.2).[269]

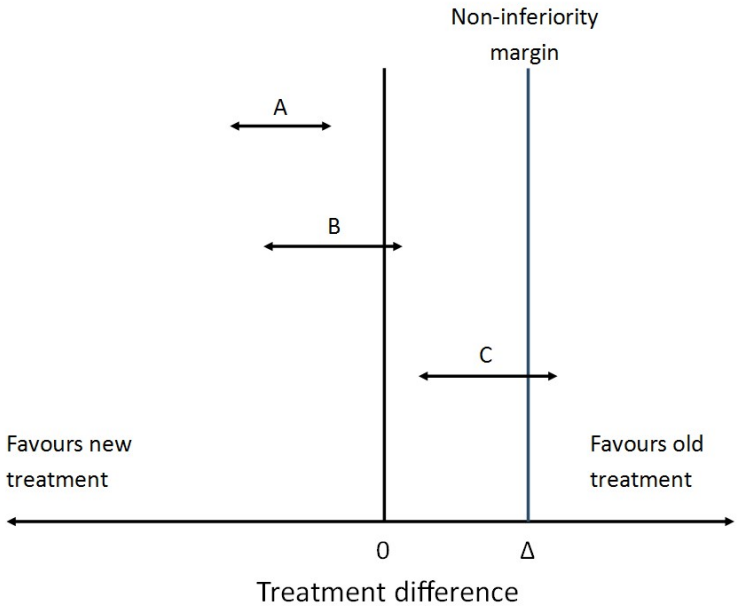


*Figure 5.2: Relationship between confidence interval and outcome*

### *Sensitivity analyses of costs*

In a sensitivity analysis, the costs in the usual care group was calculated using data on length of stay prior to the start of the study. Within the study, low risk DECAF patients who were due to go home the day they were identified by the research team were not recruited. By definition, HAH is a treatment without which the patient would require in-hospital care. Therefore, the length of stay in the usual care arm can

increase compared to historical controls. However, the trial may reduce length of stay in the usual care group by reassuring clinicians and patients that earlier discharge is appropriate.

### *5.7.2 Effectiveness*

*Calculation of health utilities and Quality Adjusted Life Years (QALYs)*

In line with NICE recommendations (NICE 2013) on outcomes in economic analyses, QALYs were measured. Data used to estimate QALYs was collected using the EQ-5D-5L. This was used to collect information about participant's health related quality of life (HRQoL) at baseline, 14 days and 90 days. The EQ-5D-5L allows HRQoL to be valued on a scale where perfect health and death are 1 and 0 respectively (1.1.6 EQ-5D-5L).

Mean QALY differentials between the groups were generated from the utility values derived from responses to the EQ-5D 5L during the follow-up period using the regression approach, controlling for baseline utility.[270] This area under the curve approach (Figure 5.3) puts a time weight onto each utility score which allows us to generate QALY values for each participant.

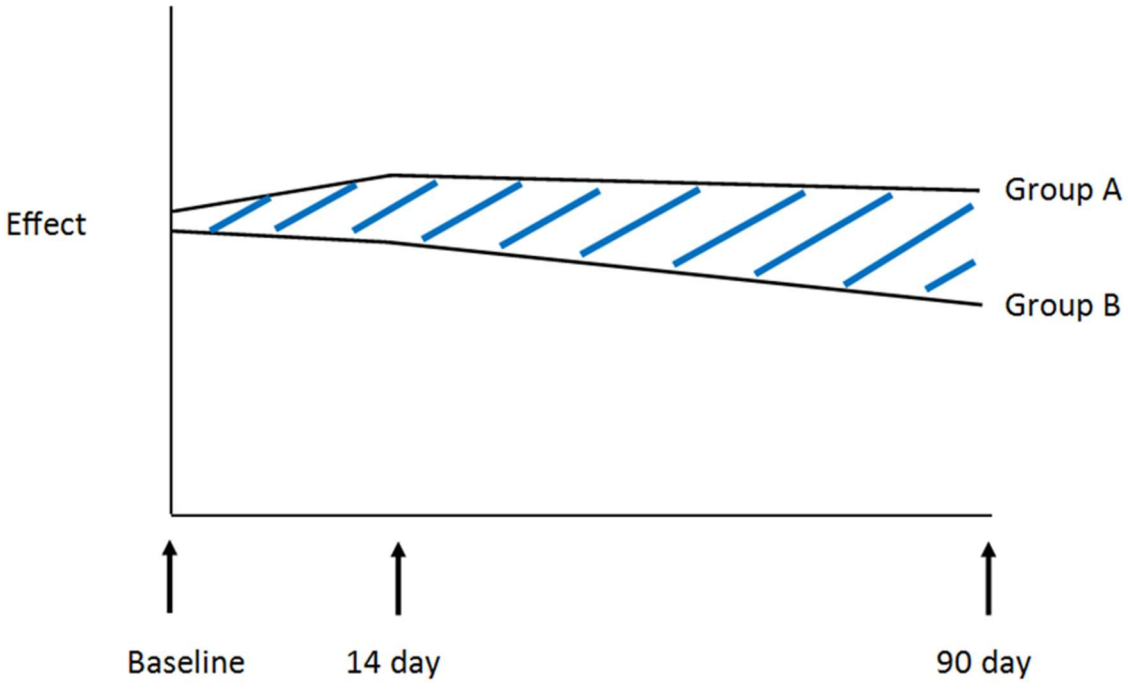


*Figure 5.3: Illustration of the area under the curve approach*

*Cost Utility Analysis*

A cost-utility analysis was performed based on incremental costs per QALY gained of the HAH intervention over usual care.

If an intervention results in improved outcomes and cost savings relative to normal care, then the intervention would, according to the economic evaluation, be regarded as the dominant option (South-East quadrant, Figure 5.4). A dominant study is the holy grail of economic evaluations. More typically, positive studies are more effective but more costly (North-East quadrant, Figure 5.4).

The incremental cost per QALY gained will be calculated, showing the rate of return of QALYs gained based on additional resources invested. The Incremental cost effectiveness ratio (ICER) is calculated by the incremental cost divided by the incremental change in QALYs. The results of the analyses will be presented as point estimates of mean incremental costs and QALYs

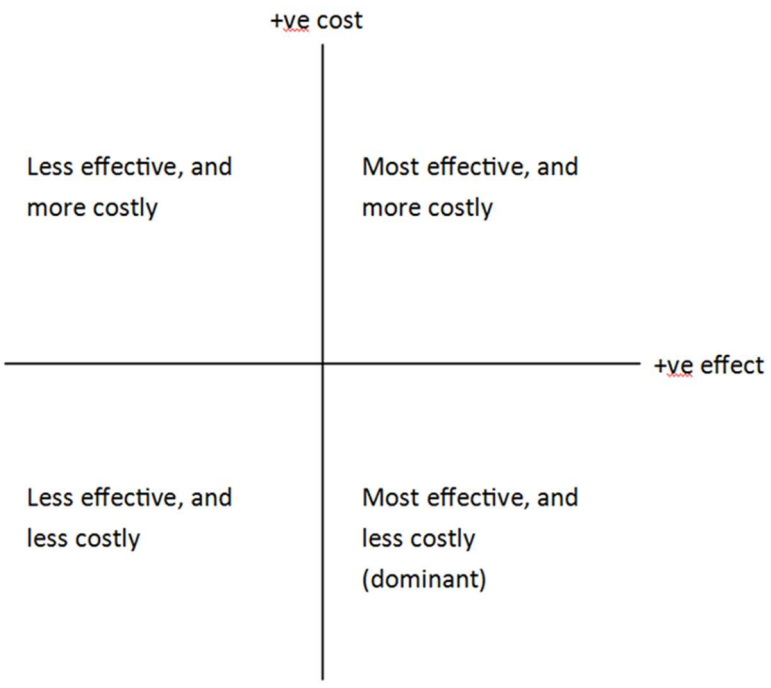


*Figure 5.4: Cost-effectiveness plane*

1000 bootstrapped samples will be undertaken to express the uncertainty around the incremental cost per life year gained/QALY ratio based on mean costs and outcomes. The results of the bootstrapping simulations will be presented on the 'cost-effectiveness plane', which highlights the preferred treatment option (Figure 5.4). If

the results lie in the north-west (NW) or south-east (SE) quadrants the preferred treatment is clear, as one option dominates the other. If the results lie in the north-east (NE) or south-west (SW) quadrants the decision as to which is the preferred treatment is less clear (i.e. one option may be less costly but also less effective, or more effective but at greater cost); the ICER may aid this decision.

A cost-effectiveness acceptability curve (CEAC) based on the net benefit approach [271] will be used to present the probability of the intervention being cost-effective, based on a range of values for society's willingness to pay for a unit of outcome. Base case results will utilise data with complete information, the 'complete cases' for both costs and effects.

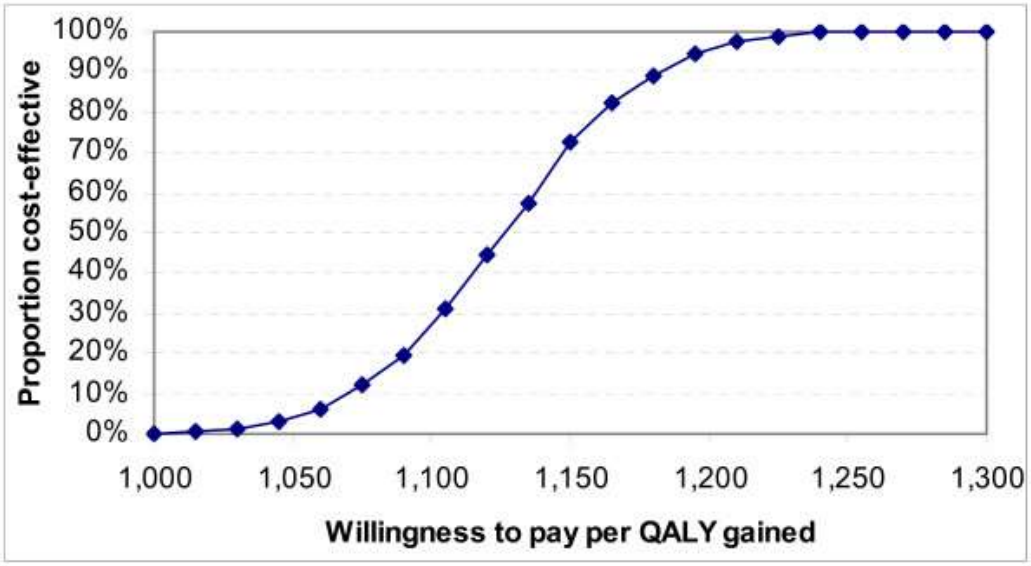


*Figure 5.5: Cost Effectiveness Acceptability Curve*

### *5.7.3 Other secondary outcomes*

*HADS, CAT and utility score*

The change in quality of life scores from baseline at 14 days and 90 days was calculated. For HADS and CAT, negative values represent improvements in health from baseline, whilst for utility scores, positive values represent improvements from baseline. The per cent of patients improving by the minimum clinically important difference (MCID) was also calculated.

*Bed days*

Bed days over 90 days were compared using a two-sample t test for 90 days. Separately, the number of days under Hospital at Home care (days in hospital and days treated at home) is presented with the number of days treated in usual care for the index admission.

# RESULTS

# Chapter 6 The validation of the DECAF score

## 6.1 Patient characteristics

Data were obtained for 880 and 845 patients in the internal and external validation cohorts respectively. Across both cohorts, mean (SD) age was 73.1 (10.3) years, 54.3% were female, and most had severe airflow obstructive; mean (SD) $FEV_1$ 45.5 (18.3) %predicted. The median DECAF score was 2 (IQR 1 to 3), 28.3% had radiographic consolidation and 18.9% had an acidaemic exacerbation (pH < 7.35). In-keeping with the UK national audit,[11] rates of co-morbidity were high, notably ischaemic heart disease and diabetes (table 2).

Significant differences between sites included: the proportion requiring institutional care, radiographic consolidation, age, gender, DECAF score, severity of airflow obstruction, the number of previous hospital admissions and the proportion with significant weight loss. Sites were broadly similar for co-morbidity, though the proportions with left ventricular dysfunction, anxiety or depression differed.

Patients with a survival of less than one year for a reason other than COPD were excluded. For the internal validation cohort, patients were not eligible as follows: survival less than one year n = 27 (12 lung cancer, 3 end stage dementia, 3 metastatic cancer, 2 metastatic bladder cancer, 2 idiopathic pulmonary fibrosis, 1 metastatic renal cancer, 1 metastatic bower cancer, 1 metastatic rectal cancer, 1 oesophageal cancer, and 1 mesenteric cancer patient), less than ten pack year smoking history n = 24, spirometry not obstructive = 42. Ten patients had no ABG results, but had supplemental oxygen or oxygen saturations that were too low to assume a DECAF acidaemia score of zero. One patient had no eosinophil count.

## 6.2 Missing data

There were no missing mortality or DECAF data. The percentage of complete data for each risk score was: BAP-65 97.2%, CURB-65 96.5%, CAPS 85.9% and APACHE II 73.2%. For individual variables, missing data were $P_aO_2$ 12.6%, albumin 12.2%, pH 12.1%, GCS 11.7%, potassium 3.3%, confusion 2.6%, temperature 2.6 %, mean arterial blood pressure 1.8%, respiratory rate 1.8%, systolic BP 1.7 %, diastolic BP 1.7%, heart rate 1.4%, haematocrit 1.2%, creatinine 0.5%, white blood cell count 0.2%, urea 0.1% and sodium 0.1%.

| | Internal validation n= 880 | | External validation n= 845 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Site A** n= 459 | **Site B** n= 421 | **Site C** n= 307 | **Site D** n= 271 | **Site E** n= 171 | **Site F** n= 96 | **All sites** N= 1725 | **P value** |
| Recruitment period | 1/1/2012-31/5/2013 | 1/1/2012-31/5/2013 | 21/8/13-26/5/14 | 1/7/13-30/4/14 | 25/4/13-14/2/14 | 1/2/2014-28/4/2014 | 1/1/12-26/5/14 | N/A |
| Recruitment/day | 0.89 | 0.82 | 1.07 | 0.89 | 0.58 | 1.12 | 0.86 | N/A |
| Died in-hospital, % | 9.8 | 7.8 | 7.5 | 6.6 | 4.7 | 5.2 | 7.7 | 0.27 |
| DECAF 0-1, % | 44.4 | 46.6 | 47.6 | 34.3 | 44.4 | 61.5 | 44.9 | 0.00018 |
| DECAF 2, % | 30.9 | 26.6 | 29.6 | 28.0 | 32.7 | 21.9 | 28.9 | 0.33 |
| DECAF 3-6, % | 24.6 | 26.8 | 22.8 | 37.6 | 22.8 | 16.7 | 26.3 | 0.00013 |
| **Sociodemographics** | | | | | | | | |
| Age, years* | 73.5 (9.9) | 73.9 (10.3) | 73.5 (10.4) | 72.0 (9.8) | 72.4 (10.7) | 70.7 (11.4) | 73.1 (10.3) | 0.025 |
| Female, % | 56.4 | 58.0 | 56.4 | 40.6 | 58.5 | 53.1 | 54.3 | 0.00012 |
| Smoking pack-yrs, n† | 41 (30-58) | 40 (30-55) | 44 (30-60) | 40 (30-56) | 45 (30-60) | 40 (30-59) | 40 (30-59) | 0.71 |
| Current smoking, % | 38.2 | 40.9 | 39.7 | 36.2 | 36.1 | 47.4 | 39.1 | 0.41 |
| Institutional care, % | 8.9 | 5.0 | 2.9 | 2.6 | 4.1 | 5.2 | 5.2 | 0.0018 |
| **Markers of disease severity** | | | | | | | | |
| eMRCD score 1-4, % | 44.7 | 49.2 | 49.5 | 35.1 | 44.4 | 68.8 | 46.4 | <0.0001 |
| eMRCD score 5a, % | 39.7 | 36.6 | 30.3 | 24.7 | 42.1 | 24.0 | 34.3 | <0.0001 |
| eMRCD score 5b, % | 15.7 | 14.3 | 20.2 | 40.2 | 13.5 | 7.3 | 19.3 | <0.0001 |
| Hospital admissions in previous year, n† | 0 (0-1) | 0 (0-1) | 1 (0-1) | 1 (0-2) | 1 (0-2) | 1.5 (0-3) | 0 (0-1) | <0.0001 |
| FEV1% predicted* | 47.8 (19.4) | 48.5 (18.5) | 44.8 (18.2) | 40.6 (14.9) | 40.5 (15.4) | 46.6 (20.4) | 45.5 (18.3) | <0.0001 |
| LTOT, % | 15.7 | 16.2 | 13.4 | 17.7 | 26.8 | 17.7 | 16.9 | 0.014 |
| Cor pulmonale, % | 5.9 | 7.4 | 10.4 | 8.5 | 8.9 | 2.1 | 7.5 | 0.052 |
| LT prednisolone, % | 8.1 | 6.7 | 5.5 | 10.0 | 9.0 | 7.3 | 7.6 | 0.38 |
| **Co-morbidity** | | | | | | | | |
| IHD, % | 27.5 | 32.3 | 31.9 | 27.7 | 26.6 | 27.1 | 29.4 | 0.46 |
| CVD, % | 13.3 | 12.4 | 13.1 | 13.7 | 5.9 | 11.5 | 12.3 | 0.14 |
| Diabetes, % | 11.3 | 11.9 | 15.0 | 13.0 | 14.8 | 17.7 | 13.1 | 0.40 |
| Atrial fibrillation, % | 14.8 | 20.7 | 16.9 | 17.7 | 16.4 | 14.6 | 17.2 | 0.33 |
| LVD, % | 8.1 | 9.3 | 18.2 | 10.0 | 4.7 | 3.2 | 9.9 | <0.0001 |
| Cognitive impairment, % | 5.0 | 5.0 | 6.8 | 8.5 | 3.6 | 1.0 | 5.5 | 0.049 |
| Anxiety, % | 13.9 | 13.3 | 37.6 | 20.3 | 7.1 | 9.4 | 18.1 | <0.0001 |
| Depression, % | 23.3 | 18.3 | 33.6 | 25.5 | 19.4 | 9.4 | 23.1 | <0.0001 |
| **Admission clinical data** | | | | | | | | |
| Acute confusion, % | 12.9 | 12.9 | 8.7 | 8.9 | 6.6 | 6.3 | 10.6 | 0.060 |
| Respiratory rate, n* | 26.5 (6.8) | 25.7 (6.0) | 21.8 (4.5) | 24.1 (6.2) | 23.9 (6.2) | 23.5 (6.3) | 24.7 (6.3) | <0.0001 |
| Pulse rate, n* | 104.9 (21.0) | 102.8 (22.8) | 97.1 (18.3) | 102.2 (20.5) | 104.7 (21.6) | 99.7 (18.4) | 102.3 (21.0) | <0.0001 |
| sBP, mmHg* | 136.5 (30.3) | 145.2 (26.6) | 130.8 (22.0) | 135.0 (26.5) | 134.5 (22.9) | 133.6 (24.2) | 137.1 (26.9) | <0.0001 |
| dBP, mmHg* | 74.6 (17.0) | 80.0 (19.0) | 71.6 (15.8) | 77.2 (18.5) | 77.3 (19.6) | 73.2 (13.7) | 76.0 (17.9) | <0.0001 |
| Temperature, $^0$C† | 36.9 (36.3-37.6) | 36.5 (36.0-37.2) | 36.8 (36.4-37.3) | 36.5 (36.0-37.1) | 36.5 (35.9-37.0) | 36.7 (36.0-37.0) | 36.7 (36.2-37.3) | <0.0001 |
| Oxygen saturation† | 92 (87-94) | 93 (88-95) | 94 (91-95) | 93 (90-95) | 93 (90-95) | 92 (91-95) | 93 (89-95) | <0.0001 |
| Pedal oedema, % | 25.8 | 21.6 | 26.8 | 27.0 | 32.7 | 5.3 | 24.9 | <0.0001 |
| BMI, kg/m$^2$ * | 25.1 (6.8) | 24.9 (6.8) | 24.5 (6.4) | 25.4 (6.4) | 24.1 (6.5) | N/A | 24.9 (6.6) | 0.28 |
| Weight loss >5%, % | 14.2 | 10.6 | 21.2 | 24.7 | 12.9 | 2.4 | 15.3 | <0.0001 |
| CXR consolidation, % | 30.5 | 34.4 | 22.8 | 30.6 | 18.7 | 19.8 | 28.3 | <0.0001 |
| **Arterial Blood Gas values** | | | | | | | | |
| pH† | 7.42 (7.37-7.46) | 7.42 (7.37-7.46) | 7.43 (7.38-7.46) | 7.40 (7.35-7.44) | 7.45 (7.38-7.48) | 7.39 (7.35-7.43) | 7.42 (7.37-7.46) | <0.0001 |
| $PaO_2$, kPa† | 8.0 (6.9-9.3) | 8.0 (6.9-9.3) | 8.6 (7.7-9.8) | 8.4 (7.3-10) | 9.4 (7.8-9.4) | 8.3 (7.5-9.4) | 8.3 (7.2-9.7) | <0.0001 |
| $PaCO_2$, kPa† | 5.6 (4.8-7.1) | 5.7 (4.8-7.3) | 5.2 (4.4-6.2) | 6.1 (5.3-7.5) | 5.6 (4.8-7.6) | 6.1 (5.1-7.1) | 5.7 (4.8-7.1) | <0.0001 |
| $HCO_3$, mmol/L* | 28.1 (6.0) | 28.7 (6.8) | 26.5 (5.5) | 28.7 (5.4) | 30.2 (8.9) | 27.8 (5.0) | 28.3 (6.4) | <0.0001 |
| pH < 7.35, % | 17.8 | 19.2 | 15.1 | 24.3 | 17.9 | 20.8 | 18.9 | 0.19 |

Sites compared by Fisher's (proportions), ANOVA or Welch (means), or Kruskal-Wallis's (median) tests. *Mean (Standard deviation); †Median (Interquartile range). CXR= chest radiograph, CVD= Cerebrovascular disease, dBP and sBP= Diastolic and systolic blood pressure, $HCO_3$= Bicarbonate, IHD= Ischaemic heart disease, LTOT= long term oxygen therapy, LT= Long Term, LVD= Left ventricular dysfunction.

*Table 6.1: Baseline characteristics by site*

### 6.3 Validation of the DECAF score

The $AUROC_{DECAF}$ curve for in-hospital mortality was: internal validation = 0.83 (95% CI 0.78 to 0.87), external validation = 0.82 (95% CI 0.77 to 0.87), and overall = 0.82 (95% CI 0.79 to 0.85). The discrimination of the DECAF score was significantly stronger than CURB-65, CAPS, APACHE II and BAP-65 for 30-day mortality. For inpatient mortality, the DECAF score was again superior, except in comparison to APACHE II where the higher discriminatory strength of DECAF was not significant (Table 6.2 and Figure 6.1).

| Prognostic score | AUROC curve (95% CI) In-hospital death | Comparison to DECAF, p value | AUROC curve (95% CI) 30-day death | Comparison to DECAF, p value |
|---|---|---|---|---|
| DECAF | 0.82 (0.79-0.85) | N/A | 0.79 (0.75-0.83) | N/A |
| CURB-65 | 0.76 (0.72-0.80) | 0.0057 | 0.73 (0.69-0.77) | 0.0051 |
| CAPS | 0.77 (0.73-0.81) | 0.038 | 0.73 (0.69-0.77) | 0.0083 |
| APACHE II | 0.78 (0.74-0.82) | 0.083 | 0.72 (0.68-0.77) | 0.0039 |
| BAP-65 | 0.77 (0.73-0.81) | 0.038 | 0.72 (0.68-0.76) | 0.0021 |

*Table 6.2: Comparison of AUROC curves for DECAF and other scores (with imputation)*

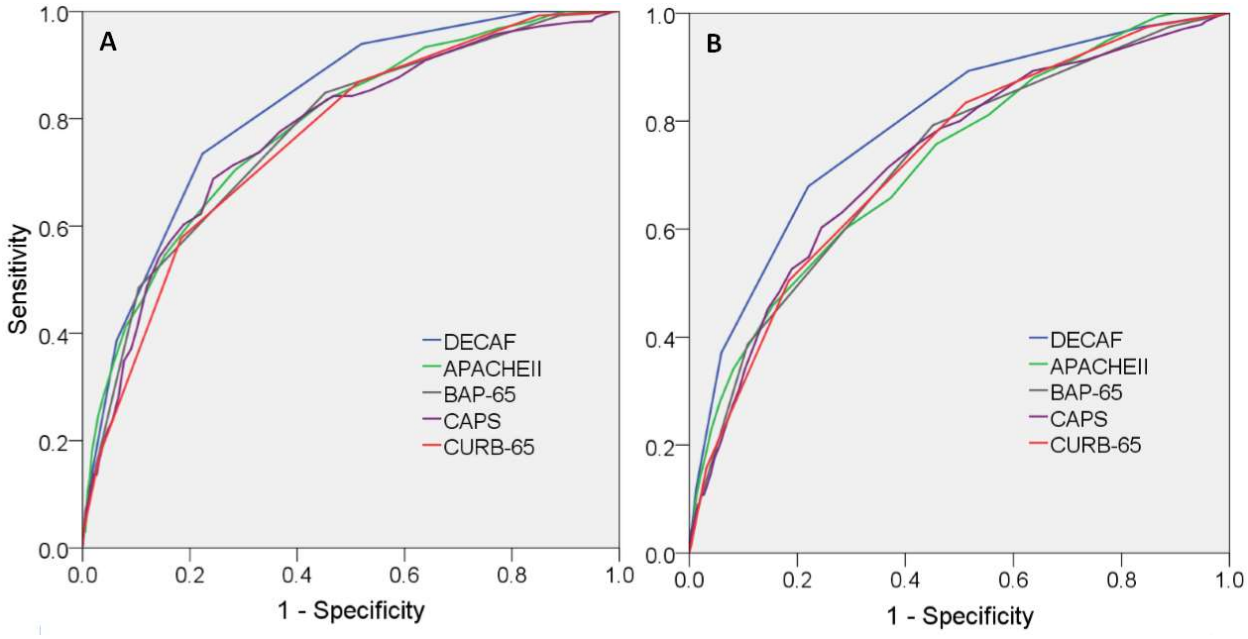


*Figure 6.1: Receiver operator characteristic curves of prognostic scores for in-hospital (A) and 30-day mortality (B)*

In a complete case analysis (without imputation), the conclusions were unchanged for 30-day mortality; for in-hospital mortality, $AUROC_{DECAF}$ curve was again the highest, but was not statistically superior to CAPS (p = 0.068) or BAP-65 (p = 0.060).

Table 6.3 shows mortality rates, sensitivity and specificity by DECAF score in the overall validation cohort, and mortality by DECAF risk group compared to our derivation cohort.[2]

Compared with the derivation study, mortality overall and in the high risk group was lower. Higher DECAF scores were again associated with higher mortality, though absolute numbers were small for DECAF 5 and 6 groups. The model was a satisfactory fit to the data (Hosmer-Lemeshow statistic= 0.48, Nagelkerke $R^2$= 24%). The previously assigned weightings of the DECAF score were confirmed on logistic regression (Table 6.4), and eMRCD score remained the strongest predictor.

| DECAF score | n | Died in-hospital, n (%) | Sensitivity | Specificity | Mortality by risk group, % Validation | Derivation | P |
|---|---|---|---|---|---|---|---|
| 0 | 255 | 0 (0) | 1.00 | 0 | | | |
| 1 | 519 | 8 (1.5) | 1.00 | 0.16 | 1.0 | 1.4 | 0.60 |
| 2 | 498 | 27 (5.4) | 0.94 | 0.48 | 5.4 | 8.4 | 0.14 |
| 3 | 301 | 46 (15.3) | 0.73 | 0.78 | | | |
| 4 | 113 | 35 (31.0) | 0.39 | 0.94 | | | |
| 5 | 37 | 15 (40.5) | 0.12 | 0.99 | 21.4 | 34.7 | 0.00046 |
| 6 | 2 | 1 (50.0) | 0.0076 | 1.00 | | | |
| Total | 1725 | 132 (7.7) | N/A | N/A | 7.7 | 10.4 | 0.016 |

*Table 6.3: DECAF score, in-hospital mortality, sensitivity and specificity*

| Index | B | OR (95%CI) | P value | Score |
|---|---|---|---|---|
| Dyspnoea | | | | |
| eMRCD 1-4 | | 1 | <0.0001 | 0 |
| eMRCD 5a | 1.13 | 3.10 (1.78-5.40) | <0.0001 | 1 |
| eMRCD 5b | 2.17 | 8.79 (5.13-15.03) | <0.0001 | 2 |
| Eosinopenia (<0.05 x$10^9$/L) | 0.90 | 2.45 (1.61-3.72) | <0.0001 | 1 |
| Consolidation | 0.90 | 2.45 (1.66-3.62) | <0.0001 | 1 |
| Acidaemia (pH <7.3) | 1.35 | 3.87 (2.38-6.31) | <0.0001 | 1 |
| Atrial Fibrillation | 0.85 | 2.35 (1.53-3.60) | <0.0001 | 1 |

*Table 6.4: DECAF indices as predictors of in-hospital mortality*

Compared to the traditional MRCD scale,[38] eMRCD had superior prognostic strength for in-hospital mortality: $AUROC_{eMRCD}$ = 0.74 (95% CI 0.70 to 0.78) v. $AUROC_{traditional\ MRCD}$ = 0.68 (95% CI 0.64 to 0.72); p < 0.0001. In the subpopulation with a pneumonic exacerbation (n = 485), eMRCD was again superior to the MRCD scale: ($AUROC_{eMRCD}$ = 0.67, 95% CI 0.60 to 0.73 v. $AUROC_{MRCD}$ = 0.62, 95% CI 0.56 to 0.69; p = 0.0070).

CURB-65 predicts 30-day mortality in patients with community acquired pneumonia, and is commonly applied to patients with a pneumonic exacerbation of COPD (pAECOPD). In the validation cohort, for the subgroup of patients with pAECOPD (n=489), the DECAF score was a non-significantly stronger predictor of 30-day mortality than CURB-65 ($AUROC_{DECAF}$= 0.76, 95% CI 0.70-0.81 v. $AUROC_{CURB-65}$= 0.68, 95% CI 0.62-0.74; p=0.057) (Table 6.5 shows sensitivity and specificities for DECAF scores, and Table 6.6 shows 30 day outcome).

| | Validation cohorts | | Derivation and validation cohorts | |
|---|---|---|---|---|
| DECAF score | Sensitivity | 1 - Specificity | Sensitivity | 1 - Specificity |
| 0 | N/A | N/A | N/A | N/A |
| 1 | 1.00 | 0.84 | 0.98 | 0.82 |
| 2 | 0.87 | 0.48 | 0.82 | 0.44 |
| 3 | 0.55 | 0.20 | 0.54 | 0.17 |
| 4 | 0.20 | 0.052 | 0.21 | 0.043 |
| 5 | 0.014 | 0.0024 | 0.0078 | 0.0015 |
| 6 | 0 | 0 | N/A | N/A |

*Table 6.5: Sensitivity and specificity of DECAF in pneumonic exacerbations of COPD*

| | Inpatient death, n (%) | | 30-day death, n (%) | |
|---|---|---|---|---|
| Score | DECAF | CURB-65 | DECAF | CURB-65 |
| 0 | N/A* | 3/55 (5.5) | N/A* | 4/55 (7.3) |
| 1 | 2/122 (1.6) | 14/182 (7.7) | 4/122 (3.3) | 20/182 (11.0) |
| 2 | 21/267 (7.9) | 31/264 (11.7) | 25/267 (9.4) | 39/264 (14.8) |
| 3 | 36/215 (16.7) | 50/219 (22.8) | 42/215 (19.5) | 57/219 (26.0) |
| 4 | 43/129 (33.3) | 24/57 (42.1) | 48/129 (37.2) | 24/57 (42.1) |
| 5 | 26/53 (49.1) | 7/11 (63.3) | 29/53 (54.7) | 5/11 (45.5) |
| 6 | 1/2 (50) | N/A | 1/2 (50) | N/A |
| Total | 129/788 (16.3) | | 149/ 744 (18.9) | |

*The lowest possible DECAF score in those with pAECOPD is 1.

*Table 6.6: Inpatient and 30-day mortality by DECAF and CURB-65 score in those with pAECOPD, derivation and validation cohorts.*

When patients with pAECOPD were pooled across the derivation and validation cohort (n=788), DECAF was superior for 30 day ($AUROC_{DECAF}$= 0.75, 95% CI 0.71-0.79 v. $AUROC_{CURB-65}$= 0.66, 95% CI 0.62-0.71; p<0.0001) and inpatient mortality ($AUROC_{DECAF}$= 0.76, 95% CI 0.71-0.80 v. $AUROC_{CURB-65}$= 0.70, 95% CI 0.65-0.75; p=0.024). The superior performance of DECAF is of particular importance for patients deemed at low risk by each score, who may be considered suitable for home treatment. Patients with a low risk DECAF score had a lower in-hospital mortality compared to those with a low-risk CURB-65 score: DECAF= 1.6% (2/122) v. CURB-

65= 7.2% (17/237); p=0.026. There were similar differences for 30-day mortality: DECAF 0-1= 3.3% (4/122) v. CURB-65 0-1= 10.1% (24/237); p=0.022.

The optimal thresholds for eosinophil count and pH were reassessed. On visual inspection of the ROC curve, the optimal cut off for eosinopenia was unchanged ($0.05 \times 10^9$/L).[2] For pH threshold, both 7.30 and 7.35 offered similar discrimination. The 7.30 threshold identified in the derivation study was retained for consistency, and because, of 58 patients with a low risk DECAF score and non-scoring acidaemia (7.30-7.34), none died. Only three patients had a DECAF score of 1 due to a pH<7.30, all of whom survived.

Patients with $SpO_2$ > 92% without supplemental oxygen in whom ABG sampling was deemed unnecessary were assigned a score of 0 for the pH component of DECAF. Of 209 such patients overall, only 6 died (2.9%); this total included 0/52 with a DECAF score of 0 and 2/67 with a DECAF score of 1.

Time to death in those who died during the index admission, and length of stay in those who survived to discharge, by DECAF score are shown in Table 6.7. Among survivors, higher DECAF scores were associated with longer length of stay.

| DECAF score | Median time to death, days (IQR) | Median length of stay, days (IQR) |
|---|---|---|
| 0 | N/A | 3 (1-5) |
| 1 | 4.5 (4-12.5) | 4 (2-7) |
| 2 | 9 (5-16) | 5 (3-10) |
| 3 | 10 (3.75-23.25) | 7 (3-13) |
| 4 | 5 (1-11) | 7.5 (5-18) |
| 5 | 2 (1-9) | 10 (6-19.5) |
| 6 | 2 (2-2) | 22 (22-22) |

*Table 6.7: Time to death in patients who died during the index admission, and median length of stay in those who survived to discharge, by DECAF score*

## 6.4 Discussion

In a large, multicentre study of patients admitted with AECOPD, we have confirmed that the DECAF score is a robust predictor of mortality that can be easily scored at the bedside using indices routinely available on admission. As in the earlier derivation study, DECAF was superior to other scores (BAP-65, CAPS, APACHE II, CURB-65) sometimes used to predict short-term mortality of patients with AECOPD.

We went to considerable lengths to capture consecutive patients, but a small number of patients who died or who were discharged shortly after admission may have been missed. In order to minimise any resulting bias and to maximise capture of all eligible patients, admission units were screened and a broad coding records search was performed. In the 2014 UK national audit,[11] mean site recruitment of patients with spirometric confirmation of COPD was 0.36 per day. In our study, recruitment was substantially higher at all sites, which supports high case ascertainment rates. Investigators in site E reported problems obtaining spirometry results, which may in part explain their comparatively lower recruitment rate.

The CHARMS checklist provides guidance on the appraisal of prediction model studies (see appendix 1).[204] The main limitation of this study is that the internal validation study was, in part, performed retrospectively. Although retrospective collection of data may bias results, this risk was mitigated as the DECAF indices were collected as part of routine clinical practice in the participating hospitals, the researchers extracting data were blinded to outcome and case ascertainment and outcome were similar to the prospective external cohort. Of importance, the latter was individually adequately powered.

Data were only regarded as “missing” once all data sources had been checked and rates of missing data were low. For key outcomes, analyses were repeated with and without multiple imputation. To improve data completeness for DECAF, patients with $SaO_2$ > 92% breathing room air, and judged by a clinician not to require ABG analysis, scored 0 for the acidaemia component of DECAF; this was justified by the low mortality in this group, and supports a similar pragmatic approach in the clinical application of the score, reducing burden for both patients and clinicians. However, we do not advise that this assumption is used to lower clinician’s threshold for performing ABG sampling.

There were important differences between site populations, in particular the receipt of institutional care, coexistent consolidation, degree of airflow obstruction and severity of DECAF score. This may in part reflect our efforts to select diverse sites for participation in the study, and the strong and consistent performance of DECAF, despite such differences in baseline characteristics, emphasises the external validity of the score.

Mortality varied between sites (from 4.7% to 9.8%) and between cohorts (internal validation = 8.9% v. external validation = 6.4%; p = 0.057). This largely reflects differences in baseline characteristics, notably the proportion of patients admitted from institutional care and with coexistent pneumonia. When these two sub-groups were excluded, mortality was 4.8% in both cohorts. Overall mortality was 7.7%, which is in keeping with the 2003 (7.7%) and 2008 (7.8%) UK national audits. In the 2014 UK audit mortality was 4.3%, though the reason for the lower mortality rate is reported as unknown. In our study, case ascertainment, co-morbidity and the proportion of patients with consolidation or an MRCD score of 5 was higher than in the 2014 UK national audit.

Since our 2012 DECAF derivation study, two further prognostic scores have been published.[213, 214] In one,[213] patients with acute ECG features of ischaemia and radiographic pulmonary congestion were included. Such patients are unlikely to have met our inclusion criterion of a primary diagnosis of AECOPD.

In the second study, the derived score showed good discrimination, and validation is awaited.[214] However, the score included subjective recognition of “use of inspiratory accessory muscles or paradoxical breathing”, reducing generalisability, especially in healthcare settings which lack specialist review within 24-hours of admission.[11, 151] Recruitment was lower than equivalent audit data,[151] because written patient consent was required, which disproportionately excludes the lowest and highest risk patients. Our methodology mirrored UK national audits; only routine data were collected so patient consent was not required.

Length of stay for AECOPD is falling, and early discharge, both supported and unsupported, is common place, with patient selection based largely on clinical judgement. However, clinical judgement of prognosis is poor [197] whilst the DECAF score has consistently shown a high sensitivity for identifying low risk patients. ESD and HAH services for patients with AECOPD are expanding.[11] NICE recommend that patient selection for these services be based on mortality risk,[4] but also highlight the (previous) lack of a robust prognostic score to guide decision-making. In the present study, DECAF 0-1 patients (including those with pneumonia or acidaemia) had an acceptably low mortality risk and comprised 45% of patients. The effect of treating this group with HAH or ESD requires a randomised controlled trial to assess clinical outcomes and associated costs. We have undertaken an RCT of Hospital at Home

compared to usual care in low risk patients, and this is described in Chapter 7. In our experience, the CURB-65 score is commonly applied in patients with pneumonic exacerbations of COPD to inform discharge planning and choice of antibiotics. Based on evidence from both the derivation and validation study, clinicians should not be reassured by “low risk” CURB-65 scores in such patients as the associated mortality is unacceptably high; we advise against its use in this population.

A high risk DECAF score is associated with both a high risk of death and, in those who die, a short time to death. The latter is particularly true of patients scoring DECAF 5 or 6, in whom the median time to death was only 2 days. Such patients may be suitable for early escalation in care, or alternative palliative care, but the window for intervention is short. Among patients who survive to discharge, length of stay increases incrementally with DECAF score.

In both the derivation and present study, dyspnoea severity measured by the eMRCD score was the strongest single predictor of mortality and a superior predictor to the traditional MRCD scale. In the 2014 UK national audit, “DECAF light” was scored retrospectively using the traditional MRCD scale (Figure 6.2). However, “DECAF light”, as opposed to the full DECAF score, was calculated only because eMRCD data was unavailable. We support the recommendation of the UK national audit that DECAF indices, including the eMRCD score, be collected on all patients admitted with AECOPD. Various versions of the traditional MRCD scale exist,[38, 43, 272] which may lead to differences in scoring. We caution against such modifications to the eMRCD score unless supported by empirical evidence.

In conclusion, we have shown that DECAF can be used in a variety of hospital settings in order accurately to stratify mortality risk in patients with AECOPD. Further research is required to quantify its impact on clinical practice, for example in the identification of patients for HAH or ESD services.

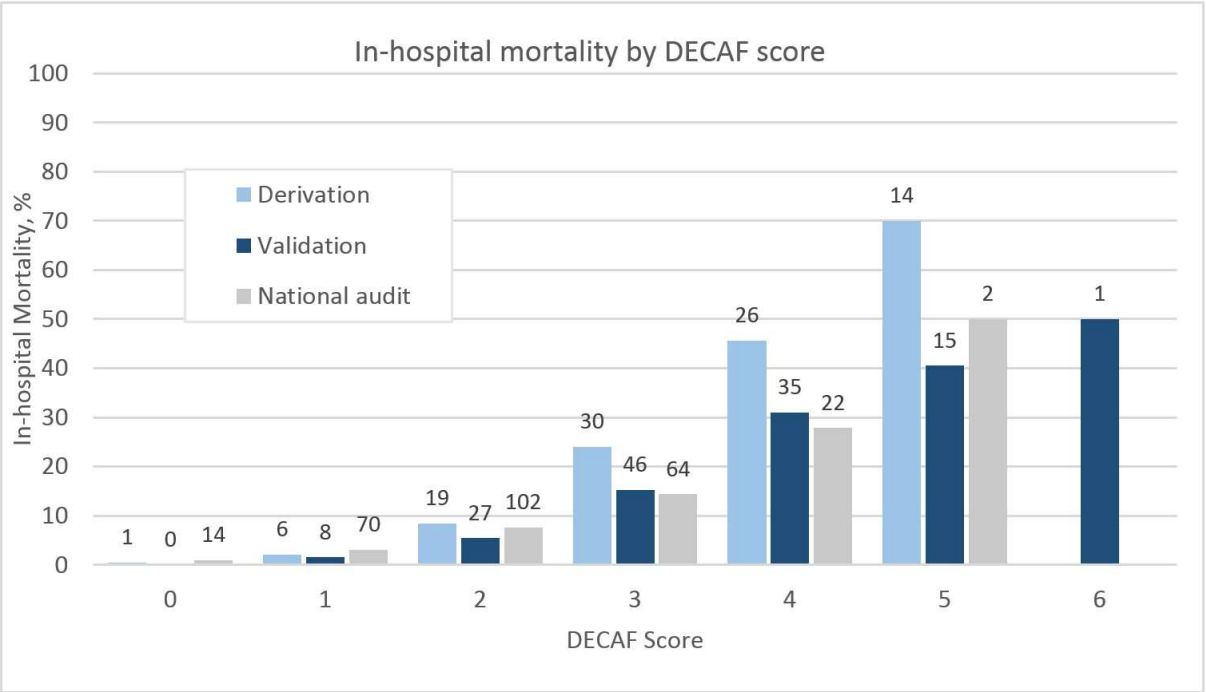


*Figure 6.2: In-hospital mortality in the DECAF derivation and validation study, and "DECAF light" from the 2014 UK National COPD Audit*

# Chapter 7 Hospital at Home and DECAF

## 7.1 Patient characteristics

Emergency hospital admissions between June 2014 to January 2016 were reviewed to ensure all patients with AECOPD were identified. Of note, sixty-four patients with a DECAF 0-1 AECOPD were planned for same-day discharge before assessment by the research team and could not be included as, by definition, HAH is not appropriate for patients who are sufficiently well for discharge.

Of 207 DECAF 0-1 AECOPD assessed for eligibility, 120 were randomised. Two patients were randomised in error, and were not included in the primary analysis. Three patients were randomised to HAH, but were intentionally treated by UC, and were analysed in their original allocation as per the intention to treat principle (Figure 7.1). No patients allocated to UC received HAH. Groups were well matched with respect to minimisation criteria and most other baseline characteristics (table 3).

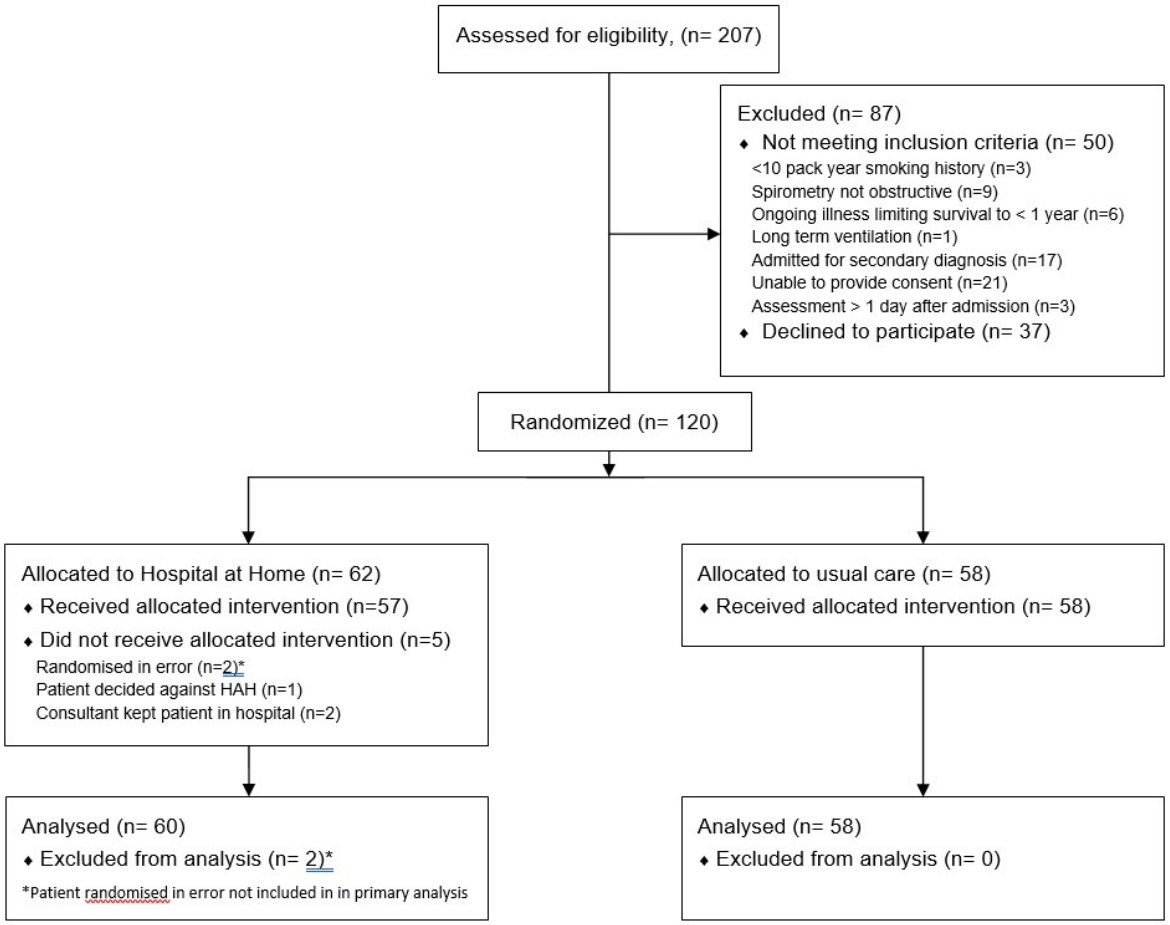


*Figure 7.1: Consort diagram*

| | HAH n=60 | UC n=58 |
|---|---|---|
| **DECAF indices** | | |
| DECAF score 1, n (%) | 43 (71.7) | 31 (53.4) |
| eMRCD Dyspnoea score 5a, n (%) repeat below | 12 (20) | 9 (15.5) |
| Eosinopenia, % | 15 (25) | 8 (13.8) |
| CXR consolidation, % | 15 (25) | 9 (15.5) |
| Acidaemia (pH < 7.30), % | 1 (1.7) | 0 |
| Atrial Fibrillation, % | 0 | 0 |
| **Minimisation criteria** | | |
| ABG management, pH < 7.35 / pCO2>6 pH ≥7.35, % | 7 (11.7)/ 40 (66.7) | 8 (13.8) / 38 (65.5) |
| Hospital admissions previous year 1 / 2, % | 12 (20) / 21 (35) | 12 (20.7) / 19 (32.8) |
| Prior social care, % | 3 (5) | 1 (1.7) |
| Cerebrovascular disease, % | 9 (15) | 9 (15.5) |
| **Sociodemographics** | | |
| Age, years* | 71.0 (9.6) | 68.7 (10.5) |
| Female, % | 32 (53.3) | 30 (51.7) |
| Smoking pack-yrs, n† | 45 (35-50) | 44 (30-60) |
| Current smoking, % | 27 (45) | 25 (43.1) |
| Reporting no qualifications on leaving school, % | 46 (76.7) | 41 (70.7) |
| Most frequently reported family income per year, £† | 5,200-10,399 | 10,400-15,599 |
| **Markers of disease severity** | | |
| FEV1% predicted* | 45.5 (18.4) | 42.1 (16.3) |
| LTOT prior to admission, % | 7 (11.7) | 2 (3.4) |
| Cor pulmonale, % | 11 (18.3) | 5 (8.6) |
| **Co-morbidity** | | |
| IHD, % | 14 (23.3) | 12 (20.7) |
| Diabetes, % | 8 (13.3) | 5 (8.6) |
| LVD, % | 1 (1.7) | 3 (5.2) |
| Anxiety, % | 9 (15.0) | 3 (5.2) |
| Depression, % | 12 (20.0) | 9 (15.5) |
| **Admission clinical data** | | |
| Respiratory rate, per minute* | 25 (4.5) | 26 (5.1) |
| Pulse rate, per minute* | 103.9 (19.6) | 104.9 (15.4) |
| sBP, mmHg* | 140.8 (21.1) | 145.1 (24.3 |
| dBP, mmHg* | 77.3 (12.2) | 80.9 (14.5) |
| Temperature, $^{0}$C† | 36.6 (36.2-37.3) | 36.5 (36.1-37.1) |
| Oxygen saturation† | 92 (89-94) | 92 (88.5-95) |
| Discoloured sputum, % | 43 (71.7) | 33 (56.9) |
| **Arterial Blood Gas values** | | |
| pH† | 7.42 (7.39-7.45) | 7.42 (7.38-7.44) |
| $PaO_2$, kPa† | 7.6 (7.2-9.3) | 7.9 (7.2-10.2) |
| $PaCO_2$, kPa† | 5.5 (5-6.25) | 5.3 (4.8-6.6) |
| $HCO_3$, mmol/L* | 27.1 (4.3) | 27.3 (4.7) |
| pH < 7.35, % | 7 (11.7) | 8 (13.8) |
| **Baseline outcome measures** | | |
| Utility score (Eq-5D-5L), n* | 0.517 (0.268) | 0.501 (0.243) |
| Hospital Anxiety and Depression Score A/ D, n† | 6 (4-10.25) / 7 (4-9) | 7 (4-10) / 5 (2-8.25) |
| Copd Assessment Tool, n† | 28.5 (21.75-33) | 27 (23-32.25) |
| **Treatment** | | |
| AECOPD treatment prior to admissions, % | 32 (53.3) | 26 (44.8) |

*Mean (Standard deviation); †Median (Interquartile range). CXR= chest radiograph, CVD= Cerebrovascular disease, dBP and sBP= Diastolic and systolic blood pressure, $HCO_3$= Bicarbonate, IHD= Ischaemic heart disease, LTOT= long term oxygen therapy, LVD= Left ventricular dysfunction.

*Table 7.1: Baseline characteristics of patients*

Groups were well matched with respect to minimisation criteria, and most other baseline characteristics (table 3). In HAH, the proportions of DECAF 1 patients, and those with chest x-ray consolidation, cor pulmonale and/ or on long term oxygen therapy was higher. This is a potential source of bias in favour of usual care.

### 7.2 Costs used in study

The full breakdown of all costs are included in the appendix.

### 7.3 Cost and cost-utility analysis

The mean health and formal social care cost over 90 days was £1,016 lower in HAH than UC. These costs included admissions, readmissions and all HAH episodes, including costs for patients with multiple HAH episodes. However, there was a wide variation in cost, and the 95% confidence interval crossed the pre-specified non-inferiority limit of £150 (Figure 7.2, "3 days": CI -2343 to 312, p = 0.10). The cost difference and distribution were greater than anticipated, supporting an adjusted non-inferiority limit of £340,[266] which was achieved.

During the index admission, median LOS in UC was three days, which was two days less than expected.[255] If this model is implemented in other hospitals, the local cost differences will be influenced by current LOS. We therefore performed a sensitivity analysis to assess the effect of LOS in UC during the index admission on health and formal social care costs. One additional bed day without medical staffing costs would increase the mean cost difference to £-1262 with a one sided 95$^{TH}$ percentile of £66, achieving the non-inferiority limit of 150 and favouring HAH. Two bed days would have been £-1508 with a one sided 95$^{th}$ percentile of £-180.

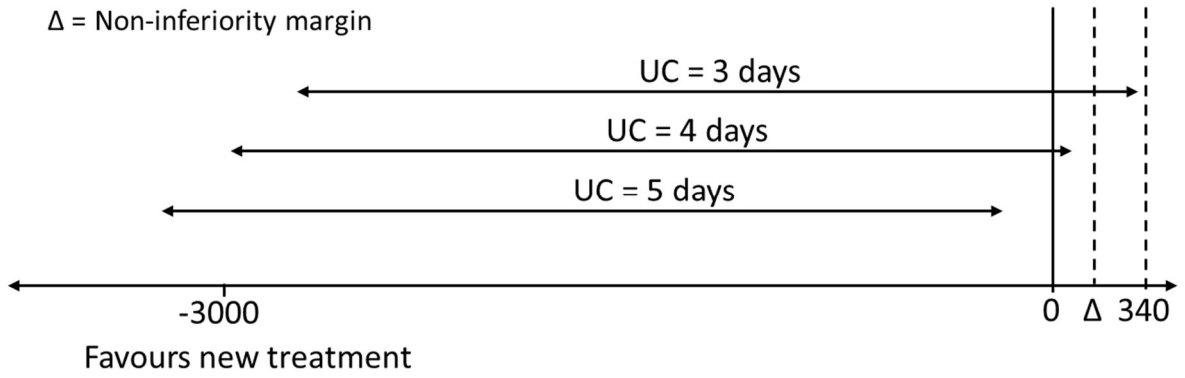


*Figure 7.2: Length of stay and cost difference (£) between HAH and UC*

The difference in cost was primarily related to inpatient and formal social services costs (Table 7.2). The cost differences for the index admission alone are shown in Table 10.3 in chapter 10, appendix C. Total QALY scores were non-significantly higher in HAH compared to UC (QALY HAH-UC= 0.005, 95% CI -0.14 to 0.25). The probability of HAH being cost-effective compared with UC was 90% at the NICE threshold of £30,000 per QALY. This is the proportion of dots beneath the diagonal line in Figure 7.3A and is represented by the vertical line in Figure 7.3B. The area under the diagonal line is comprised of instances in which: HAH is both more effective and cheaper than UC (area "1"); HAH is more effective and more expensive but within the NICE threshold (area "2"); and c) UC is more effective, but also more expensive and exceeds the NICE threshold (area "3"). HAH is therefore the dominant intervention compared to UC in that it is both cheaper and more effective for most patients treated (74% probability).

| | HAH, £ | UC, £ | Bootstrapped mean Difference (£) | Bootstrapped 95% CI* of cost difference |
|---|---|---|---|---|
| **Overall costs** | | | | |
| Health and formal social care | 3857.8 | 4873.5 | -1015.7 | -2735.5 to 644.8 |
| Healthcare | 3819.2 | 4755.8 | -936.6 | -2645.4 to 709.9 |
| Oxygen therapy | 38.4 | 18.3 | 20.1 | -1.73 to 42.0 |
| Medication | 422.5 | 458.9 | -36.4 | -150.1 to 75.7 |
| **Hospital costs** | | | | |
| Bed stay | 1540.8 | 2775.2 | -1234.4 | -2524.8 to -82.0 |
| Inpatient healthcare review | 417.7 | 514.3 | -96.7 | -288.4 to 96.4 |
| Laboratory and diagnostic tests | 375.1 | 358.7 | 16.4 | -128.1 to 169.1 |
| NIV costs | 44.4 | 158.2 | -113.8 | -255.4 to 8.12 |
| **HAH costs** | | | | |
| HAH visits and travel time** | 383.9 | 0.0 | 383.9 | 319.2 to 455.3 |
| Telephone calls costs | 5.8 | 5.4 | 0.5 | -3.57 to 5.33 |
| **Community costs** | | | | |
| Formal social care | 38.6 | 117.7 | -79.0 | -299.2 to 55.2 |
| Home visits after discharge | 43.7 | 39.2 | 4.5 | -19.2 to 31.8 |
| A+E and outpatient appointments | 546.8 | 427.6 | 119.2 | -22.6 to 243.0 |

*The 95% confidence interval (CI) in the table is two sided (0.025 to 0.975) calculated with the bootstrap approach. For health and formal social care (the primary outcome) the one sided 95% CI (0.95) was £312.

** 55% of time on HAH visits was spent with the patient. (45% on travel time)

*Table 7.2: Health and formal social care average costs at 90 days*

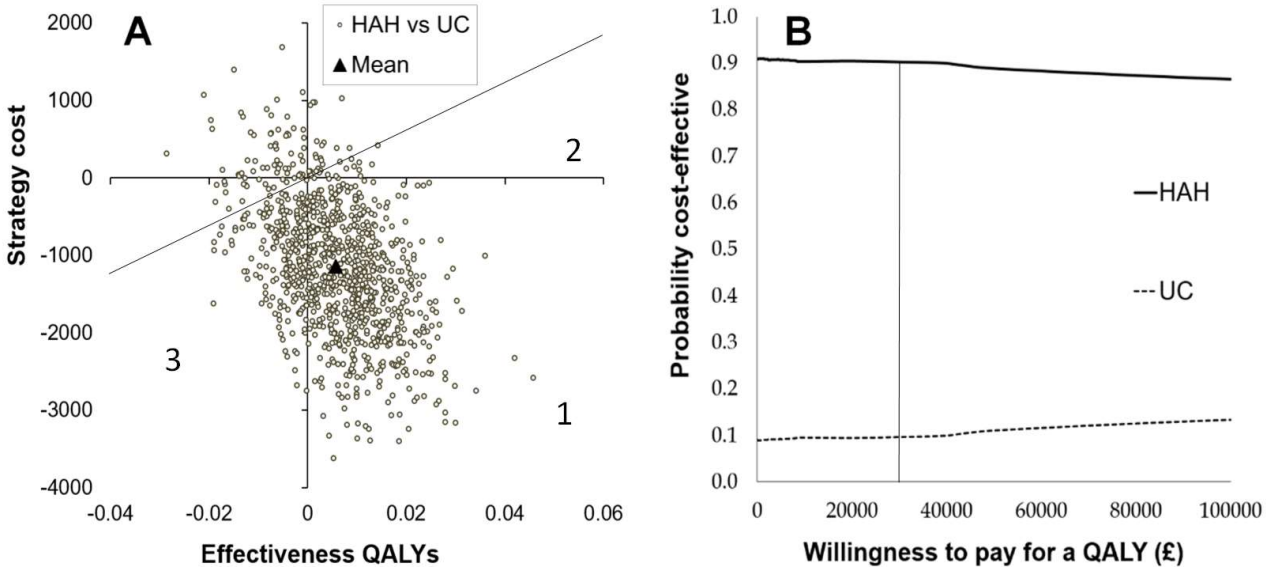


*Figure 7.3: Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B).*

*Figure 7.3A: the cost effectiveness plane for HAH and UC, with the diagonal line representing the NICE cut-off at £30,000 per QALY. Area 1= HAH cheaper and more effective, 2= HAH more effective and more expensive but less than the NICE cut-off, and 3= UC is more effective, but more expensive and exceeds the NICE cut-off. Figure 3B: The probability of cost-effectiveness is shown over a range of willingness to pay for a QALY, to inform decisions to accept or reject new technologies. There is a 90% probability HAH will be cost-effective at the NICE threshold (vertical line).*

The analysis was repeated using multiple imputation for missing data. This resulted in 78% of values in the dominant quadrant on the cost-effectiveness plane, and the probability of cost-effectiveness was essentially unchanged (Figure 7.4).

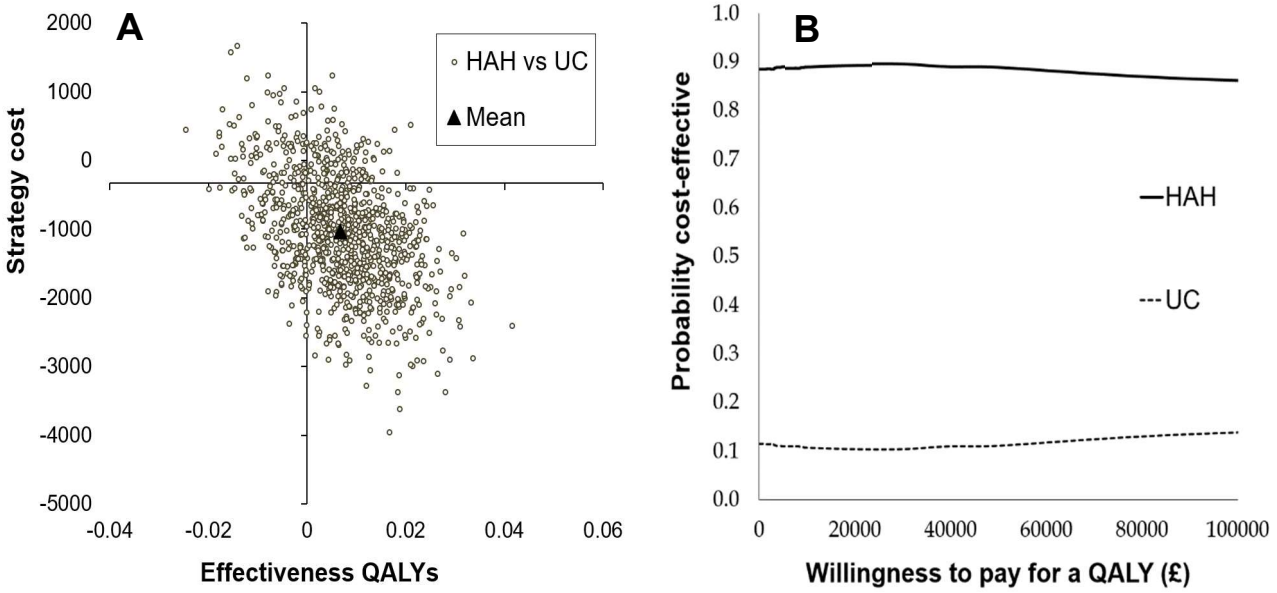


*Figure 7.4: Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B), multiple imputation.*

### 7.4 Hospital at Home

Of the 60 patients allocated to HAH, 53 (88.3%) had a zero or one day stay. Most patients incurring an overnight stay were admitted in the afternoon or evening. Patients received a median of 4 (IQR 2 to 5) overnight days HAH care per HAH episode. Including travel time, healthcare professionals spent a median of 7.2 hours (IQR 4.7 to 10.8) on home visits per HAH spell (median RSN visits = 7.1 hours, IQR 4.4 to 10.1). There were 342 visits for 57 episodes: RSN = 327, physiotherapy = 13, psychology = 1, and respiratory support worker = 1.

During HAH, two patients returned to hospital for assessment (which included a respiratory consultant review, repeat chest radiograph and blood testing) and returned home the same day. One patient returned to hospital and stayed overnight before returning home to complete their HAH spell.

### 7.5 Other outcomes

There were no deaths in the acute period (within 14 days) in either arm. Within 90 days, there was one death in each arm. There was a statistically significant reduction in bed days over 90 days in those treated with HAH (HAH = 1, IQR 1-7 compared to UC = 5, IQR 2-12; p = 0.001). Readmission rates were similar in both arms with 22 (36.7%) in HAH and 23 (39.7%) in UC. Further detail is provided in Table 10.4 in chapter 10, appendix C. There was a strong preference for HAH treatment at 14 days in both arms stated by 54 of 60 in HAH and 51 of 57 in UC.

Table 5 shows the change in quality of life scores from baseline at 14 days and 90 days. For HADS and CAT, negative values represent improvements in health from baseline, whilst for utility scores, positive values represent improvements from baseline. The per cent of patients improving by the minimum clinically important difference (MCID) is also shown. The improvements in health status in HAH compared to UC were clinically meaningful for HADS-anxiety score at 14 days and CAT at 90 days, but this could be a chance finding.[37, 274] On multiple imputation the difference in the benefit of CAT at 90 days was 1.5, but the utility score at 14 days was 0.51 which is above the MCID (Table 7.3).

| | HAH | | | UC | | |
|---|---|---|---|---|---|---|
| | Unit change* | % MCID† | missing | Unit change | % MCID | missing |
| HADS-A 14 day | -1.0 | 48.3 | 0 | 0.5 | 33.9 | 2 |
| HADS-A 90 day | 0 | 33.3 | 6 | 0 | 38.2 | 3 |
| HADS-D 14 day | -1.0 | 38.3 | 0 | 0 | 26.8 | 2 |
| HADS-D 90 day | -0.5 | 37.0 | 6 | 0 | 27.3 | 3 |
| CAT 14 day | -4.0 | 61.7 | 0 | -3.0 | 57.9 | 1 |
| CAT 90 day | -3.0 | 51.9 | 6 | -1.0 | 36.4 | 3 |
| Utility 14 day (EQ-5D-5L) | 0.091 | 56.7 | 0 | 0.055 | 49.1 | 1 |
| Utility 90 day (EQ-5D-5L) | 0.003 | 43.9 | 3 | 0.007 | 41.1 | 2 |

*Values are median, except for utility which is mean. Unit change is the difference in absolute values between follow up and baseline. Improvements in health status are negative for HADS and CAT, and positive for utility scores. †The percentage of patients who improved by a Minimal Clinically Important Difference, which is 1.5 for HADS-A and HADS-D, 2 for CAT and 0.051 for the EQ-5D-5L.

*Table 7.3: Changes in quality of life scores from baseline*

## 7.6 Patients declining participation

As part of an audit of practice, baseline characteristics of patients who declined to participate in the HAH study were reviewed. Patients who declined enrolment were not more unwell than study participants based on co-morbidity and measures of disease severity (Table 7.4).

| | Decliners | HAH | UC |
|---|---|---|---|
| Female | 54.3 | 53.3 | 51.7 |
| Age (SD) | 70.6 (9.8) | 71.0 (9.6) | 68.7 (10.5) |
| Pack years (IQR) | 40 (40-60) | 45 (35-50) | 44 (30-60) |
| FEV1 % predicted (SD) | 45.1 (19.6) | 45.5 (18.4) | 42.1 (16.3) |
| DECAF 1, % | 65.7 | 71.7 | 53.4 |
| eMRCD 5a, % | 8.6 | 20 | 15.5 |
| CXR consolidation, % | 25.7 | 25 | 15.5 |
| pH less than 7.35, % | 2.9 | 10 | 10.3 |
| PaO2 kPa (SD) | 8.0 (7.35 to 9.0) | 7.6 (7.2-9.3) | 7.9 (7.2-10.2) |
| One previous admission 12 months, % | 22.9 | 20 | 20.7 |
| Two previous admissions 12 months, % | 25.7 | 35 | 32.8 |
| Prior social care, % | 5.7 | 5 | 1.7 |
| IHD, % | 25.7 | 23.3 | 20.7 |
| Diabetes, % | 17.1 | 13.3 | 8.6 |
| LV dysfunction, % | 5.7 | 1.7 | 5.2 |
| Anxiety, % | 11.4 | 15 | 5.2 |
| Depression, % | 14.3 | 20 | 15.5 |

*Table 7.4: Characteristics of decliners, and patients in HAH and UC*

## 7.7 Discussion

Hospital at Home is clinically more effective than usual care with a five-fold reduction in bed days over 90 days. AECOPD and inhospital stay are associated with a reduced quality of life, which may be improved by HAH treatment; there were clinically meaningful improvements in HADS-anxiety at 14 days and CAT score at 90 days in the HAH group compared to UC group. Crucially, 90% of patients across both arms stated they would prefer HAH to UC for future exacerbations of similar severity.

In an economic evaluation, extensive costs were obtained, and health-related quality of life was measured with the EQ-5D-5L. This showed that HAH was less expensive and more effective than usual care. AECOPD is one of the commonest reasons for hospital admission, and DECAF identifies approximately 50% of patients as low risk. Therefore, the potential clinical and cost benefits of the implementation of HAH is large. Furthermore, low risk patients can be identified objectively, consistently and safely with the DECAF score. This allows replication of our model of Hospital at Home, and may also lead to a reduction in length of stay in usual care.

This study has several strengths. We assessed the impact of using the DECAF score to guide HAH treatment, replicating how we anticipate the tool will be used in clinical practice. The DECAF score is the only prognostic tool for COPD exacerbation that has undergone the gold standard of derivation, internal and external validation, and impact assessment; such studies are extremely rare despite being strongly recommended.[265] We performed a detailed and extensive cost analysis, recording all important aspects of health and social care. Several sources of data capture were used, including patient diaries and primary and secondary care records, and patients were contacted every two weeks to ensure that data were accurate and as complete as possible. Rates of missing data were low for health-related quality of life data. Multiple imputation was used to demonstrate that the results were robust. Randomisation was performed by an external agency using minimisation, based on a regression analysis of DECAF 0-1 patients, to identify the strongest predictors of readmission or death

One of the key limitations of the study was the choice of £150 as the non-inferiority limit. Data on the primary outcome, total health and social care cost over 90 days, was not available. The pre-specified non-inferiority limit was based on the estimated difference in healthcare costs for a single admission, which was £-470. This estimate

was less than half the actual difference in total health and social care costs over 90 days of £-1016. A more appropriate non-inferiority limit would have been £340. The number of patients discharged prior to assessment by the research team, thus not eligible to participate, was larger than expected. This resulted in a more unwell and costly study population.

Due to the under-representation of short stay patients, the median length of stay in UC should have been longer than the expected five days; the median LOS was actually two days shorter. Patients who declined participation were not more unwell than study participants. Those with a DECAF 0-1 exacerbation who met exclusion criteria may have had a longer length of stay. However, they were outnumbered by the groups above so their exclusion cannot account for the lower median LOS. A more likely explanation is that the use of the DECAF score and study participation reduced length of stay, as well as costs, within usual care. Only UC patients expressed disappointment with their allocated arm, and some requested discharge; such decisions lay entirely with the responsible clinicians. In an embedded qualitative study, clinicians reported that UC patients were probably discharged sooner than is typical. Bed pressures may have exerted additional influence. There were no acute deaths in UC, which suggests that low risk DECAF score may be used to inform safe early discharge.

Another limitation is that the study was performed in three hospitals within one healthcare trust, potentially reducing the generalisability of the results. However, the structure of care, including availability of early supported discharge, differed between sites. We have previously shown that the DECAF score effectively identifies low risk patients in six different hospitals, with different populations and structures of care.[255] Some hospitals may currently lack the nursing infrastructure to deliver HAH selected by DECAF, but investment is justified as there is a 90% chance of this model being cost-effective with further possible cost savings through reduced LOS in UC. Training costs of nurses were included in our analysis.

Meta-analyses of previous studies considered HAH and rarely supported discharge (ESD) together. These showed that HAH/ESD report reduced readmission rates and a trend towards a lower mortality with limited evidence for the effect on health related quality of life.[3, 158] Three studies performed a cost analysis, showing that HAH/ ESD was less expensive, [159, 226, 240] but these were not economic evaluations. An

economic evaluation requires the measurement of costs and clinical effectiveness in two or more arms of a study. This approach is important as the benefit of the intervention can be estimated in terms of the cost per QALY. Measuring costs alone fails to identify the degree of clinical benefit or harm to the patient, and so there is no meaningful context for any expenses/ savings. Furthermore, such analyses should include health and social costs to ensure that apparent health savings are not simply transferred from to social care. Goossens et al. performed a detailed economic evaluation of health and social costs: at three months HAH/ ESD was 168 Euros less expensive than UC from a healthcare perspective, but 908 Euros more expensive when societal costs were included.[241] As most of these previous studies are of ESD services rather than HAH, comparison to our study should be guarded. For example, in the study by Goossens et al., LOS in the ESD treatment arm was the same as our UC arm (three days for the index episode). Ricauda et al. compared an experienced HAH service to UC and showed cost savings, with a reduction in readmission rates. They only included patients of 75 and over, and excluded those with severe hypoxia, acidaemia, cancer and those without family and social support.[159]

Previous studies of HAH/ ESD had extensive eligibility criteria to identify suitable, low risk patients and typically excluded those with co-existent pneumonia and acidaemia on blood gas.[225, 226, 238 159, 227, 229, 239] Ordinarily, clinicians would be reluctant to allow these patients into HAH/ ESD services, but we treated such patients successfully with no difference in mortality between groups. This result is consistent with findings from the DECAF derivation and validation study, which showed that DECAF 0-1 patients with pneumonia or acidaemia had a low acute mortality risk.[2, 255]

In common with many previous studies, we did not include return to hospital during HAH treatment as a readmission, but rather an escalation in level of care. If return to hospital during HAH was counted as a readmission, the readmission rate would be biased in favour of UC patients as they are not exposed to this risk during their acute stay; we have previously discussed this important issue,[3] though it does not affect our primary outcome.

This randomised controlled trial shows that Hospital at Home selected by low risk DECAF score is safe, clinically effective, preferred by most patients, and cost-effective compared to usual care. In combination with data from our derivation and

validation studies, this implementation study supports the use of DECAF in clinical practice to select low risk patients for HAH services.

# Chapter 8 The PEARL readmission score

## 8.1 Patient characteristics

In the derivation, internal validation and external validation cohorts 824 (Dec 2008-June 2010), 802 (Jan 2012-May 2013) and 791 (April 2013-May 2014) patients survived to hospital discharge of whom 309 (37.5%), 297 (37.0%) and 330 (41.7%) were readmitted or died within 90 days of discharge. The justification for this outcome is described previously (4.2.7 Outcome). The population characteristics of each cohort are shown and compared in Table 8.1. A diverse population of patients with AECOPD were recruited, exemplified by significant differences between cohorts in median eMRCD score, admissions in the previous year, and proportions with left ventricular failure and cor pulmonale. The population characteristics of individual hospitals are described elsewhere.[2, 255]

| | Derivation | Internal validation | External validation | P value |
|---|---|---|---|---|
| Number of patients, n | 824 | 802 | 791 | N/A |
| Sociodemographic details | | | | |
| Female, % | 54.2 | 56.4 | 51.5 | 0.14 |
| Age* | 72.3 (9.9) | 73.1 (10.2) | 72.2 (10.4) | 0.14 |
| Institutional care, % | 5.2 | 6.0 | 3.0 | 0.013 |
| Cigarette pack years, n† | 45 (32-60) | 40 (30-56) | 40 (30-60) | 0.00015 |
| Preadmission details | | | | |
| eMRCD† | 4 (3-5a) | 5a (4-5a) | 5a (4-5a) | <0.0001 |
| Admissions in previous year, n† | 0 (0-1) | 0 (0-1) | 1 (0-2) | <0.0001 |
| Weight loss >5%, % | 21.6 | 11.9 | 18.5 | <0.0001 |
| FEV1 % predicted* | 44.5 (18.1) | 48.4 (19.2) | 43.0 (16.9) | <0.0001 |
| Long term oxygen, % | 11.3 | 15.6 | 17.3 | 0.0015 |
| Long term prednisolone, % | 8.7 | 7.4 | 7.8 | 0.58 |
| Left ventricular failure, % | 7.4 | 10.7 | 12.3 | 0.0033 |
| Cor pulmonale, % | 9.8 | 6.1 | 8.0 | 0.022 |
| Diabetes, % | 14.7 | 11.6 | 14.3 | 0.13 |
| Chronic Kidney Disease, % | 5.7 | 11.3 | 13.4 | <0.0001 |
| Cerebrovascular Disease, % | 12.6 | 12.7 | 11.0 | 0.52 |
| Atrial Fibrillation, % | 10.9 | 16.0 | 15.8 | 0.0034 |
| Asthma, % | 5.1 | 7.2 | 10.2 | 0.00042 |
| Cognitive impairment, % | 4.6 | 4.4 | 5.4 | 0.58 |
| Admission details | | | | |
| Length of stay, n† | 6 (4-11) | 5 (3-10) | 4 (2-8) | <0.0001 |
| Radiographic consolidation, % | 29.9 | 29.7 | 23.0 | 0.0041 |
| Ineffective cough, % | 9.3 | 9.6 | 3.4 | <0.0001 |

* Mean (Standard deviation); † Median (Interquartile range). P value compares proportions, means and median values across all three groups.

*Table 8.1: Demographics and candidate predictors by cohort*

## 8.2 Missing data

Missing data for all indices, prognostic scores and patients are shown in Table 8.2.

| | Missing data, % | | |
|---|---|---|---|
| | Derivation | Internal validation | External validation |
| Number or patients, n | 824 | 802 | 791 |
| Patients with missing data | 2.9 | 3.6 | 16.9 |
| Excluding weight loss | 0 | 2.2 | 6.4 |
| Sociodemographic details | | | |
| Gender | 0 | 0 | 0 |
| Age | 0 | 0 | 0 |
| Residence | 0 | 0 | 0 |
| Cigarette pack years | 0 | 0 | 0 |
| Preadmission details | | | |
| eMRCD | 0 | 0 | 0 |
| Admissions in previous year | 0 | 0 | 2.1 |
| Recent weight loss | 2.9 | 1.4 | 12.4 |
| FEV1 % predicted | 0 | 0.75 | 1.5 |
| Long term oxygen | 0 | 0 | 0.38 |
| Long term prednisolone | 0 | 0 | 0.63 |
| Left ventricular failure | 0 | 0 | 0.25 |
| Cor pulmonale | 0 | 0 | 0.25 |
| Diabetes | 0 | 0 | 0.38 |
| Chronic Kidney Disease | 0 | 0 | 0.13 |
| Cerebrovascular Disease | 0 | 0 | 0.51 |
| Atrial Fibrillation | 0 | 0 | 0 |
| Asthma | 0 | 0 | 0.25 |
| Cognitive impairment | 0 | 0 | 0.38 |
| Admission details | | | |
| Admission hospital | 0 | 0 | 0 |
| Length of stay | 0 | 0 | 0.76 |
| Radiographic consolidation | 0 | 0 | 0 |
| Cough effectiveness | 0 | 0.37 | 1.5 |
| Variables from other prognostic with missing data | | | |
| BMI | 2.9 | 21.3 | 25.4 |
| Exacerbations | 11.9 | 61.5 | 18.2 |
| Severe exacerbations | 0 | 0 | 1.3 |
| Current smoking status | 0 | 0.62 | 0.38 |
| Missing data by prognostic score | | | |
| PEARL | 0 | 0 | 2.4 |
| ADO (original and updated) | 0 | 1.9 | 1.5 |
| BODEX | 2.9 | 22.1 | 26.2 |
| CODEX | 0 | 1.9 | 2.7 |
| DOSE | 11.9 | 62.6 | 19.1 |
| LACE | 0 | 0 | 1.9 |

*Table 8.2: Percentage of missing data per variable in each cohort*

Of the candidate indices shown in table 2, all had 1% or less missing data for each cohort except for pH (derivation 6.6%, internal validation 9.4% and external validation 16.2%), weight loss (derivation 2.9%, internal validation 1.4%, external validation 12.4%), admissions per year (derivation 0%, internal validation 0%, external validation 2.1%), and cough effectiveness (derivation 0%, internal validation 0.37%, external validation 1.5%).

### 8.3 Development of a predictive score

The following indices were categorised: age <80 or 80+; cigarette pack years <45 or 45+; eMRCD score 1-3, 4, 5a or 5b; forced expiratory volume in one second (FEV1) %predicted <50 or 50+; previous admissions (<2 or 2+ in the past year); and length of stay as per the LACE study (0, 1, 2, 3 ,4-6, 7-13, or 14+ days).[221] The ROC curves for eMRCD score, admissions in the previous year and age as a continuous indices are shown in Figure 8.1. The arrows represent the cut-offs that were selected for categorisation of the indices.

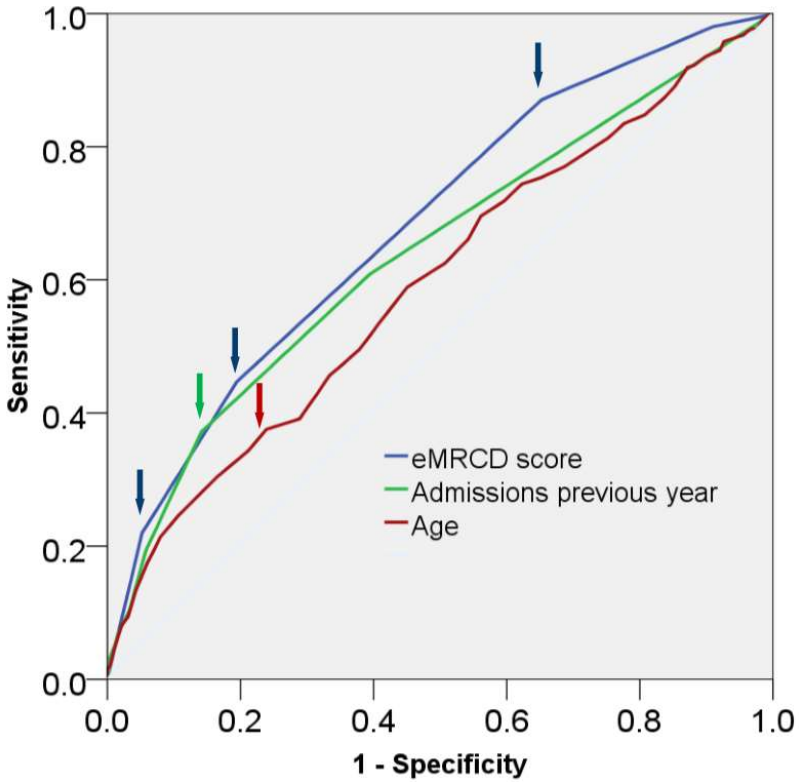


*Figure 8.1: ROC curves for categorised indices that appear in PEARL score*

All candidate indices were analysed using backwards multivariate logistic regression (Table 8.1). Weight loss was not entered into the model due to the high rate of missing data. Indices with high missing data rates may provide biased estimates as the test may only be performed in select patients; furthermore, collecting this index was labour intensive, a problem which would likely recur in clinical practice.[256]

The indices retained in the final model were: **P**revious admissions, **e**MRCD score, **a**ge 80 or more, cor pulmonale ("**r**ight ventricular failure") and **l**eft ventricular failure, and were collectively named the PEARL score (Table 8.3 and Table 8.4). The PEARL regression equation was compared within the derivation cohort by Akaike

Information Criterion (AIC), entering age as a categorical and continuous variable: $PEARL_{age\ catergorical}$ AIC = 940.4, $PEARL_{age\ continuous}$ AIC= 940.8. This is the recommended approach to compare the relative quality of two related models,[204] and shows no difference, supporting the categorisation of age for ease of application of the score.

As continuous variables were dichotomised, primarily to ensure ease of use, the regression coefficients (the column entitled "B" in Table 8.3) show the relative contribution of each index. The coefficients were used to assign initial weights to each index in the derivation cohort. There are various approaches to adjust models to improve prediction and generalisability;[246, 275] this can involve combining derivation and validation data sets.[246] The assigned weights were re-evaluated after pooling all three cohorts. The original weightings assigned in the derivation cohort were appropriate, except "previous admissions", which should optimally be weighted as three (Table 8.3).

| | Derivation cohort | | | All cohorts | Updated |
|---|---|---|---|---|---|
| PEARL indices | B | P value | Odds ratio (95% CI) | B | Weighting |
| Previous admissions (2 or more) | 1.04 | <0.0001 | 2.84 (1.98-4.07) | 1.14 | 3 |
| eMRCD score 4 | 0.67 | 0.0017 | 1.96 (1.29-2.98) | 0.37 | 1 |
| eMRCD score 5a | 1.13 | <0.0001 | 3.10 (1.89-5.10) | 0.85 | 2 |
| eMRCD score 5b | 2.02 | <0.0001 | 7.51 (4.17-13.52) | 1.09 | 3 |
| Age 80 or more | 0.38 | 0.032 | 1.47 (1.03-2.08) | 0.38 | 1 |
| Right ventricular failure | 0.50 | 0.050 | 1.66 (1.00-2.74) | 0.63 | 1 |
| Left ventricular failure | 0.52 | 0.080 | 1.68 (0.94-3.00) | 0.52 | 1 |
| Constant | -0.78 | <0.0001 | 0.46 (0.36-0.58) | -0.95 | |
| | | | | Maximum PEARL score | 9 |

Hosmer-Lemeshow statistic= 0.83, Nagelkerke r square= 0.21

*Table 8.3: Predictors of death or readmission, the PEARL indices*

## 8.4 Performance and calibration of the PEARL score

The AUROC for the PEARL score (Table 8.4) for 90-day readmission/ death without readmission was: derivation = 0.73 (95% CI 0.70-0.77); internal validation = 0.68 (95% CI 0.64-0.72); and external validation = 0.70 (95% CI 0.66-0.73). In all three cohorts combined the AUROC for 90-day readmission/ death without readmission was 0.70 (95% CI 0.68-0.73). For 90-day readmission only (not including death) the AUROC was 0.69 (95% CI 0.67-0.71).

| Index | Score |
|---|---|
| Previous admissions (2 or more within past year) | 0 / 3 |
| Dyspnoea | |
| eMRCD 1-3 | 0 |
| eMRCD 4 | 1 |
| eMRCD 5a | 2 |
| eMRCD 5b | 3 |
| Age 80 or more | 0 / 1 |
| Right ventricular failure (Cor pulmonale) | 0 / 1 |
| Left ventricular failure | 0 / 1 |
| Total PEARL score | 9 |

*Table 8.4: The PEARL score*

The risk of readmission or post-discharge death increases with higher PEARL scores (Table 8.5).

| Risk | PEARL Score | Derivation cohort, % (n) | Validation cohort, % (n) | All cohorts, % by risk group |
|---|---|---|---|---|
| Low | **0** | 15.1 (25/ 166) | 16.4 (29/ 177) | 20.7 (184/ 890) |
| | **1** | 23.6 (49/ 208) | 23.9 (81/ 339) | |
| Intermediate | **2** | 33.8 (48/ 142) | 36.3 (116/ 320) | 42.1 (454/ 1078) |
| | **3** | 51.2 (44/ 86) | 41.7 (111/ 266) | |
| | **4** | 59.1 (55/ 93) | 46.8 (80/ 171) | |
| High risk | **5** | 65.2 (43/ 66) | 60.1 (95/ 158) | 66.4 (298/ 449) |
| | **6** | 67.5 (27/ 40) | 69.2 (63/ 91) | |
| | **7** | 72.2 (13/ 18) | 70.2 (40/ 57) | |
| | **8** | 100 (4/ 4) | 77.8 (7/ 9) | |
| | **9** | 100 (1/ 1) | 100 (5/ 5) | |
| Total | | 37.5 (309/ 824) | 39.4 (627/ 1593) | 38.7 (936/ 2417) |

*Table 8.5: 90 day death/ readmission without death probability by PEARL score*

Further details of all cohorts, and data on readmission and death as lone outcome are shown in the appendix (Table 10.1); across all three cohorts, risk was similar with all p-values >0.05 showing that predictions are consistent. We grouped scores into low (0-1), intermediate (2-4), and high risk (5+) PEARL scores. Sensitivity and 1-

specificty for the PEARL score are shown in the online supplement (Table 8.6). In the low risk group (PEARL 0-1) only 2.5% (22/ 890) died post-discharge within 90 days.

| PEARL score | Sensitivity | 1 – Specificity |
|---|---|---|
| 0 | 1.00 | 1.00 |
| 1 | 0.92 | 0.73 |
| 2 | 0.76 | 0.42 |
| 3 | 0.61 | 0.24 |
| 4 | 0.46 | 0.15 |
| 5 | 0.29 | 0.080 |
| 6 | 0.15 | 0.035 |
| 7 | 0.058 | 0.010 |
| 8 | 0.016 | <0.0001 |
| 9 | 0.0032 | <0.0001 |

*Table 8.6: PEARL score sensitivity and 1- specificity, derivation cohort*

Calibration was further assessed by plotting “expected probability” (calculated from the full regression equation) against the “observed probability”. Calibration tends to perform best in derivation cohorts, so the derivation and validation cohorts were plotted separately. Again, PEARL was well calibrated (perfect calibration would fall on the 45 degree line, Figure 8.2).

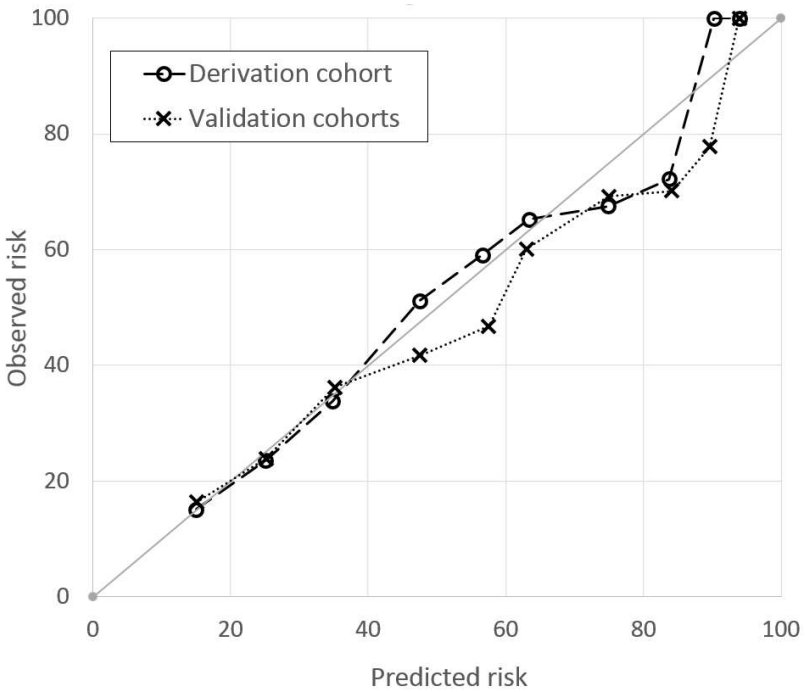


*Figure 8.2: Calibration curve showing predicted risk compared to observed risk by PEARL score.*

### 8.5 Comparison to other prognostic scores

ROC curves for each prognostic score are shown in Figure 8.3 for the validation cohorts combined. Comparison within the derivation cohort favours the developed tool, so the derivation cohort is not included within the graph.

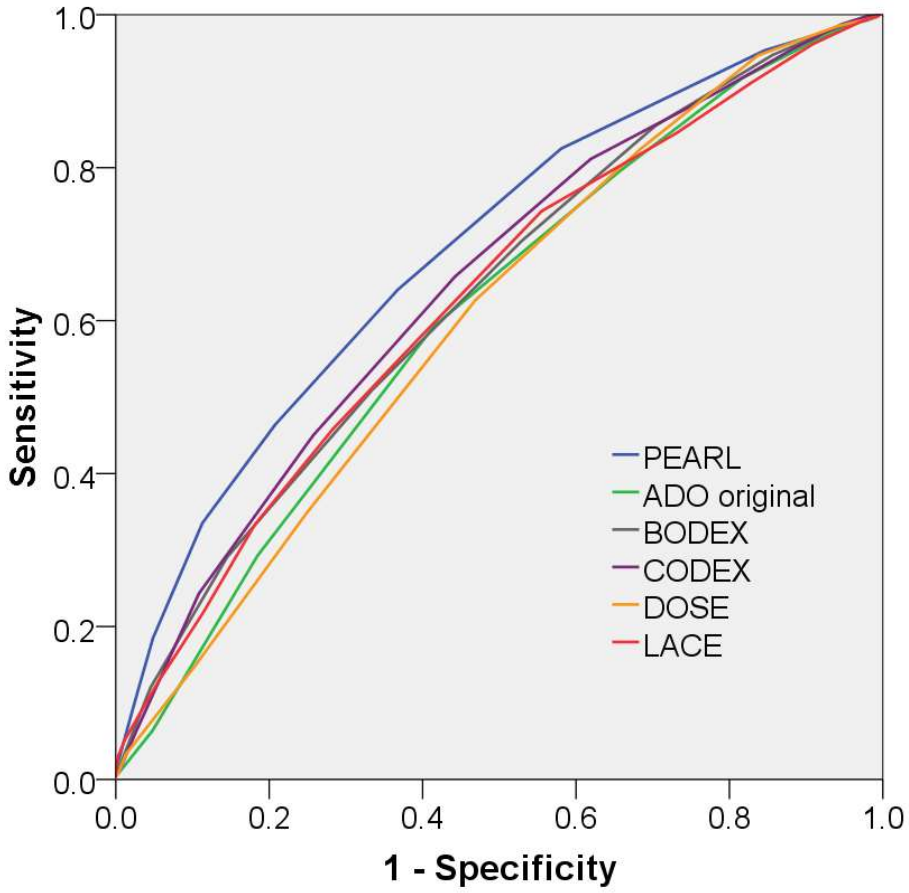


*Figure 8.3: ROC curves for PEARL, ADO, BODEX, CODEX, DOSE and LACE for 90 day readmission or death, validation cohorts combined*

Table 8.7 shows the comparison between PEARL and all other tools for each individual cohort. PEARL was superior to ADO, BODEX, DOSE and LACE in all three cohorts, and to CODEX within the derivation and external validation cohorts. Results were unchanged with complete case analysis.

Thirty day comparisons are shown online (Table 8.8). PEARL was also superior to the original ADO score, the eMRCD score (the strongest of the PEARL indices), and the DECAF score (appendix Table 10.2).

| Prognostic score | Derivation | Internal validation | External validation |
|---|---|---|---|
| PEARL | 0.73 (0.70-0.77) | 0.68 (0.64-0.72) | 0.70 (0.66-0.73) |
| ADO* | 0.67 (0.63-0.71)† | 0.64 (0.60-0.67)‡ | 0.58 (0.54-0.62)* |
| BODEX | 0.65 (0.61-0.69)* | 0.64 (0.60-0.68)x | 0.62 (0.58-0.66)* |
| CODEX | 0.69 (0.65-0.73)‡ | 0.66 (0.63-0.70)NS | 0.62 (0.58-0.66)* |
| DOSE | 0.63 (0.59-0.67)* | 0.59 (0.55-0.64)† | 0.61 (0.57-0.65)* |
| LACE | 0.65 (0.61-0.69)* | 0.61 (0.57-0.65)‡ | 0.65 (0.61-0.68)x |

AUROC curves of each score compared to PEARL by method of DeLong: *<0.0001, †<0.001, ‡<0.01, x<0.05, NS not significant
Missing data >20% for BODEX and DOSE. On complete case analysis, BODEX= 0.63 (0.59-0.67), DOSE= 0.60 (0.53-0.66)

*Table 8.7: 90 day readmission or death, AUROC curves, with data imputation*

| Prognostic score | Derivation | Comparison to PEARL, p value | Internal validation | Comparison to PEARL, p value | External validation | Comparison to PEARL, p value |
|---|---|---|---|---|---|---|
| PEARL | 0.70 (0.66-0.74) | N/A | 0.64 (0.60-0.69) | N/A | 0.64 (0.60-0.69) | N/A |
| ADO | 0.63 (0.59-0.68) | 0.0021 | 0.61 (0.56-0.65) | 0.082 | 0.56 (0.51-0.60) | 0.00047 |
| BODEX | 0.63 (0.59-0.68) | 0.0027 | 0.61 (0.57-0.66) | 0.16 | 0.58 (0.53-0.62) | 0.0046 |
| CODEX | 0.65 (0.61-0.70) | 0.014 | 0.62 (0.58-0.67) | 0.28 | 0.59 (0.54-0.63) | 0.0064 |
| DOSE | 0.61 (0.57-0.66) | 0.00064 | 0.58 (0.53-0.63) | 0.016 | 0.59 (0.54-0.63) | 0.021 |
| LACE | 0.66 (0.61-0.70) | 0.087 | 0.61 (0.57-0.66) | 0.26 | 0.59 (0.55-0.64) | 0.038 |

AUROC curves of each prognostic score compared to DECAF by method of DeLong.

*Table 8.8: 30 day readmission or death, AUROC curves, with data imputation*

## 8.6 Time to death or readmission, and readmission frequency

Time to death or readmission was available to 90 days in all three cohorts and to one year in the derivation and internal validation cohorts. Higher PEARL risk groups were associated with a shorter time to death or readmission (Figure 8.4 and Table 8.9).

The cumulative risk up to 90 days for readmission or death without readmission was 20.8*, 41.8% and 67.3% for low, intermediate and high risk groups respectively.

PEARL risk group identifies those at risk of frequent admissions. For risk groups 0-1, 2-4 and 5-9 the median (IQR) number of readmission was 0 (0-1), 1 (0-2) and 2 (1-3). When adjusted for death (time exposed to readmission), the risk was 0 (0-1.8), 1 (0-3) and 3 (1-6) respectively.

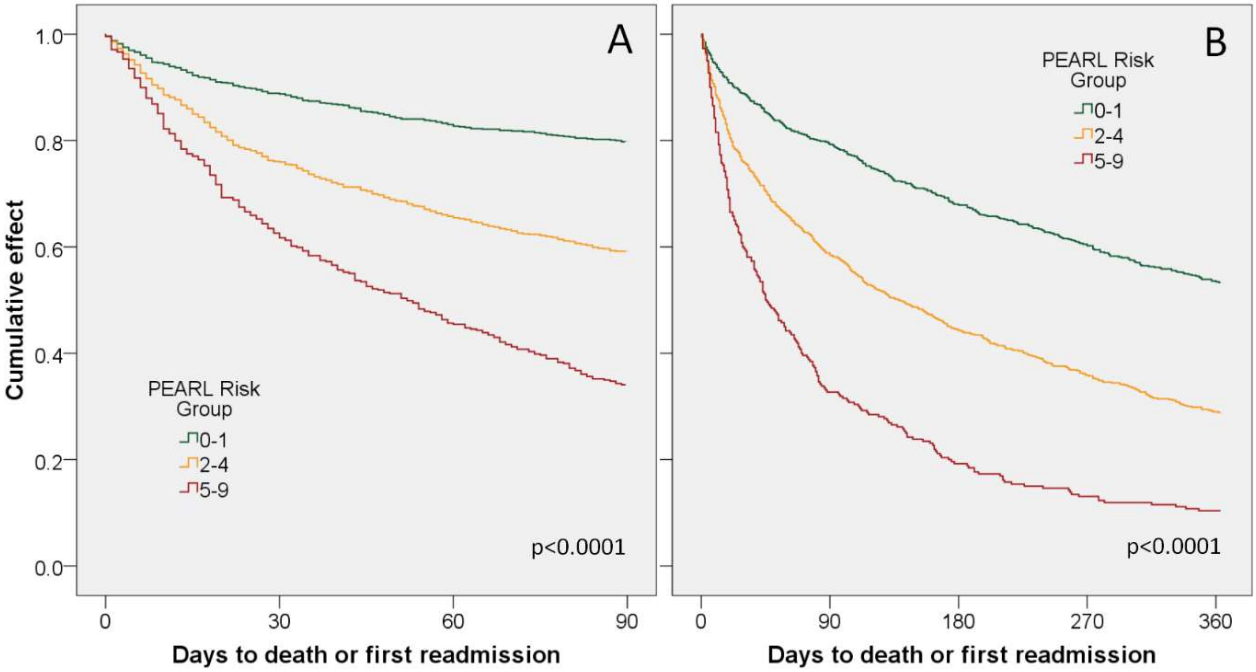


*Figure 8.4: Time to readmission or death, by PEARL risk group: A) in all cohorts up to 90 days, B) in the derivation and internal validation cohort up to 365 days (comparison using the log rank test)*

| PEARL risk group | PEARL score | Days to readmission or death, % | | | | No readmission or death, % | Total, n |
|---|---|---|---|---|---|---|---|
| | | 0 to 30 | 31 to 60 | 61 to 90 | 91 to 365 | | |
| Low | 0-1 | 11.3% | 6.5% | 3.0% | 25.9% | 53.3% | 664 |
| Intermediate | 2-4 | 24.1% | 10.0% | 7.7% | 29.2% | 29.1% | 702 |
| High | 5-9 | 40.4% | 15.4% | 11.5% | 22.3% | 10.4% | 250 |
| | Total | 21.5% | 9.4% | 6.4% | 26.8% | 36.0% | 1626 |

*Table 8.9: Time to readmission or death, by PEARL risk group, derivation and internal validation cohort*

## 8.7 Discussion

We have developed and validated a model to predict 90-day readmission/ death without readmission in patients hospitalised with an AECOPD; the “PEARL score”. The tool was designed to be easily applied at the bedside using indices routinely available at admission, and performance was superior to alternative scores. The risk

of readmission/ readmission without death was considerably higher in the first 90 days than during the rest of the year, both overall and within the moderate and high risk PEARL groups, which justifies our chosen timeframe. Rates of readmission were similar to those seen in the European National Audit 2016.[10] Our composite endpoint is more appropriate than readmission alone, as the latter would include both those who are neither readmitted nor die and those who die without readmission in the "favourable" outcome group. Accurate risk stratification of patients should help efficiently direct resources aimed to reduce readmissions, such as supported discharge services, pulmonary rehabilitation, education programmes, and possibly azithromycin therapy, though the impact of these strategies requires assessment. Furthermore, identification of patients who are at risk of death without readmission may allow services to be put in place to facilitate early recognition of deterioration, and readmission.

The study has a number of strengths, most importantly consecutive recruitment of patients and high case ascertainment. This is supported by excellent recruitment rates at all sites which were substantially higher than the 2015 UK national COPD audit, as detailed previously.[255] Generalisability is supported by consistent performance in three cohorts, including the prospective external validation cohort (the "gold standard" for assessing performance). The six hospitals which took part had different structures of care and varied populations, with respect to readmission avoidance schemes, COPD prevalence, socioeconomics, and rurality. Furthermore, data were collected by a variety of healthcare professional, including physicians and specialist nurses.

The eligibility criteria were inclusive; few patients were excluded due to poor prognosis (expected survival less than one year for an illness other than COPD): in the internal validation cohort, for example, this comprised only 27 patients (3.4%), principally due to metastatic malignancy. Definitions were aligned with usual clinical practice, and were pragmatic to reduce missing data and the consequent risk of bias. This approach is regarded as a key strength in prognostic research.[204, 251] Primary outcome data was available in all patients, missing data rates were low, and multiple imputation and complete case analyses showed that results were robust. Further study strengths can be seen in the appendix (Appendix B: Charms checklist for PEARL study)[204] which provides a framework to critique prognostic studies.

There are several limitations within the study. Most patients in the internal validation cohort were identified retrospectively which may have compromised performance. However, the risk of any consequent bias is probably low as the relevant indices were recorded during the patients' admission prior to the outcome. When extracting data, researchers were blind to outcome. Furthermore, the external validation cohort was prospective and individually powered.

Varied rates of cor pulmonale and left ventricular failure may reflect inconsistency in clinical assessment, or could represent true population differences, supporting external validity. Despite variation in rates, both were associated with readmission/ death without readmission in all three cohorts. Dichotomising continuous indices, such as age, allows a score to be calculated at the bedside without the full regression equation and a computer. When this approach is adopted, concern about consequent loss of prognostic strength may be raised. However, the impact of dichotomising (or categorising) continuous variables on performance may be minimal if the relation between the index and risk of outcome is non-linear, and the prognostic threshold(s) appropriately selected.[251] The impact of dichotomising age on the performance of the PEARL score was negligible. We did not differentiate between different causes of readmission such as respiratory or non-respiratory. This would require the derivation and validation of separate scores, and based on data from our validation cohorts most admissions are respiratory (more than three in four). Furthermore, differentiating between cardiac and respiratory causes of readmission can be challenging. Whilst PEARL performed well in all cohorts, and participating units were chosen to ensure variation in population and structure of care, confirmation of performance in healthcare settings outside of the United Kingdom is desirable. A final limitation, which is common to all prognostic research, is that the strength of the association of the predictor with the outcome may vary between patients.[276]

Other prognostic research shows that accurate prediction of readmission is challenging.[223] The discrimination of PEARL (external validation AUROC = 0.70) is superior to all other tools that predict readmission or death in AECOPD, and substantially stronger than clinical judgement (AUROC = 0.56 to 0.59).[215] An extensive literature search was performed to ensure the inclusion of all potential predictor variables that could be easily collected at the bedside. All of the indices in the PEARL score have been previously shown to predict our outcome, except for eMRCD score. This is important as eMRCD (along with previous admissions) was

the strongest predictor. In our study, associated pneumonia, non-invasive ventilation and institutional care (nursing or residential home) did not appear in the final model. This does not mean that they are not predictors, but rather that they did not add prognostic power to the PEARL indices which were stronger predictors. Furthermore, eMRCD includes a measure of frailty which may, at least in part, capture the risk associated with such indices. The strongest predictors of readmission/ death without readmission tended to be measures of underlying disease severity, frailty and co-morbidity rather than measures related to the acute event. For instance, DECAF contains eosinopenia (a marker of acute inflammation/ sepsis), consolidation and acidaemia; it is an excellent predictor of acute mortality, but not medium and long-term outcomes in those who survive to discharge.

The lack of novel predictors, such as cardiac biomarkers, neural respiratory drive,[277] four meter gait speed,[278] and quadriceps size by ultrasound [279] may be seen as a limitation. The inclusion of too many indices in model development risks overfitting and loss of performance in the validation cohorts.[251] Furthermore, the inclusion of indices that are not routinely collected may introduce bias as missing data is large,[280, 281] and any association may be due to case selection only. For example, in our study only 17% of patients had troponin tests performed, and levels were not related to outcome on univariate analysis. We were unable to capture psychological wellbeing, social support networks and treatment concordance. These variables are complex to measure and may reduce a tool's usability.

Previous studies have shown a relationship between anxiety and depression and readmission,[260, 261] although this was not seen in our derivation cohort (based on a preadmission clinical diagnosis). It is possible that an alternative approach to assessing anxiety, such as measurement of the Hospital Anxiety and Depression score at the point of discharge, may add predictive information.

FEV1 is associated with exacerbations and hospital admissions in patients with stable COPD and guides treatment,[5, 122, 123] but in our derivation cohort it was not an independent predictor of the primary outcome. The better performance of FEV1 in the derivation cohorts of tools such as ADO, BODEX, CODEX and DOSE probably reflects differences in population and measured outcome.

PEARL was superior to ADO, updated ADO, BODEX, CODEX, DOSE and LACE. The CODEX study was developed in a large number of hospitals, the population is

clearly described and model performance is appropriately assessed. In its derivation study it was superior to ADO and BODEX for 90-day readmission or death, though this comparison favours CODEX.[216] In our study, it was the second best performing tool. LACE was developed in unselected patients, rather than those with AECOPD,[223] for 30-day (and not 90-day) outcome. Of importance, PEARL was superior at both time-points. The LACE score was selected for comparison as it was derived in a well-conducted study, demonstrated better discrimination than other generic tools and is used in some hospitals. The requirement to score the full Charlson index limits the bedside application of both CODEX and LACE.

A number of studies have shown positive outcomes from interventions aimed to reduce readmission.[282-284] There is room for further research to improve outcome, particularly in COPD.[285, 286] The lowest risk group (PEARL 0 to 1) comprise almost a third of the population. Such risk stratification can inform research by excluding low risk groups (of importance, the risk of death alone was only 2.5% in the low risk, PEARL 0-1 group), or by using randomisation techniques that include stratification or minimisation by risk group.

In current practice, clinician judgement is used to identify and target resources towards patients with a high readmission risk, although this judgement is known to be poor.[215] The PEARL score offers robust and consistent prediction of 90-day readmission or death, and is superior to alternative tools. PEARL may aid clinical decision-making and resource allocation, although quantification of the impact of PEARL in terms of cost and patient outcomes requires further research.

# Chapter 9 Conclusions

- Many established treatments for AECOPD are not supported by robust evidence, and further research is required to: a) better quantify the risks and benefits of corticosteroids beyond single courses and identify which subgroups benefit from this treatment; and c) identify who will benefit from antibiotic therapy to improve antibiotic stewardship.
- In a meta-analysis, ESD/HAH was associated with a lower rate of readmission, though this depended on whether return to hospital was considered a readmission. Although few trials reported costs, Early Supported Discharge and Hospital at Home for AECOPD were associated with lower healthcare costs.
- The DECAF score is a robust predictor of inpatient death using indices that are routinely available at admission, and is superior to other prognostic scores.
- In pneumonic AECOPD, CURB-65 0 and 1 scores are not low risk, and should therefore not guide treatment in this patient group.
- In an RCT and implementation study, the DECAF score can be used to select low risk patients for Hospital at Home. Compared to usual care, this approach is safe, cost-effective and preferred by 90% of patients.
- Five independent variables to predict readmission/ death without readmission, formed the PEARL score: Previous admissions, eMRCD score, Age, Right sided heart failure, and Left sided heart failure. Overall, PEARL was superior to other such scores and was also associated with time to readmission.
- On February 1st 2017 the UK national COPD audit moved to continuous data collection and included the DECAF indices for all patients admitted to hospital with AECOPD. This will likely lead to wide uptake of the DECAF score in the UK. The awaited RCT publication will guide clinicians on how to use the DECAF score to direct care.

# Chapter 10 Appendices

## Appendix A: Charms checklist for DECAF validation study

### Source of Data

1) Source of data (e.g. cohort, case-control, randomised trial participants, or registry data)

- The external validation cohort was prospective, and individually adequately powered. The internal validation cohort was partially prospective, with retrospective extension.

### Participants

1) Participant eligibility and recruitment method (consecutive participants, location, number of centres, setting, inclusion and exclusion criteria)

**Eligible patients analysis**

- All eligible patients were included in the validation cohorts, except those that did not have complete data for all DECAF indices. This was approximately 1% of the population, and mainly comprised of patients with SpO2 92% or less in whom arterial blood gas analysis was not performed

**Eligible patients excluded**

- Exclusion criteria were few. For the internal validation study, patients were excluded for the following reasons: survival <1 year n=27 (12 lung cancer, 3 end stage dementia, 3 metastatic cancer, 2 metastatic bladder cancer, 2 idiopathic pulmonary fibrosis, 1 metastatic renal cancer, 1 metastatic bower cancer, 1 metastatic rectal cancer, 1 oesophageal cancer, and 1 mesenteric cancer), less than ten pack year smoking history n=24, spirometry not obstructive= 42. Ten patients had no ABG results, but had supplemental oxygen or oxygen saturations that were too low to assume a DECAF acidaemia score of 0. One patient had no eosinophil count. Robust data is not available for the external validation cohort.

**Consecutive patients**

- Extensive efforts were made to capture consecutive patients, including a broad coding search. Patients were captured by daily screening (Monday to Friday) on admission units and medical wards (external validation cohort) by a dedicated team.
- In the internal validation cohort, patients were mainly identified retrospectively using a broad coding search, with cross referencing to patients identified by clinical staff who routinely review patients admitted with AECOPD. This methodology was compared to prospective screening over three months, showing superior capture overall, and only one eligible patient was identified by prospective screen alone.

**Location, centres, setting, and inclusion and exclusion criteria**

- Six UK centres were involved: the two sites included in the derivation study took part in the internal validation cohort, and four geographically distinct hospitals took part in the external validation. All patients in the study were recruited from secondary care. Inclusion and exclusion criteria are described.

2) Participant description

- Detailed description of participants by different sites in table 2

3) Details of treatments received, if relevant

- Medical treatment for acute exacerbations of COPD included antibiotics, steroids, nebulised bronchodilators, and non-invasive ventilation. In creating a score that is intended for use to guide management, it is not appropriate to include acute treatments as predictors. The research team did not influence clinical treatment.

4) Study dates

- Given for each site in table 2

### Outcome to be predicted

1) Definition and method for measurement of outcome

- Outcome clearly defined- Inpatient death

2) Was the same outcome definition (and method for measurement) in all patients?

- Yes

3) Type of outcome single or combined endpoints?

- Single endpoint

4) Was the outcome assessed without knowledge of the candidate predictors (I.e., blinded)?
- The DECAF indices were apparent to the team reporting in-hospital death, however in-hospital death is inherently objective, therefore the risk of bias is minimal/absent.

5) Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?
- No

6) Time of outcome occurrence or summary of follow-up
- Inpatient death. Presence or absence of outcome captured in all patients.

**Candidate predictors**

1) Number and type of predictors (eg. Demographics, patient history, physical examination, additional testing, disease characteristics)
- Candidate predictors refers to indices for derivation study, not the validation study, so the number of predictors is not relevant here. The analysis of inpatient mortality was only performed with the five DECAF indices.

2) Definition and methods for measurement of candidate predictors
- Candidate predictors described in derivation study. In validation study, definitions and methods of measurement provided. Each research site was provided with a data collection guide which included definitions of terms and diseases. eMRCD score as per table 1, eosinophil count cut-off provided, presence of chest radiograph based on assessment from consultant post-take ward round, acidaemia based on arterial blood gas analysis, and atrial fibrillation based on electrocardiogram and/ or history of (paroxysmal) atrial fibrillation.

3) Timing of predictor measurement of candidate predictors (e.g. at patients presentation, at diagnosis, at treatment initiation)
- DECAF indices were assessed on admission (see table 1).

4) Were predictors assessed blinded for outcome, and for each other (if relevant)?
- Predictors were assessed blinded from the outcome. The external validation cohort was identified prospectively, so variables were collected prior to the outcome. The internal validation study was performed retrospectively. Three DECAF variables, eosinopenia, acidaemia and atrial fibrillation, are objective. Potentially, there may be a degree of inter-observer variation in the reporting of chest radiograph consolidation and the eMRCD score, however the research team relied on the observations of the attending clinicians. For patients identified retrospectively, the researcher obtaining the information from the notes was blinded to the outcome. Collection of individual predictors was not blinded from other DECAF indices, although the consequent risk of bias is low.

5) Handling of predictors in the modelling (e.g. Continuous, linear, non-linear transformations or categorised)
- The DECAF variables were applied as per the derivation study. eMRCD score is categorised, eosinophil score and pH are dichotomised, and AF and chest x-ray consolidation are binary. Dichotomising variables can cause a loss of discrimination, depending on their relationship with the outcome. This was not an issue as the continuous varibles related to DECAF show a non-linear relationship to mortality, and the pre-define threshold was optimal. Discrimination of DECAF was very good, and similar to that of the derivation study, in both validation cohorts.

**Sample size**

1) Number of participants and number of outcomes/events
- The internal and external cohorts were individually adequately powered. Internal cohort: 880 participants, 78 events; external cohort 845 participants, 54 events.

2) Number of outcomes/events in relation to the number of candidate predictors (events per variable)
- This approach to sample size calculation is only relevant to the derivation study.

**Missing data**

1) Number of participants with any missing value (include predictors and outcomes)
2) Number of participants with missing data for each predictor

- 1+2) Number of missing values and number of participants with missing data provided

3) Handling of missing data (e.g. complete-case analysis, imputation, or other methods)

- 3) Low rates of missing data. Multiple imputation used; complete-case analysis also performed.

### Model development

1) Modeling method (eg logistic. survival, neural networks, or machine learning techniques)
2) Modeling assumptions satisfied
3) Methods for selection of predictors for inclusion in multivariable modelling (e.g. all candidate predictors, pre-selection based on unadjusted association with the outcome)
4) Method for selection of predictors during multivariable modeling (e.g. full model approach, backward or forward selection) and criteria used (e.g. p-value, Akaike Information Criterion)

- 1-4) The DECAF model was developed in the DECAF derivation study; these aspects do not apply to the validation study.

5) Shrinkage of predictor weights or regression coefficients (e.g. no shrinkage, uniform Shrinkage, penalized estimation)

- 5) Shrinkage refers to adjusting coefficients to protect against overfitting and loss of discrimination in validation studies. In developing the DECAF score, the prognostic indices were weighted based on their coefficients. The same weighting was used for both validation cohorts, and discrimination remained good in both validation cohorts.

### Model performance

1) Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log rank) measures with confidence intervals

- Hosmer-Lemeshow test is provided, and observed risk from derivation and validation cohorts described and compared. The validation study showed good calibration. Although the absolute risk differed between the derivationa and validation study for high risk patients, this reflects differences in overall mortality rates and a large and stepwise increase in mortality is seen between different risk groups.

2) Classification measures (e.g sensitivity, specificity, predictive values, net reclassification improvement) and whether a priori cut points were used

- 2) Sensitivity and specificity are provided. Reclassification measures, such as net reclassification improvement, look at the value in adding a single predictor to a prediction model. Due to the very strong performance of the DECAF score, no reclassification measures were performed or required.

### Model evaluation

1) Methods used for testing model performance: development dataset only (random split of data, resampling methods, e.g. bootstrap or cross-validation, none) separate external validation (e.g. temporal, geographical, different setting, different investigators)

- Internal validation: involved the same hospitals as the derivation study, but at a different time period (a form of temporal validation) and additional investigators.
- External validation was performed in hospitals that are geographically distinct. Hospitals were chosen to ensure variation in population characteristics (rurality and socioeconomic factors) and structures of care to maximise generalisability. The research staff within external sites were not involved in the derivation study.2) In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)
- Not applicable

### Results

1) Final and other multivariable models (e.g. basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard or confidence Intervals)

2) Any alternative presentation of the prediction models. e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance
3) Comparison of the distribution of predictors (including missing data) for development and validation datasets

- 1+2+3) These points apply to prognostic research in which data is extracted for systematic reviews, so is not applicable. Predictor weights and regression coefficients are given for the DECAF score.

**Interpretation and discussion**

1) Interpretation of presented models (confirmatory, if model useful for practice versus exploratory, is more research needed)

- The performance of DECAF is excellent in two separate, and individually adequately powered, validation cohorts. This confirms that DECAF can risk stratify patients effectively. The value of using DECAF to inform clinical practice, such as to identify patients for Hospital at Home, requires further research.

2) Comparison with other studies, discussion of generalisability strengths and limitations.

- DECAF is compared to other prognostic scores, with discussion of the strengths and limitations.

## Appendix B: Charms checklist for PEARL study

**Source of Data**

1) Source of data (e.g. cohort, case-control, randomised trial participants, or registry data)

- The derivation and external validation cohorts was prospective. The internal validation cohort was retrospective, with prospective collection data.

**Participants**

1) Participant eligibility and recruitment method (consecutive participants, location, number of centres, setting, inclusion and exclusion criteria)

**Eligible patients analysis**

- Patients who did not survive to discharge were appropriately excluded as the main outcome was readmission or death at 90 days from discharge. Otherwise, all patients were included in the derivation cohort. The primary outcome for the three cohorts was for inpatient mortality, which led to the development of the DECAF score. The readmission analysis was a pre-specified study. In the validation cohort, those that did not have complete data for all DECAF indices were not included in the analysis, although this was only 1% of the population, and mainly comprised of patients that had oxygen saturations sufficiently low to warrant arterial blood gas analysis but that declined this investigation.

**Eligible patients excluded**

- Exclusion criteria were few. For the internal validation cohort, patients were not eligible as follows: survival <1 year n=27 (twelve lung cancer, three end stage dementia, three metastatic cancer, two metastatic bladder cancer, two idiopathic pulmonary fibrosis, one metastatic renal cancer, one metastatic bower cancer, one metastatic rectal cancer, one oesophageal cancer, and one mesenteric cancer patient), less than ten pack year smoking history n=24, spirometry not obstructive= 42. Ten patients had no ABG results, but had supplemental oxygen or oxygen saturations that were too low to assume a DECAF acidaemia score of zero. One patient had no eosinophil count. Robust data for the derivation and external validation cohort is unavailable.

**Consecutive patients**

- Extensive efforts were made to capture consecutive patients, including a broad coding search. Patients were captured by daily screening (Monday to Friday) on admission units and medical wards (derivation and external validation cohorts) by a dedicated team. In the internal validation cohort, patients were mainly identified retrospectively using a broad coding search, with cross referencing to clinical staff whose role it is to review patients with exacerbation of COPD. In the internal validation cohort, a dedicated team screened the admission units and medical wards for three months and compared patient capture to the coding records search and clinical team capture. Only one patient was identified by daily screening that was missed by coding or the clinical team.

**Location, centres, setting, and inclusion and exclusion criteria**

- Six UK centres were involved: the same two sites that were included in the derivation cohort took part in the internal validation cohort, and four geographical distinct hospitals took part in the external validation cohort. All patients in the study were recruited from secondary care. Inclusion and exclusion criteria are described.

2) Participant description

- Detailed description of participants by different sites in DECAF validation study.(publication awaited) A detailed description of patients in each cohort is shown in table 1.

3) Details of treatments received, if relevant

- Treatments to reduce hospital readmission include smoking cessation, inhaled corticosteroids, long-acting beta agonists, and long-acting muscarinic agonists, and pulmonary rehabilitation. The score is intended to be used to inform management, so including treatments as predictors is not appropriate. Also, other indices are more strongly associated with readmission or death at 90 days. The research team did not influence clinical treatment.

4) Study dates

- Dates for recruitment period of each hospital discussed in previous publications.[2](awaiting publication)

**Outcome to be predicted**

1) Definition and method for measurement of outcome

- Readmission or death without readmission 90 days from discharge in patients surviving to discharge. Readmission was clearly defined- a patient had to be admitted to hospital and reviewed by a member of the clinical team.

2) Was the same outcome definition (and method for measurement) in all patients?

- Yes.

3) Type of outcome single or combined endpoints?

- Combined outcome. We did not wish to create a score that identified those at risk of readmission, but missed those at risk of death without readmission, as some of these deaths may be preventable. Predictors of readmission and death are similar.

4) Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?

- The indices were apparent to the research team for death. Readmission data was collected blind to the candidate predictors. Readmission and death are regarded as objective outcome and the associated risk of bias is low.

5) Were candidate predictors part of the outcome (e.g. in panel or consensus diagnosis)?

- No

6) Time of outcome occurrence or summary of follow-up

- All patients were followed up. The outcome was 90 days after discharge.

**Candidate predictors**

1) Number and type of predictors (e.g. demographics, patient history, physical examination, additional testing, disease characteristics)

- The type of predictors is described. There were 20 candidate predictors.

2) Definition and methods for measurement of candidate predictors

- The methods for measuring each index is provided, as well as the definitions of those in the PEARL score. A data collection guide was provided to each hospital which included definitions and guidance on data collection.

3) Timing of predictor measurement of candidate predictors (e.g. at patients presentation, at diagnosis, at treatment initiation)

- Predictors were collected at the time of admission up to the point of the post-take ward round.

4) Were predictors assessed blinded for outcome, and for each other (if relevant)?

- The derivation cohort and external validation cohort were prospective. The internal validation cohort was performed retrospectively, but predictors were assessed blinded to the outcome. Collection of predictors were not blinded from each other, though the consequent risk of bias is low.

5) Handling of predictors in the modelling (e.g. Continuous, linear, non-linear transformations or categorised)

- Some predictors were categorised which is described.

**Sample size**

1) Number of participants and number of outcomes/events

2) Number of outcomes/events in relation to the number of candidate predictors (events per variable)

- 1+2) In the derivation cohort, internal validation and external validation cohorts there were 824, 802 and 791 patients. There were 20 candidate predictors in the derivation cohort, and 309 events, or 15.5 events per index. The power calculation for the derivation cohort and each individual validation cohort is described.

**Missing data**

1) Number of participants with any missing value (include predictors and outcomes)

2) Number of participants with missing data for each predictor

3) Handling of missing data (e.g. complete-case analysis, imputation, or other methods)

- 1+2+3) Missing data by participant and by index provided. Missing data rates were low. Multiple imputation was used, and the approach and number of datasets used described. Five datasets were used which is regarded as sufficient given the amount of missing data; complete-case analysis was performed.

### Model development

1) Modeling method (e.g. logistic, survival, neural networks, or machine learning techniques)

- Logistic regression used; methods described.

2) Modeling assumptions satisfied

- Yes

3) Methods for selection of predictors for inclusion in multivariable modelling (e.g. all candidate predictors, pre-selection based on unadjusted association with the outcome)

- Predictors for inclusion selected based on literature search and clinical experience.

4) Method for selection of predictors during multivariable modeling (e.g. full model approach, backward or forward selection) and criteria used (e.g. p-value, Akaike Information Criterion)

- Backwards logistic regression used, criteria (p-values) described. The PEARL (full model) and PEARL (age continuous) were compared with -2 log likelihood. The Akaike Information Criterion is calculated based on the -2 log likelihood and the number of indices in the model. Here, the number of indices is the same (five) so this part of the score is constant. There was no difference in the -2 log likelihood.

5) Shrinkage of predictor weights or regression coefficients (e.g. no shrinkage, uniform Shrinkage, penalized estimation)

- 5) Shrinkage refers to adjusting coefficients to protect against overfitting and loss of discrimination in validation studies. Weightings were assigned to the PEARL score.

### Model performance

1) Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log rank) measures with confidence intervals

- Hosmer-Lemeshow test provided. Actual and observed risks are shown in a calibration plot, and observed risk across all cohorts shown in table 4. Discrimination was calculated with AUROC curves (and confidence intervals provided).

2) Classification measures (e.g. sensitivity, specificity, predictive values, net reclassification improvement) and whether a priori cut points were used

- Sensitivity and specificity are provided, with PEARL scores used as cut-offs. Reclassification measures, such as net reclassification improvement, look at the value in adding a single predictor to a prediction model. No reclassification measures were performed.

### Model evaluation

1) Methods used for testing model performance: development dataset only (random split of data, resampling methods, e.g. bootstrap or cross-validation, none) separate external validation (e.g. temporal, geographical, different setting, different investigators)

- Internal validation involved the same hospitals as the derivation cohort, but at a different time period (a form of temporal validation). Geographical validation (external validation) was performed with four hospitals. Hospitals were chosen for their differences, as described in the paper, to maximise generalisability. The research staff within external sites were not involved in the derivation or internal validation cohorts.

2) In case of poor validation, whether model was adjusted or updated (e.g. intercept recalibrated, predictor effects adjusted, or new predictors added)

- Not applicable

### Results

1) Final and other multivariable models (e.g. basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard or confidence Intervals)

2) Any alternative presentation of the prediction models. e.g. sum score, nomogram, score chart, predictions for specific risk subgroups with performance
3) Comparison of the distribution of predictors (including missing data) for development and validation datasets

- 1+2+3) Predictor weights and regression coefficients are given for the PEARL score. All models have AUROC calculated with confidence intervals. No subgroup analysis performed. Missing data rates for both all three cohorts was low.

### Interpretation and discussion

1) Interpretation of presented models (confirmatory, if model useful for practice versus exploratory, is more research needed)

- The performance of PEARL is shown in three cohorts, with consistent risk stratification. Quantifying the impact of using PEARL requires further research.

2) Comparison with other studies, discussion of generalisability, strengths and limitations.

- Described in discussion

## Appendix C: Tables, including breakdown of costs for RCT

| Risk | Score | | Expected probability derivation cohort | Observed probability derivation cohort | Observed probability internal validation cohort | Observed probability external validation cohort | P value | Readmission or death within 90 days | Death alone within 90 days | Readmission alone within 90 days | Readmission or death within 30 days | Total (all patients) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Low | **0** | n | | 25 / 166 | 17 / 97 | 12 / 80 | 0.84 | 54 | 7 | 50 | 32 | 343 |
| | | % | 15.0 | 15.1 | 17.5 | 15.0 | | **15.7** | 2.0 | 14.6 | 9.3 | |
| | **1** | n | | 49 / 208 | 47 / 193 | 34 / 146 | 0.98 | 130 | 15 | 125 | 69 | 547 |
| | | % | 25.1 | 23.6 | 24.4 | 23.3 | | **23.8** | 2.7 | 22.9 | 12.6 | |
| Intermediate | **2** | n | | 48 / 142 | 60 / 178 | 56 / 142 | 0.51 | 164 | 46 | 149 | 93 | 462 |
| | | % | 34.8 | 33.8 | 33.7 | 39.4 | | **35.5** | 10.0 | 32.3 | 20.1 | |
| | **3** | n | | 44 / 86 | 51 / 126 | 60 / 140 | 0.29 | 155 | 58 | 125 | 100 | 352 |
| | | % | 47.5 | 51.2 | 40.5 | 42.9 | | **44.0** | 16.5 | 35.5 | 28.4 | |
| | **4** | n | | 55 / 93 | 35 / 77 | 45 / 94 | 0.16 | 135 | 33 | 120 | 69 | 264 |
| | | % | 56.6 | 59.1 | 45.5 | 47.9 | | **51.1** | 12.5 | 45.5 | 26.1 | |
| High risk | **5** | n | | 43 / 66 | 40 / 63 | 55 / 95 | 0.62 | 138 | 24 | 127 | 79 | 224 |
| | | % | 63.4 | 65.2 | 63.5 | 57.9 | | **61.6** | 10.7 | 56.7 | 35.3 | |
| | **6** | n | | 27 / 40 | 28 / 40 | 35 / 51 | 1.00 | 90 | 28 | 83 | 51 | 131 |
| | | % | 74.8 | 67.5 | 70.0 | 68.6 | | **68.7** | 21.4 | 63.4 | 38.9 | |
| | **7** | n | | 13 / 18 | 16 / 24 | 24 / 33 | 0.90 | 53 | 14 | 49 | 31 | 75 |
| | | % | 83.7 | 72.2 | 66.7 | 72.7 | | **70.7** | 18.7 | 65.3 | 41.3 | |
| | **8** | n | | 4 / 4 | 1 / 2 | 6 / 7 | 0.37 | 11 | 6 | 10 | 6 | 13 |
| | | % | 90.2 | 100 | 50 | 85.7 | | **84.6** | 46.2 | 76.9 | 46.2 | |
| | **9** | n | | 1 / 1 | 2 / 2 | 3 / 3 | N/A | 6 | 3 | 6 | 5 | 6 |
| | | % | 93.9 | 100 | 100 | 100 | | **100** | 50 | 100 | 83.3 | |
| Total | | n | | 309 / 824 | 297 / 802 | 330 / 791 | 0.11 | 936 | 234 | 844 | 535 | 2417 |
| % | | | 37.5 | 37.5 | 37.0 | 41.7 | | **38.7** | 9.7 | 34.9 | 22.1 | |

P value compares the three observed proportions by Fishers test (the comparison of expected to observed probabilities is shown separately by the Hosmer-Lemeshow statistic and the calibration curve).

*Table 10.1: Online supplemental table showing observed probabilities for all cohorts, and outcome at 30 and 90 days*

*"Expected probability" refers to the predicted risk of 90-day readmission or death calculated from the full regression model, and the "observed probability" is the measured outcome rate for each PEARL score in the each cohort.*

| | Prognostic score | Derivation | Internal validation | External validation |
|---|---|---|---|---|
| 30 day readmission or death | PEARL score | 0.70 (0.66-0.74) | 0.64 (0.60-0.69) | 0.64 (0.60-0.69) |
| | ADO (updated) | 0.62 (0.57-0.67) | 0.60 (0.55-0.64) | 0.56 (0.51-0.60) |
| | eMRCD score | 0.64 (0.59-0.68) | 0.60 (0.55-0.64) | 0.57 (0.53-0.62) |
| | DECAF score | 0.57 (0.53-0.62) | 0.59 (0.54-0.64) | 0.54 (0.49-0.59) |
| 90 day readmission or death | PEARL score | 0.73 (0.70-0.77) | 0.68 (0.64-0.72) | 0.70 (0.66-0.73) |
| | ADO (updated) | 0.65 (0.61-0.69) | 0.63 (0.59-0.66) | 0.58 (0.54-0.62) |
| | eMRCD score | 0.68 (0.65-0.72) | 0.61 (0.57-0.65) | 0.61 (0.57-0.65) |
| | DECAF score | 0.59 (0.55-0.63) | 0.57 (0.53-0.61) | 0.57 (0.53-0.61) |
| PEARL AUROC (95% CI) are superior to all the above scores ($p<0.05$) by method of DeLong. | | | | |

*Table 10.2: 30 day readmission or death, AUROC curves, for updated ADO score, eMRCD and DECAF*

| | HAH, £ | UC, £ |
|---|---|---|
| Bed stay | 385.3 | 1040.1 |
| Inpatient healthcare review | 186.8 | 266.1 |
| Diagnostic tests | 69.4 | 101.3 |
| Laboratory tests | 67.4 | 70.0 |
| NIV costs | 9.87 | 73.2 |

*Table 10.3: Costs associated with the index admission*

| | HAH n=60 | UC n=58 |
|---|---|---|
| Length of hospital stay at 90 days, n (IQR) | 1 (1-7) | 5 (2-12) |
| Length of hospital stay (index admission), n (IQR) | 1 (1-1) | 3 (2- 4.25) |
| Length of stay within HAH, n (IQR) | 4 (IQR 2-5) | N/A |
| Patients with one or more hospital readmission, n | 22 | 23 |
| Patients readmitted requiring ITU, n | 0 | 0 |
| Patients readmitted requiring NIV, n | 2 | 6 |
| Patients with one or more A+E attendances post discharge, n | 29 | 26 |
| Patients with one or more GP attendance post discharge, n | 26 | 30 |
| Patients with one or more secondary care appointment, n | 48 | 41 |
| Patients with a social care package post discharge, n | 7 | 5 |

*Table 10.4: Length of stay, readmission, appointment and social care data.*

## 7.2 Costs used in the study

This section continues from section 7.2 in chapter 7.

### *7.2.1 Medication*

The British National Formulary was the source used to calculate the unit cost for individual medication doses (Table 10.5). This was multiplied by the number of administrations of each medication over the 90 day period. For inpatient care and Hospital at Home care, all individual doses were recorded on a hospital kardex. It was assumed that all patients received 14 days of their usual medication at discharge from UC or HAH. Long-term medication were cross-referenced with the GP. Out-of-hospital medication were costed on the assumption that the patient took their medication without missing doses (if a patient receives a medication but does not take it, the cost remains). There were 358 unique formulations of medication taken by patients in the study.

| Type of medication | Cost (£) | Type of medication | Cost (£) | Type of medication | Cost (£) |
|---|---|---|---|---|---|
| Acamprosate Ca E.C. 333mg | 0.171 | Epilim Chrono MR 500mg | 0.291 | Olanzapine 2.5mg | 0.031 |
| Accrete D3 | 0.049 | Eprosartan 600mg | 0.499 | Omeprazole 10mg | 0.277 |
| Acetylctsteine nebulisers | 2.126 | Ertapenem 1g iv | 31.65 | Omeprazole 20mg | 0.232 |
| Aciclovir 200mg | 0.065 | Erythromycin 250mg | 0.182 | Omeprazole 40mg iv | 1.294 |
| Aciclovir 800mg | 0.108 | Escitalopram 20mg | 0.057 | Oromorph/oral morphine 10mg/5ml | 0.018 |
| Aclidinium bromide | 0.477 | Esomeprazole 20mg | 0.121 | Oxybutynin 5mg | 0.038 |
| Acitretin 10mg | 0.397 | Esomeprazole 40mg | 0.141 | Pantoprazole 40mg | 0.048 |
| Adcal D3 400/1.5g | 0.026 | Etanercept injection 50mg/ml | 89.38 | Paracetamol dispersible 500mg | 0.076 |
| Alendronic acid 70mg | 0.230 | Felodipine MR 10mg | 0.202 | Paracetamol iv 1gm | 1.133 |
| Alfentanil 500mcg/ml | 0.634 | Ferrous fumarate 210mg | 0.033 | Paracetamol oral | 0.026 |
| Allopurinol 100mg | 0.031 | Ferrous sulphate 200mg | 0.063 | Paracetamol suspension 250mg/5ml | 0.010 |
| Amiloride 5mg | 0.240 | Fexofenadine 120mg | 0.105 | Paroxetine 20mg | 0.066 |
| Aminophylline iv 250mg/10ml | 0.650 | Finasteride 5mg | 0.049 | Paroxetine 30mg | 0.060 |
| Aminophylline MR 225mg | 0.043 | Fluconazole 150mg | 0.890 | Peptac | 0.004 |
| Amitriptyline 10mg | 0.030 | Fluconazole 50mg | 0.126 | Perindopril 2 mg | 0.038 |
| Amitriptyline 25mg | 0.031 | Fluoxetine 20mg | 0.033 | Perindopril 4mg | 0.046 |
| Amitriptyline 50mg | 0.037 | Fluoxetine 60mg | 0.479 | Phenoxymethylpenicillin 250mg | 0.039 |
| Amlodipine 10mg | 0.031 | Folic Acid | 0.032 | Phosphate enema(standard) | 0.031 |
| Amlodipine 5mg | 0.029 | Fondaparinux 5mg/ml | 6.279 | Phyllocontin 225mg | 0.043 |

| | | | | | |
|---|---|---|---|---|---|
| Amoxicillin 1g iv | 1.096 | Fortisip | 1.400 | Piroxicam 20mg | 0.129 |
| Amoxicillin 250mg | 0.057 | Fortisip compact drink | 2.020 | Pramipexole 180mcg | 0.041 |
| Amoxicillin 500mg | 0.068 | Furosemide iv 50mg | 0.660 | Pravastatin 40mg | 0.057 |
| Amoxicillin 500mg iv | 0.548 | Furosemide 20mg | 0.029 | Prednisolone 5mg | 0.035 |
| Amoxicillin suspension 250mg/5ml | 0.012 | Furosemide 40mg | 0.028 | Prednisolone 5mg soluble | 1.783 |
| Anusol ointment | 0.083 | Furosemide iv 20mg/2mls | 0.350 | Prednisolone Gastro-res 5mg | 0.051 |
| Aqueous cream | 0.010 | Gabapentin 100mg | 0.025 | Pregabalin 100mg | 1.150 |
| Arachis oil enema | 37.50 | Gabapentin 300mg | 0.034 | Pregabalin 200mg | 1.150 |
| Aspirin 300mg | 0.105 | Gaviscon susp | 0.014 | Pregabalin 300mg | 1.150 |
| Aspirin 75mg | 0.035 | Gentamicin iv 80mg/2ml | 1.000 | Pregabalin 75mg | 1.150 |
| Aspirin dispersible 75mg | 0.027 | Gliclazide 40mg | 0.120 | Pro-cal shots 30ml | 0.024 |
| Aspirin EC 75mg | 0.030 | Gliclazide 80mg | 0.035 | Procyclidine | 0.127 |
| Atenolol 25mg | 0.028 | Glycopyrronium inhaler 44mcg | 0.917 | Prostap 3 DCS | 225.7 |
| Atenolol 50mg | 0.028 | Goserelin implant 10.8mg | 235.0 | Pulmicort turbohaler 400 | 0.277 |
| Atorvastatin 10mg | 0.037 | GTN 5mg iv | 14.76 | Quetiapine 150mg | 0.043 |
| Atorvastatin 20mg | 0.043 | GTN spray 400mcg | 0.017 | Quinine Sulphate 200mg | 0.067 |
| Atorvastatin 40mg | 0.050 | Hydrocortisone 100mg iv | 0.917 | Quinine Sulphate 300mg | 0.075 |
| Atorvastatin 80mg | 0.086 | Hydromol cream | 0.044 | Ramipril 1.25mg | 0.038 |
| Aveeno cream 1% | 0.040 | Hydromol ointment | 0.023 | Ramipril 10mg | 0.043 |
| Azithromycin 250mg | 0.385 | Hydroxocobalamin 1mg/ml | 2.182 | Ramipril 2.5mg | 0.037 |
| Beclometasone nasal spray 50mcg | 0.011 | Hydroxychloroquine 200mg | 0.081 | Ramipril 5mg | 0.036 |
| Bendroflumethiazide 2.5mg | 0.026 | Hyoscine hydrobromide s/c 400mcg | 3.775 | Ranitidine 150mg | 0.022 |
| Betnovate cream 0.1% | 0.132 | Hypotonic saline neb 3 or 6% | 0.649 | Risedronate 35mg | 0.248 |
| Biotene oral gel | 0.089 | Hypromellose eye drops 0.3% | 0.109 | Rivaroxaban 15mg | 1.800 |
| Bisacodyl 5mg | 0.035 | Ibuprofen 400mg | 0.043 | Rivaroxaban 20mg | 1.800 |
| Bisoprolol 1.25mg | 0.037 | Ibuprofen Gel 10% | 0.049 | Ropinirole 500mcg | 0.074 |
| Bisoprolol 10mg | 0.031 | Ibuprofen gel 5% | 0.046 | Salbutamol evohaler 100mcg | 0.008 |
| Bisoprolol 2.5mg | 0.034 | Imipramine 25mg | 0.041 | Salbutamol nebules 2.5mg | 0.096 |
| Bisoprolol 5mg | 0.030 | Indapamide 2.5mg | 0.051 | Salbutamol nebules 5mg | 0.191 |
| Budesonide formoterol inhaler | 0.275 | Instillagel 10ml | 0.234 | Saline nebs 2.5ml | 0.675 |
| Bumetanide 1mg | 0.043 | Ipratropium nebs 500 mcg | 0.144 | Sando K | 0.077 |
| Calcichew D3 | 0.077 | Isosorbide mononitrate 10mg | 0.038 | Sando phosphate | 0.164 |
| Calcichew/calcium carbonate | 0.093 | Isosorbide mononitrate 20mg | 0.032 | Senna 7.5mg | 0.058 |
| CalcichewD3 Forte | 0.071 | Isosorbide mononitrate 40mg | 0.043 | Seretide evohaler 125 | 0.292 |
| Calcipotriol Ointment | 0.193 | Isosorbide mononitrate MR 60mg | 0.375 | Seretide accuhaler 100 | 0.300 |
| Calcium and ergocalciferol | 0.545 | Ivabradine 7.5mg | 0.717 | Seretide accuhaler 250 | 0.583 |

| | | | | | |
|---|---|---|---|---|---|
| Calogen | 0.021 | K CEE L syrup | 0.015 | Seretide accuhaler 500 | 0.682 |
| Candesartan 16mg | 0.051 | Lacri-lube ointment | 0.840 | Seretide evohaler 250 | 0.496 |
| Candesartan 2mg | 0.163 | Lactulose solution | 0.005 | Sertraline 50mg | 0.056 |
| Carbamazepine M.R.200mg | 0.093 | Lansoprazole 15mg | 0.037 | Simple linctus | 0.004 |
| Carbocisteine 375mg | 0.108 | Lansoprazole 30mg | 0.046 | Simvastatin 20mg | 0.030 |
| Carbocisteine liquid 250/5ml | 0.028 | Latanoprost eye drops 50mcg/ml | 0.700 | Simvastatin 40mg | 0.034 |
| Celluvisc 1% eye drops | 0.100 | Laxido | 0.142 | Slow K 600mg | 0.043 |
| Cetirizine 10mg | 0.032 | Lercanidipine 10mg | 0.053 | Sodium chloride flush 5 mls | 0.211 |
| Chlorhexidine Gluconate 0.2% mouthwash | 0.012 | Lercanidipine 20mg | 0.058 | Sodium valproate MR 500mg | 0.202 |
| Chlorpheniramine 4 mg | 0.030 | Levofloxacin 500mg | 1.832 | Solifenacin 5mg | 0.921 |
| Ciprofibrate 100mg | 3.954 | Levothyroxine 100mcg | 0.066 | Spironalactone 100mg | 0.081 |
| Ciprofloxacin 500mg | 0.099 | Levothyroxine 25mcg | 0.096 | Sulphasalazine suspension 250mg/5ml | 0.085 |
| Ciprofloxacin 750mg | 0.800 | Levothyroxine 50mcg | 0.066 | Symbicort 200/6 | 0.317 |
| Citalopram 10mg | 0.030 | Lidocaine 5% patch | 2.413 | Symbicort 400/12 | 0.633 |
| Citalopram 20mg | 0.033 | Lisinopril 2.5mg | 0.029 | Tamiflu 75mg | 1.541 |
| Citalopram 40mg | 0.037 | Lisinopril 20mg | 0.034 | Tamsulosin MR 400mcg | 0.349 |
| Clarithromycin 500mg | 0.194 | Lisinopril 5mg | 0.030 | Tazocin iv 4.5g | 12.90 |
| Clarithromycin 500mg iv | 9.450 | Loperamide oral solution 1mg/5ml | 0.012 | Teicoplanin 200 iv | 0.140 |
| Clarithromycin suspension 250mg/5ml | 0.068 | Loratidine 10mg | 0.032 | Temazepam 10mg | 0.209 |
| Clenil Modulite 100mcg | 0.037 | Lorazepam 1mg | 0.084 | Temazepam Elixir 10mg/5ml | 0.354 |
| Clopidogrel 300mg | 0.233 | Losartan 100mg | 0.042 | Terbinafine 250mg | 0.102 |
| Clopidogrel 75mg | 0.058 | Losartan 25mg | 0.034 | Terbutaline turbohaler | 0.069 |
| Clotrimazole 1% cream | 0.058 | Losartan 50mg | 0.035 | Theophylline M/R 300mg | 0.085 |
| Co-amoxiclav suspen sugar free 250mg/5ml | 0.750 | Magnesium Aspartate sachets 243mg | 0.895 | Theophylline M/R 400mg | 0.101 |
| Co-amoxiclav 625mg | 0.136 | Magnesium Sulphate 2 mmol/ml | 5.834 | Theophylline M/R 200mg | 0.053 |
| Co-amoxiclav iv 1.2g | 1.060 | Meropenem 1g iv | 15.35 | Thiamine 100mg | 0.116 |
| Co-amilofruse 2.5/20mg | 0.107 | Mesalazine SR 1g | 0.615 | Ticagrelor 90mg | 0.975 |
| Co-amilofruse 5/40mg | 0.105 | Metformin 1g MR | 0.152 | Tigecycline iv 50mg | 32.31 |
| Co-careldopa 25mg/100mg | 0.157 | Metformin 500mg | 0.045 | Tinzaparin 23,000u (40,000u vial) | 34.20 |
| Co-codamol 8mg/500mg | 0.034 | Metoclopromide 10mg | 0.030 | Tinzaparin 10,000u | 5.950 |
| Codeine 15mg | 0.037 | Metoclopromide iv 10mg | 0.323 | Tinzaparin 11,000u (12000u syringe) | 7.140 |
| Codeine 30 | 0.043 | Metoprolol 50mg | 0.063 | Tinzaparin 12,000u | 7.140 |
| Codeine linctus 15mg/5ml | 0.009 | Metronidazole 400mg | 0.065 | Tinzaparin 18,000u | 10.71 |
| Co-dydramol 30mg/500mg | 0.122 | Metronidazole 500mg iv | 3.100 | Tinzaparin 2,500u | 1.980 |
| Colecalciferol 20,000u | 0.967 | Miconazole oral gel | 0.055 | Tinzaparin 3,500u | 2.771 |
| Colecalciferol 800 u (Fultium) | 0.120 | Micralax enema | 0.406 | Tinzaparin 4,500u | 3.563 |
| Colomycin neb | 5.600 | Midazolam s/c 5mg/5mls | 0.600 | Tinzaparin 8,000u | 4.760 |

| | | | | | |
|---|---|---|---|---|---|
| Colpermin capsules | 0.122 | Mirtazapine 15mg | 0.050 | Tiotropium (respimat) 2.5mcg | 0.542 |
| Combivent nebs | 0.397 | Mirtazapine 30mg | 0.049 | Tiotropium 18mcg | 1.117 |
| Co-trimoxazole 960mg | 0.235 | Mirtazapine 45mg | 0.062 | Tirofiban 250 mcg/ml iv | 146.1 |
| Creon 10,000 | 0.129 | Mometasone nasal spray | 0.017 | Tizanidine 4mg | 0.233 |
| Creon 40,000 | 0.418 | Monomil XL 60mg | 0.375 | Tolterodine 2mg | 0.045 |
| Cyclizine iv | 1.730 | Montelukast 10mg | 0.063 | Tramadol 50mg | 0.033 |
| Cyclizine oral | 0.093 | Morphine iv 10mg | 0.936 | Trimethoprim 100mg | 0.033 |
| Dexamethasone 2mg | 0.982 | Morphine Sulphate 30mg | 0.208 | Trimethoprim 200mg | 0.215 |
| Diazepam 2mg | 0.031 | Morphine sulphate M.R. 10mg | 0.087 | Trospium 20mg | 0.317 |
| Diclofenac Gel 1.16% | 0.056 | Morphine sulphate M.R. 60mg | 0.405 | Ultibro Breezhaler | 1.083 |
| Difflam mouthwash | 0.022 | Moxonidine 200mcg | 0.061 | Uniphyllin MR 200mg | 0.053 |
| Dihydrocodeine 30mg | 0.048 | Mupirocin ointment | 1.297 | Uniphyllin MR 400mg | 0.101 |
| Diltiazem M/R 180mg | 0.237 | Naseptin nasal cream | 0.149 | Varenciline 1mg | 0.975 |
| Diltiazem M/R 240mg | 0.411 | Nefopam | 0.406 | Venlafaxin 75mg | 0.047 |
| Diltiazem MR 120mg | 0.185 | Nicorandil 10mg | 0.048 | Verapamil 40mg | 0.024 |
| Diltiazem MR 90mg | 0.130 | Nicorandil 20mg | 0.097 | Viscotears | 0.260 |
| Docusate sodium 100 mg | 0.070 | Nicotine inhalater 15mg | 0.756 | Vitamin B Co | 0.062 |
| Dosulepin 75mg | 0.056 | Nicotine Gum 4mg | 0.107 | Warfarin 1mg | 0.030 |
| Doxycycline 100mg | 0.121 | Nicotine patch 14mg | 1.343 | Warfarin 3mg | 0.032 |
| Duoresp 160/4.5 | 0.250 | Nicotine patch 21mg | 1.424 | Warfarin 5mg | 0.033 |
| Duoresp 320/9 | 0.500 | Nicotine patch 7mg | 1.303 | Water for injections 2ml | 0.275 |
| Enalapril 20mg | 0.056 | Nicotine patch 25mg | 1.481 | Zomorph 10mg | 0.058 |
| Enalapril 10mg | 0.039 | Nifedipine MR 40mg | 0.480 | Zomorph 30mg | 0.138 |
| Ensure | 0.009 | Nifedipine SR 30mg | 0.245 | Zomorph 60 mg | 0.270 |
| Ensure compact | 2.988 | Nitrofurantoin 50mg | 0.334 | Zopiclone 3.75mg | 0.050 |
| Ensure plus juice | 0.009 | Nystatin suspension 100,000 units/ml | 0.079 | Zopiclone 7.5mg | 0.048 |
| Ensure plus milk | 0.006 | Octenison wash | 0.005 | | |
| Epilim Chrono MR 300mg | 0.175 | Olanzapine 10mg | 0.094 | | |

*Table 10.5: Unit costs of medication per dose*

### *7.2.2 Accident and Emergency attendances*

These were costed from the NHS Reference Costs (2015) (Department of Health 2015), as shown in Table 10.6.[1] An alert was sent to the research team when a patient attended accident and emergency. To ensure no episodes were missed, patients were asked to keep a record of their attendances (in case they attended accident and emergency in a different healthcare trust) and all electronic records were reviewed after the follow up period.

| Type of attendance | Cost (£)* | Source |
|---|---|---|
| A+E attendance VB01Z | 377.9 | NHS reference cost 2015. EM type 1. Service code VB01Z. |
| A+E attendance VB02Z | 347.5 | NHS reference cost 2015. EM type 1. Service code VB02Z. |
| A+E attendance VB03Z | 252.3 | NHS reference cost 2015. EM type 1. Service code VB03Z. |
| A+E attendance VB04Z | 227.0 | NHS reference cost 2015. EM type 1. Service code VB04Z. |
| A+E attendance VB05Z | 189.5 | NHS reference cost 2015. EM type 1. Service code VB05Z. |
| A+E attendance VB06Z | 133.7 | NHS reference cost 2015. EM type 1. Service code VB06Z. |
| A+E attendance VB07Z | 164.1 | NHS reference cost 2015. EM type 1. Service code VB07Z. |
| A+E attendance VB08Z | 153.0 | NHS reference cost 2015. EM type 1. Service code VB08Z. |
| A+E attendance VB09Z | 108.4 | NHS reference cost 2015. EM type 1. Service code VB09Z. |
| A+E attendance VB10Z | 112.5 | NHS reference cost 2015. EM type 1. Service code VB10Z. |
| A+E attendance VB11Z | 90.2 | NHS reference cost 2015. EM type 1. Service code VB11Z. |

*Costs inflated for 2015-16 prices

*Table 10.6: Accident and emergency attendances*

### *7.2.3 Primary and secondary care outpatient attendances*

| Type of attendance | Cost (£)* | Source |
|---|---|---|
| Anaesthetic clinic, consultant | 109.4 | NHS reference cost 2015. Service code 190 consultant. |
| Anaesthetic clinic, nurse | 87.9 | NHS reference cost 2015. Service code 190 non consultant. |
| Cardiology clinic, consultant | 142.4 | NHS reference cost 2015. Service code 320 consultant. |
| Clinical psychology | 195.4 | NHS reference cost 2015. Service code 656 non consultant. |
| Dietetics clinic | 71.2 | NHS reference cost 2015. Service code 654 non consultant. |
| Endocrine clinic, consultant | 158.2 | NHS reference cost 2015. Service code 302 consultant. |
| ENT clinic, nurse | 72.7 | NHS reference cost 2015. Service code 120 non consultant. |
| Gastroenterology clinic, consultant | 141.7 | NHS reference cost 2015. Service code 301 consultant. |
| General surgery clinic, consultant | 140.5 | NHS reference cost 2015. Service code 100 consultant. |
| GP attendance | 44.6 | Curtis 2015, 11.7m patient contact. |
| GP attendance, bloods by nurse | 11.2 | Curtis 2015, 15.5m patient contact. |
| GP attendance, practice nurse review | 11.2 | Curtis 2015, 15.5m patient contact. |
| Haematology clinic, consultant | 164.2 | NHS reference cost 2015. Service code 303 consultant. |
| Haematology ward attendance | 347.5 | NHS reference cost 2015. Service code DCRDN, band 2. |
| Maxillo-Facial surgery clinic, consultant | 115.4 | NHS reference cost 2015. Service code 144 consultant. |
| Neurosurgery clinic, consultant | 215.4 | NHS reference cost 2015. Service code 150 consultant. |
| Oncology clinic, consultant | 173.1 | NHS reference cost 2015. Service code 370 consultant. |
| Ophthalmology clinic, technician | 64.8 | NHS reference cost 2015. Service code 130 non consultant. |
| Ophthalmology clinic, consultant | 97.4 | NHS reference cost 2015. Service code 130 consultant. |
| Orthopaedic clinic, consultant | 116.3 | NHS reference cost 2015. Service code 110 consultant. |
| Orthopaedic clinic, nurse | 93.7 | NHS reference cost 2015. Service code 110 non consultant. |
| Physiotherapy rehabilitation session | 39.2 | NHS reference cost 2015. Service code 342 non consultant. |
| Plastic surgery clinic, consultant | 95.6 | NHS reference cost 2015. Service code 160 consultant. |
| Podiatry clinic, podiatrist | 39.7 | NHS reference cost 2015. Service code 653 non consultant. |
| Respiratory clinic, consultant | 165.9 | NHS reference cost 2015. Service code 340 consultant. |
| Respiratory clinic, nurse | 120.4 | NHS reference cost 2015. Service code 340 non consultant. |
| Respiratory clinic, nurse | 120.4 | NHS reference cost 2015. Service code 340 non consultant. |
| Respiratory clinic, oxygen nurse | 120.4 | NHS reference cost 2015. Service code 340 non consultant. |
| Urology clinic, consultant | 103.5 | NHS reference cost 2015. Service code 101 consultant. |
| Urology clinic, nurse | 78.0 | NHS reference cost 2015. Service code 101 non consultant. |

*Costs inflated for 2015-16 prices

*Table 10.7: Cost of attendances*

These were mostly costed from the NHS Reference Costs (2015) (Department of Health 2015) and are shown in Table 10.7.

Patients kept a record of outpatient attendances (including attendances at external healthcare trusts), and this was cross-referenced with electronic medical records. If a patient cancelled a clinic attendance, no cost was allocated. If a patient did not attend their appointment without informing clinic, the cost was allocated.

### *7.2.4 Diagnostic tests*

These were mostly costed from the NHS Reference Costs (2015) (Department of Health 2015) and are shown in Table 10.8. Tests were recorded from medical electronic records (covering primary and secondary care), and cross referenced with records maintained by patients.

| Type of test | Cost (£)* | Source |
|---|---|---|
| 24 hour tape | 155.0 | NHS reference cost 2015. Currency code EY51Z |
| CT one area, post contrast | 173.3 | NHS reference cost 2015. Currency code RD21A |
| CT scan pelvis | 114.5 | NHS reference cost 2015. Currency code RD23Z 2 areas without contrast |
| CT two areas, with contrast | 156.0 | NHS reference cost 2015. Currency code RD24Z 2 areas with contrast |
| DEXA bone scan | 59.8 | NHS reference cost 2015. Currency code RD50Z |
| Diagnostic endoscopic upper GI tract | 510.7 | NHS reference cost 2015. Currency code FZ60Z |
| ECG | 18.4 | Galasko GI, Barnes SC, Collinson P, et al. What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination? European heart journal. 2006 Jan;27(2):193-200. |
| Echocardiogram | 65.9 | NHS reference cost 2015. Currency code RD51A |
| Lower endoscopy | 373.9 | NHS reference cost 2015. Currency code FZ51Z |
| MRCP liver | 138.8 | NHS reference cost 2015. Currency code RD01A outpatient |
| MRI one area, no contrast | 127.7 | NHS reference cost 2015. Currency code RD01A MRI one area no contrast |
| MRI one area, post contrast only | 431.6 | NHS reference cost 2015. Currency code RD02A MRI one area post contrast |
| Plain film x-ray | 30.4 | NHS reference cost 2015. Currency code DAPF. |
| Sleep study | 212.8 | NHS reference cost 2015. Currency code DZ50Z |
| Spirometry | 54.7 | 52 for 2012 secondary care from "HTA report 2015" (for multiplier look in PRSSU). Adjusted 2014/15 |
| Tilt room test | 142.9 | Krahn AD, Klein GJ, Yee R, et al. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. J Am Coll Cardiol. 2003 Aug 6;42(3):495-501. PubMed PMID: 12906979. |
| Ultrasound | 64.8 | NHS reference cost 2015. Currency code RD40Z less than 20 minutes |

*Costs inflated for 2015-16 prices

*Table 10.8: Cost of diagnostic tests*

### *7.2.5 Laboratory tests*

Individual laboratory tests, including add-on costs, were provided by Northumbria Healthcare NHS trust and are shown in Table 10.9.

| Laboratory test name | Cost | Laboratory test name | Cost | Laboratory test name | Cost |
|---|---|---|---|---|---|
| ABG (arterial blood gas) | 6.56 | GGT | 0.53 | PTH | 7.86 |
| Albumin | 0.47 | HbA1c | 1.49 | Random urine protein | 1.33 |
| Alpha-1-Antitrysin | 8.79 | HEP B surface | 9.12 | Retics | 3.9 |
| Amylase | 0.85 | HIB Antibody | 16.39 | Rheumatoid factor | 1.86 |
| Antigens (urine) | 42.7 | Immunoglobulins | 4.65 | Routine faeces | 19.99 |
| Blood bank | 7.23 | INR | 4.53 | Serum immunofixation | 31.12 |
| Blood cultures | 14.7 | Intrinsic factor | 10.41 | Sputum culture | 7.59 |
| Blood film | 3.39 | Lactate | 1.13 | T3 | 2.44 |
| Blood glucose | 0.51 | LFTs | 2.44 | T4 | 2.11 |
| blood ketones | 6.31 | Lipids | 0.41 | TB culture | 27.74 |
| Bone profile | 1.48 | Magnesium | 0.54 | Theophylline | 23.28 |
| Calcium | 0.52 | Mixing studies APTT | 4.59 | Total CK | 1.01 |
| Cholesterol | 0.51 | MRSA rejected sample | 5.93 | TRF saturation | 1.23 |
| Coagulation screening | 7.46 | MRSA screen | 7.66 | Troponin T (HS) | 4.73 |
| CRP | 0.73 | Mycoplasma | 10.62 | TSH | 1.95 |
| D-Dimer | 19.06 | NT pro BNP | 19.33 | Unsuitable sample | 6 |
| EGFR | 0.47 | Osmolality | 3.84 | Urate | 0.8 |
| ESR | 3.86 | Paraprotein screen | 3.44 | Urea and electrolytes | 2.58 |
| FBC | 3.9 | Phosphate | 0.51 | Urine immunofixation | 31.12 |
| Ferritin | 4.51 | Point of care FBC | 21.46 | Urine Microscopy and culture | 6.58 |
| Flu assay (PCR) | 57.92 | Procalcitonin | 17.62 | Vitamin B12 | 4.82 |
| Folate | 4.55 | Prolactin | 3.49 | Vitamin D | 9.86 |
| Gastric parietal cell antibody | 9.75 | Prostate specific antigen | 2.82 | | |

*Table 10.9: Cost of laboratory tests*

### *7.2.6 Health care staff*

The Personal Social Services Research Unit's *Unit Costs of Health and Social Care 2015* cost compendium was used to allocated most costs, and are shown in Table 10.10. All contacts included add on costs and qualifications.

We had recorded start and end times for 105 medical clerkings, which averaged 0.75 hours for a non-consultant and 0.33 for a consultant. These averages were used in instances in which no end time was stated. Inpatient reviews were assumed to be 15

minutes in duration, unless otherwise documented, again based on average review times. The duration of reviews during the Hospital at Home period was recorded for all visits, which included travel time and time spent with the patient.

| Type of healthcare worker | Cost (£)* | Source |
|---|---|---|
| Community psychiatric nurse | 20.1 | PSSRU Unit costs of health and social care 2015 |
| Dietician band 5 | 39.2 | PSSRU Unit costs of health and social care 2015 |
| Dietician band 6 | 44.5 | PSSRU Unit costs of health and social care 2015 |
| Dietician home visit | 11.0 | PSSRU Unit costs of health and social care 2015, 15m |
| District nurse home visit | 12.5 | PSSRU Unit costs of health and social care 2015, 15m |
| Doctor consultant | 153.0 | PSSRU Unit costs of health and social care 2015 |
| Doctor F1 | 42.5 | PSSRU Unit costs of health and social care 2015 |
| Doctor F2 | 50.1 | PSSRU Unit costs of health and social care 2015 |
| Doctor ST1 | 64.7 | PSSRU Unit costs of health and social care 2015 |
| Doctor ST2 | 67.0 | PSSRU Unit costs of health and social care 2015 |
| Doctor registrar ST3 | 68.4 | PSSRU Unit costs of health and social care 2015 |
| Doctor registrar ST4 | 70.0 | PSSRU Unit costs of health and social care 2015 |
| Doctor registrar ST5 | 71.7 | PSSRU Unit costs of health and social care 2015 |
| Doctor registrar ST6 | 73.3 | PSSRU Unit costs of health and social care 2015 |
| Doctor registrar ST7 | 75.0 | PSSRU Unit costs of health and social care 2015 |
| GP doctor home visit | 43.4 | PSSRU Unit costs of health and social care 2015 |
| GP doctor phone call | 27.1 | PSSRU Unit costs of health and social care 2015 |
| GP nurse home visit | 11.1 | PSSRU Unit costs of health and social care 2015 |
| NHS 111 | 8.0 | Department of health, NHS 111 |
| Occupational therapist | 39.2 | PSSRU Unit costs of health and social care 2015 |
| Occupational therapist home visit | 22.1 | PSSRU Unit costs of health and social care 2015, 30m |
| Pharmacist, band 6 | 50.2 | PSSRU Unit costs of health and social care 2015 |
| Physio home visit, band 6 | 11.1 | PSSRU Unit costs of health and social care 2015 |
| Physiotherapist band 5 | 39.2 | PSSRU Unit costs of health and social care 2015 |
| Physiotherapist band 6 | 44.5 | PSSRU Unit costs of health and social care 2015 |
| Physiotherapist band 7 | 49.5 | PSSRU Unit costs of health and social care 2015 |
| Psychology | 52.2 | PSSRU Unit costs of health and social care 2015 |
| Rapid response team | 51.2 | PSSRU Unit costs of health and social care 2015 |
| Respiratory Specialist Nurse Band 6 | 46.2 | PSSRU Unit costs of health and social care 2015 |
| Respiratory Specialist Nurse Band 7 | 60.2 | PSSRU Unit costs of health and social care 2015 |
| Respiratory Specialist Nurse Band 8a | 68.6 | PSSRU Unit costs of health and social care 2015 |
| Respiratory Specialist Nurse home visit | 46.2 | PSSRU Unit costs of health and social care 2015 |
| Social worker | 57.2 | PSSRU Unit costs of health and social care 2015 |
| Speech and language therapist, band 5 | 38.1 | PSSRU Unit costs of health and social care 2015 |
| Support worker, band 2 | 24.1 | PSSRU Unit costs of health and social care 2015 |

*Table 10.10: Cost of contact with healthcare staff*

The PSSRU unit of costs does not provide the hourly rate for registrars of different grade, but provides information on calculating costs. The actual salaries for doctors of all grades was calculated by obtaining basic salaries, adding a 50% banding supplement and adjusting for a 48 hour week. The salary on-costs were changed accordingly based on the actual salary.

For the Respiratory Specialist Nurses the average cost of the band 6, 7 and 8a nurses was calculated (several new appointments were made over the time course of the study, so most band 6 nurses were at the low end of the band 6 pay scale, whilst band 7 and 8a nurses were at the top end). The salary on-costs were changed accordingly based on the actual salary.

### *7.2.7 Inpatient ward stay costs*

The cost of a day in hospital was micro-costed by the trust, and are shown in Table 10.11. This included direct, indirect and overhead costs. Certain costs were removed to ensure they were not double counted, such as drug costs and pharmacy input. For the cost of a day on the medical admissions unit, an average day was obtained from costs over a two year period (2013-2015) and adjusted for current prices. In the instance that a patient spent less than a day on the unit, an hourly rate was applied. The cost of a rehab bed day was calculated in the same way. The cost of a day on a respiratory ward was calculated from two difference respiratory wards over a two year period (2013-2015) to give an average bed day cost.

| Ward stay type of cost per bed day | Cost (£) | Source |
|---|---|---|
| Medical admissions unit | 294.9 | Micro-costed by healthcare trust |
| Medical ward | 246.2 | Micro-costed by healthcare trust |
| Rehabilitation ward | 168.8 | Micro-costed by healthcare trust |

*Table 10.11: Ward costs*

### *7.2.8 Other inpatient stays/ procedures*

Some patients had inhospital stays at other healthcare trusts. The cost of the episode was obtained from the provider and/ or a tariff cost was used, as shown in Table 10.12.

| Reason for admission | Cost (£) | Source |
|---|---|---|
| Intermediate hip procedure for trauma | 7452.3 | NHS reference cost 2015. Currency code HT14A. |
| Osteonecrosis | 2383.0 | Cost of admission provided by external healthcare trust |
| Myocardial infarction with percutaneous intervention | 4613.0 | Cost of admission provided by external healthcare trust |
| Myocardial infarction with percutaneous intervention, short stay | 2554.0 | Cost of admission provided by external healthcare trust |
| Urinary retention | 1881.0 | Cost of admission provided by external healthcare trust |
| Crohn's disease | 2763.5 | NHS reference cost 2015. Currency code FZ37K X1.0132 |
| Minor hip procedure for trauma | 2517.5 | NHS reference cost 2015. HT15Z. X1.0132 |
| Surgical tooth removal | 462.0 | Cost of admission provided by external healthcare trust |

*Table 10.12: Cost of other inpatient stays/ procedures*

### *7.2.9 Oxygen therapy*

Patients who received oxygen therapy either already had long term oxygen therapy in place or were given a hospital oxygen concentrator to avoid delays in returning home. The cost of LTOT therapy is £2.29 per day, adjusted to current prices.[273] The cost of the hospital oxygen concentrator is £0.57 per day (Airsep Visionaire = £900, plus five-year warranty and maintenance = £140). The Respiratory Specialist Nurse delivered and set up the oxygen and provided education, which was captured separately within the patient visit time. We had concerns that using the cost £0.57 was too conservative, therefore we used a daily cost of oxygen at £2.29 per day for everyone. The additional cost of running a home oxygen assessment and review services were captured elsewhere.

### *7.2.10 Non-invasive ventilation*

The cost of non-invasive ventilation was calculated based on the cost of a machine over a five year period, and the costs of other equipment. NIV is provided on a respiratory support unit with higher staffing costs, and 1.5 hours of nursing time was included. Other care/ treatment over and above the average patient with AECOPD in terms of physiotherapy, doctors, diagnostic tests, laboratory tests (including arterial blood gas analysis) and medication was captured separately.

| Type of cost | Unit cost (£) | Cost per day (£) |
|---|---|---|
| V60 Ventilator (machine, servicing, etc.) | 12000 | 6.6 |
| Circuit (tubing and mask changed weekly) | 50.8 | 7.3 |
| Filter (changed x2 per week) | 2.7 | 0.8 |
| Nebuliser T piece | 1.3 | 0.2 |
| Face shield (used one in three episodes) | 77.7 | 3.7 |
| cleaning of machine- band 6, 10 mins, once per episode | 8.5 | 2.4 |
| Nurse time (1.5 hours extra per patient per day) band 6 | 51 | 76.5 |
| Overall (includes adjustment to 2015/16) | | 98.7 |

*Table 10.13: Cost of non-invasive ventilation*

## Appendix D: Hospital at Home manual

## Hospital at Home selected by low risk DECAF score

Chronic Obstructive Pulmonary Disease (COPD) is a common lung disease characterised by progressive breathlessness, cough and phlegm. Acute exacerbations (AECOPD) are episodes, often triggered by infection, during which symptoms deteriorate and are the second commonest reason for hospital admission.

Hospital at home (HAH) manages patients in their own home for a condition that otherwise would require inpatient care. The National Institute for Health and Care Excellence endorse HAH for AECOPD and highlight that selection should be based on prognosis, but acknowledge the (previous) lack of a suitable tool. To address this shortfall, we developed the DECAF score (*Steer, Thorax 2012* and *Echevarria, Thorax 2016*), which accurately predicts survival in patients hospitalised with AECOPD. Of importance, approximately 50% of patients currently admitted to hospital have a low risk of death (1 - 1.4%), thus are potentially suitable for HAH. This is more than twice the proportion of patients included in earlier trials. Our model of HAH includes 24/7 clinical and social support, tailored to the individual patient's needs. The range of healthcare disciplines and level of support available are greater than typically seen in previous trials of HAH or Early Supported Discharge, reflecting the broad selection criteria.

We conducted a Randomised Controlled Trial (RCT) at Northumbria Hospitals to compare HAH to usual inpatient care in patients with AECOPD and low risk DECAF score (supported by a Research for Patient Benefit grant). This model of HAH proved to be safe (no acute deaths), clinically effective (no increase in readmissions), cost-effective and was preferred by 90% of patients. To explore factors influencing wider implementation of this model of care, patients, carers, clinicians and hospital managers were interviewed. Patients valued the availability of home comforts, greater independence and continuity of care provided by the HAH specialist team. Positive influences on perceived rate of recovery, sleep quality, mood, convenience for friends and family (particularly grandchildren visiting) and carer burden were also reported. A few patients were concerned about being alone, particularly at night (a 9pm phone call was valued), or professionals visiting their home. In the early phase of the trial, clinician concerns occasionally delayed return home. Nurses cited greater workload and responsibility, but providing HAH was viewed positively. Operational

concerns included keeping medical records in a patient's home and inability to capture activity within current payment systems.

**Useful numbers:**

- Respiratory Specialist Nurse for Hospital at Home: XXXX
- Respiratory Consultant (NSECH): XXXX
- HOOF: XXXX
- Adult Social Care, Northumbria patients (Wansbeck General Hospital): XXXX
- Adult Social Care, North Tyneside General Hospital: XXXX
- Escalation plan number NE Ambulance Service: XXXX
- Consultant clinical psychologist: XXXX

## What support is offered within Hospital at Home?

Prior to return home under HAH, patients will be reviewed by a respiratory consultant and respiratory specialist nurse (RSN) to confirm the diagnosis, eligibility and both acute and chronic disease management. The HAH package of care is tailored to the individual patient's needs. The patient will be reviewed by a physiotherapist regarding breathing control, sputum clearance, home exercise programme and subsequent early pulmonary rehabilitation. Access to a pharmacist, occupational therapist and same day short term social support is available. Both a nebuliser and temporary controlled oxygen therapy will be supplied, with instruction on use at home, if required. The specialist nurse will accompany the patient during return home and oversee clinical management at home.

Patients receiving HAH are seen at least once daily by a RSN and undergo monitoring of their respiratory rate, oxygen saturation, heart rate, blood pressure, temperature and, if they have significant dependent oedema, daily weight. They have access to most of the medical treatments available in hospital, including intravenous therapy, but excluding acute non-invasive ventilation. The RSNs provide 24-hour telephone support throughout the duration of HAH, with consultant support.

During HAH, the specialist respiratory team retain clinical responsibility for the patient. At the end of Hospital at Home the patient will be "discharged" as if they had been in hospital.

## Return to Hospital

“Return to Hospital” is the term used to describe a patient returning to hospital during a period of HAH and is regarded as an increase in the level of care, not a readmission. The patient remains under the care of the specialist team throughout the HAH period, and will contact the RSN directly if they are concerned. The RSN may provide reassurance or arrange a home visit and/or return to hospital, in liaison with the on-call respiratory consultant. “Readmission” describes the patient returning to hospital after they have been discharged from HAH.

## Identifying eligible patients

Patients with an exacerbation of COPD triaged for hospital admission who are low risk (DECAF 0 or 1) should be considered for Hospital at Home treatment. Patients will be primarily identified by the RSNs screening and assessing new respiratory admissions.

### Selection criteria

- Primary diagnosis of AECOPD
- DECAF score 0 or 1
- No other acute condition which necessitates hospital admission
- Absence of acute confusion precluding discharge

### DECAF score

Dyspnoea: please remember to ask the patient about breathlessness on a good day within the last three months, not on admission.

Acidaemia: if an arterial blood gas has not been performed, provided the patient’s $SpO_2$ is 92% or greater breathing room air, it is highly unlikely that the patient’s pH < 7.30 (threshold required to score). If a venous blood gas pH is not acidaema, the arterial pH cannot be acidaemia (arterial pH = venous pH + 0.03).

### Management pathway

Patients with a low risk DECAF score managed in hospital are unlikely to require an escalation in care. When this does occur, the patient is usually hypercapnic on admission and their condition typically deteriorates within the first 24 hours. Patients

who are acidaemic on admission but otherwise low risk by DECAF remain at low risk (Echevarria Thorax 2016).

The timing of return home under hospital at home is determined by the admission arterial blood gas.

- Normal $PaCO_2$ or $SpO_2$ >92% breathing room air & ABG considered clinically unnecessary = return home as soon as possible (most patients).
- Hypercapnia, normal pH = return home if not deteriorating at 24hrs.
- Hypercapnia and pH < 7.35 = return home within 24 hrs of resolution of acidaemia, and discontinuation of acute NIV if provided.

## In hospital planning for Hospital at Home

### RSN review

The RSNs screen and assess new admissions to the acute respiratory admissions unit. Some eligible patients may have already been identified by medical staff, and will be highlighted to the RSN.

When a suitable patient is identified for HAH, the RSN will ensure all required clinical assessments have been performed and that adequate support is in place. This may involve delegating tasks to ward staff. The RSN will facilitate return home. For HAH to work effectively, flexibility and clear communication is required.

#### *AECOPD proforma*

The AECOPD proforma includes an initial assessment sheet, which should be completed by the RSN on the day the patient returns home, and daily review sheets to be completed on subsequent days during HAH.

#### *Assessment of needs*

Following review by the RSN and respiratory consultant, a management plan will be put in place including: 1) acute management of this exacerbation; 2) review and optimisation of long-term COPD management; and 3) assessment of home circumstances. This may involve reviewing patients on a non-respiratory ward. On occasion, if the consultant is not available, the medical review may be performed by a specialist respiratory registrar. The RSN and ward staff will identify the patient's

social support needs. Adult social support should be contacted immediately if same day support is required.

### *Hospital at Home COPD return home checklist*

This will be completed prior to the patient returning home, and is a simple checklist to ensure all the practical aspects of discharge have been met.

### *Patients' medical notes and admission file*

The AECOPD proforma should be filed in red admission file with the admission clerking, nursing notes, drug kardex and observation chart. The red admission file will follow the patient home and remain with them throughout the HAH period of care. Prior to return home, a photocopy of the current admission documentation in the red file should be made and filed in volume 1 of the medical notes (retained on the respiratory ward for the duration of HAH to ensure ease of access if required). There is a consent form related to retention of the red file in the patient's home during HAH. The RSN will ensure this is signed by the patient.

If the patient returns to hospital during HAH the red file **must** accompany the patient. Whilst such patients require a thorough review, they will not need a new clerking or new drug Kardex. On discharge from HAH, the red file should be returned to the respiratory ward and the original complete admission documents filed in volume 1 of the patients notes, replacing the earlier photocopy.

### *Medication prior to return home*

Not all RSNs have completed the prescribing course. All medication, including anticipated medication, should be prescribed before the patient leaves hospital. See below "Procedure for Completion of Drug Chart for Patients receiving HAH" below for further information.

### *Antibiotic protocol for Hospital at Home*

*No allergies / History of intolerance*

1. Not previously treated, or treated with Amoxicillin: First line- Doxycycline; Second line- Co-amoxiclav.
2. Previously treated with Doxycycline: First line- Co-amoxiclav; second line- Levofloxacin 500mg bd.

*Intolerant of Doxycycline*

First line- Co-amoxiclav; second line- Levofloxacin 500 mg bd.

*Intolerant of Penicillin*

First line- Doxycycline; second line- Levofloxacin 500 mg bd.

If a patient is colonised with Haemophilus Influenza (recurrent positive cultures), an extended course of co-amoxiclav of 10-14 days is appropriate.

If pseudomonas is cultured, consider oral ciprofloxacin or intravenous antibiotics depending on sensitivities. Discuss dose and duration with a consultant.

*Proton Pump Inhibitors*

Proton pump inhibitors are (PPI) commonly stopped in patients when starting antibiotics due to the risk of Clostridia Difficile (C diff). It is important to balance the risks.

GI bleed within 12 months score 2; GI bleed > 12 months score 1; Female score 1; Co-prescription antiplatelet therapy, NSAIDS or SSRIs score 1; Co-prescription oral anticoagulant score 1; Chronic renal disease GFR < 60 score 1; BMI < 19 score 1.

Total risk score:

- 2+ continue PPI
- 1 switch to H2 antagonist for the duration of antibiotic therapy plus 7 days
- 0 withhold PPI for the duration of antibiotic therapy plus 7 days
- No existing indication for PPI on review – discontinue.

***Procedure for Completion of Drug Chart for Patients receiving HAH***

Patients suitable for HAH treatment will already have had their inpatient drug chart completed with the necessary medicines to treat the acute exacerbation. Prior to the patient being sent home the RSN should ensure that the following medication is prescribed:

***Regular medication:***

1. Tinzaparin prophylaxis if deemed necessary on VTE assessment – discontinue once the patient achieves their normal level of mobility.

2. Salbutamol 2.5mg nebules four times a day – with a note to be reviewed 48 hours post admission.
3. Ipratropium Bromide 500 microgram nebules four times a day – with a note to be reviewed 48 hours post admission.
4. Prednisolone 30mg once daily for 5 days
5. First line antibiotic including stop/ review date – according to antibiotic protocol.
6. Patient's regular inhalers – if patient on a LAMA place a cross in the administration box for the first 48 hours and a note to withhold whilst on regular ipratropium nebules.
7. Patient's regular medication – this should be reconciled by the pharmacy team prior to return home. If the patient hasn't been seen by a member of the pharmacy team (due to time of admission etc.), please ensure this is reviewed by a doctor. All appropriate medication must be prescribed.
8. Oxygen – if the patient needs oxygen, this must be prescribed on the drug chart.
9. Nicotine patches and short acting nicotine replacement (inhalator, gum or lozenge) if patient a current smoker and willing to have NRT – if patient smokes >20/day start 21mg patch.

***As required medication:***

1. Salbutamol 2.5mg Nebules for shortness of breath.
2. Ipratropium bromide 500 microgram nebules for shortness of breath.
3. Salbutamol Inhaler (or Terbutaline) – whichever short acting beta2 agonist the patient was using prior to admission.
4. Paracetamol as required.
5. Carbocisteine – 375-750mg up to three times a day if problems clearing sputum (if not already on regular carbocisteine).
6. Sando K tablets – 2 tablets up to three times a day for hypokalaemia. To be commenced only if blood results indicate hypokalaemia.
7. Furosemide – 40-80mg once daily prn if the patient develops worsening dependent oedema. Only to be commenced on discussion with consultant. Occasionally higher dose or intravenous diuretic may be required.
8. OR if not on an ACE-inhibitor, angiotensin receptor blocker or potassium sparing diuretic: Co-amilofruse 5/40 1-2 tablets once daily prn if patient develops worsening dependent oedema. Only to be commenced on discussion with consultant.

***Supply of medication:***

The RSN should obtain all medication the patient will require during HAH prior to return home. Any medication that the patient takes home with them must either be over-labelled or dispensed from pharmacy: i.e. patients must not go home with unlabelled medication. This includes the patients' regular medication as patients should not have to contact their GP for a prescription during HAH. If required, the

RSN will also supply a nebuliser, temporary oxygen concentrator and venturi mask (to achieve target $SpO_2$ = 88-92%).

Restricted antibiotics (ciprofloxacin and levofloxacin) will be available via the Omnicell cabinets to ensure strict controls are in place.

***Discharge from Hospital at Home:***

When the patient is discharged from HAH the patient should receive a copy of their discharge letter and the nursing staff must ensure that the patient has sufficient supplies of medication. If a rescue pack is considered appropriate, this must also be included in the discharge letter and supplied to the patient with written and verbal information.

*Overlabelled Medication Available Hospital at Home:*

1. Anoro (1 inhaler)
2. Amoxicillin 500mg capsules (box of 21)
3. Carbocisteine 375 mg capsules (box of 120)
4. Co-amilofruse 5/40 tablets (box of 28)
5. Co-amoxiclav 625mg tablets (box of 21)
6. Ciprofloxacin 250mg tablets
7. DuoResp 320/9 (1 inhaler)
8. Doxycycline 100mg capsules (box of 8)
9. Furosemide 40mg tablets (box of 28)
10. Ipratropium 500microgram Nebules (box of 20)
11. Levofloxacin 500mg tablets
12. Nicotine 21mg patches (box of 7 patches)
13. Prednisolone 5mg tablets – (box of 28 for acute course and 42 for rescue pack)
14. Salbutamol 100 microgram/puff inhaler (1 inhaler)
15. Salbutamol 2.5mg Nebules (box of 20)
16. Sando K tablets (tube of 20)
17. Seebri (1 inhaler)
18. Tiotropium 18 microgram Inhaler (1 inhaler)
19. Ultibro (1 inhaler)

Procedure for Completion of Drug Chart written by: XXX, Senior Clinical Pharmacist.

### *Organising transport for return home*

Patients who do not require controlled oxygen therapy or other assistance during transfer home may use private transport. Plans for transfer home will be reviewed by the RSN. If an ambulance is required the RSN should contact Ambulance Control and request an urgent ambulance (1-2 hour response). The RSN will review return home to help establish the patient in their own home.

A patient should be flagged up to the NEAS (North East Ambulance Service) by sending a referral form (see appendix) to the following email address: XXX The patient can be removed once they are discharged, or will automatically come off the system after 2 weeks.

## Maintaining the Patient at Home

### RSN review

The patient will have been reviewed by a RSN prior to returning home. Where possible, the RSN for HAH will accompany the patient home or, if not feasible, visit them shortly after return home. A detailed handover of HAH patients must occur when one RSN takes over from another on the rota. The RSN will have a standard set of equipment that they take to see the patient (see Hospital at Home equipment checklist).

The patient will be reviewed daily during HAH, seven days per week. As well as nurse visits, patients will be routinely contacted by telephone in the evening. In particular, patients living alone often value an evening phone call.

### *AECOPD proforma*

A new daily review sheet should be completed each day. This includes prompts to: review the patient's symptoms and social support needs; perform an examination (recording physiological observations); review treatments (including pulmonary

rehabilitation) and the need for bloods/ ABGs; and deliver education to the patient and carer.

***Kardex***

This will be reviewed and updated by the RSN daily. With consent, it is useful to review the patients' medication store to get an impression of the patient's understanding of, and concordance with, their usual medication. This will inform patient education strategies and medication choice.

***Smoking Cessation***

Smoking cessation is the most effective treatment for COPD. Highlight that smoking not only causes progression of COPD, but also increases the risk of flare ups / exacerbations. Patients who smoke should have nicotine patches and short term NRT prescribed prior to discharge. Patients are more likely to smoke in their own home compared to hospital; be vigilant. If a patient is smoking during HAH this should be documented, and smoking cessation advice and support should be offered in the patient's home.

***MRSA eradication***

The results of any MRSA swabs will not be available before the patient returns home. If the patient is MRSA positive, MRSA eradication therapy should be started.

***Oxygen***

If a patient requires temporary controlled oxygen therapy, the RSN will facilitate the transfer of an oxygen concentrator to the patient's home. The oxygen concentrator may require two people for transfer and set-up, however such patients are more likely to need other support, such as HCAs, OT, or physiotherapy. Oxygen should be prescribed and to maintain saturations between 88-92%, with point of care arterial blood gas monitoring if required.

***Blood monitoring***

Patients will have venous bloods checked at home by the RSN as and when required, for analysis in hospital. Arterial blood gases (ABG) should be analysed in the patient's home using the point of care analyser. If this is unavailable, the ABG sample should be taking just before leaving the patient's home and transferred to the

hospital for immediate analysis on ice: the longer the time to analysis, the greater chance of error.

### Occupational therapy

Patients' OT needs will have been identified in the hospital, though new needs may be identified when the RSN returns home with the patient. A key safe will help with access to the house for those patients that are unable to answer the door independently. Key safes will be stored with both the RSNs and with OT. There is an array of available equipment to help patients at home to sit upright in bed, and OTs will choose the best option based on their assessment of the patient.

### Physiotherapy

The patients will be assessed by a physiotherapist prior to return home or within the first few days of return home. This will include assessment and education on breathing control, sputum clearance and an individual exercise plan, working towards pulmonary rehabilitation. Where possible, a joint assessment with the RSN will be performed.

Outside of this formal assessment, patients who need assistance with chest clearance will be identified by the RSN, who will contact the physiotherapist to provide additional support. All patients will be offered pulmonary rehabilitation, to commence within 4 weeks of discharge. Pulmonary rehabilitation is one of the most successful treatments for COPD, and patients may be more receptive to this intervention when education is provided to them and their family in the patient's home.

### Psychological Therapy

XXXXXX should be contacted if it is felt that patients could benefit from psychological therapy. Please see appendix "Working with and managing psychological distress in the Hospital at Home project" for further information.

### Adult Social Care

Patients who have care needs will be seen by HealthCare Assistants with basic training in COPD. RSN should coincide their visits with HCA visits where possible as this will be helpful, and also an opportunity to deliver additional training and support.

### Out of hours calls

Patients will be able to phone the RSN on call for HAH at any time of the day. Based on our experience, the call volume is expected to be low. A routine evening phone call can address any issues, and help prioritise morning visits if there is more than one patient in Hospital at Home, which may minimise overnight calls.

## Return to Hospital

### Identifying patients who need to return to hospital

The decision to have a patient return to hospital will be made by the RSN. Where possible, the RSN should discuss the patient with a respiratory consultant, and have the results of upto-date bloods and arterial blood gases available to inform the decision. In some instances, it may be unclear if the patient needs to return to stay in hospital: such a patient can be brought back to hospital for a chest x-ray and medical review, and could return home if sufficiently well. Ideally, this should be carefully co-ordinated to allow a timely review once the chest x-ray, bloods and ABG have been performed.

### Ambulance transfer from Hospital at Home to hospital

A minority of patients receiving Hospital at Home may need to return to hospital. NEAS will be informed of, and maintain a record of, all patients receiving Hospital at Home.

All patients will have **medical notes (red file) and a drug Kardex** at home, which **must return to hospital** with the patient. If oxygen is required it should be delivered by Venturi mask (target saturations 88-92%).

Patients returning to hospital via this route will bypass Accident and Emergency and go directly to the acute respiratory ward NSECH.

### Organising the ambulance for return to hospital

1. The patient contacts Respiratory Special Nurse (RSN); outside of office hours, the nurse will either:
    a. Offer phone advice and visit the patient in the morning
    b. Organise return to hospital

2. If return to hospital is required, the RSN will contact the bed manager to arrange a bed on the acute respiratory ward. Patients will bypass Accident and Emergency.
3. The RSN will phone for an ambulance, indicating the level of urgency and the patient's destination.

**MRSA and C. Diff.**

If a patient has watery stools (stool type 7 on the Bristol Stool Scale) or is found to be MRSA positive, then the patient will need to be isolated when they return to hospital. The bed manager should be informed as early as possible.

## Discharge from Hospital at Home

The COPD care bundle should be completed for all patients who are discharged from Hospital at Home, as occurs in hospital. A copy will be sent by the RSN to hospital pharmacist. The RSN will liaise with pharmacy to let them know the patient has been discharged so they can perform a one week follow-up phone call (including review of education regarding rescue medication).

The decision to discharge a patient from Hospital at Home will be made by the RSN in liaison with the respiratory consultant. It is expected that the average duration of HAH will be similar to the length of hospital stay for an acute exacerbation of COPD managed as an inpatient (4-5 days).

The criteria below can be used to help guide when a patient is ready for discharge. All patients will vary, and the patient's baseline status must also be considered.

- Symptoms improving (breathlessness, sputum)
- Oxygen saturations >88% on room air, or if on LTOT usual oxygen requirements
- Pulse less than 110
- Respiratory rate less than 25
- Systolic blood pressure greater than 90mmHg
- Apyrexial for greater than 24 hours
- Off nebulisers for greater than 24 hours
- Mobility adequate
- Social support adequate and in place

The discharge from HAH date must be clearly documented in the notes and a discharge letter will be dictated on G2 by the RSN (with copies for the patient, their

GP and the medical notes). If the patient needs a 2-week supply of medication and an emergency pack this will need to be prescribed.

The red file will be returned to the hospital by the RSN. It should be given to the ward clerk on the ward from which the patient returned home. Patients in HAH remain eligible for all treatments and services that are available for those being discharged from hospital, such as Supported Pulmonary Discharge (NTGH) and community matron review (WGH). Patients should have 6 week follow-up in respiratory clinic, either with a respiratory nurse or doctor. The patient should be seen by a doctor of they have consolidation on their chest x-ray.

# Hospital at Home Appendix

## Hospital at Home Return Home Checklist

| | Required | Done |
|---|---|---|
| Patient reviewed by consultant (resp or gen med) | | |
| Patient reviewed by respiratory consultant or registrar | | |
| All jobs addressed from consultant ward rounds | | |
| Discharge medications organised | | |
| Family/carer informed patient is returning home | | |
| RSN phone number given to patient and family/ carer | | |
| Letter faxed to GP + filed in notes | | |
| Admission details photocopied; copy left in hospital notes | | |
| Consent from for admission notes to return home signed | | |
| Inform North East Ambulance service | | |
| Inform Northern Doctors | | |
| | | |
| Dementia CQUIN target completed | | |
| VTE (DVT) CQUIN target completed | | |
| | | |
| Oxygen concentrator organised, forms signed | Yes / No | |
| OT organised | Yes / No | |
| Physio organised * | Yes / No | |
| Adult social care organised | Yes / No | |
| Ambulance organised | Yes / No | |
| - Patient flagged on NE ambulance service system | | |
| | | |
| Equipment prepared for home visit | | |

*All patients should receive early pulmonary rehabilitation

## Equipment check for Home visits

| Required? | YES | NO |
|---|---|---|
| Medication pack | | |
| Salbutamol nebules | | |
| Ipratropium bromide nebules | | |
| Amoxillin (low dose and high dose) | | |
| Co-amoxiclav | | |
| Doxycycline | | |
| Ciprofloxacin | | |
| Prednisolone | | |

| | | |
|---|---|---|
| Furosemide | | |
| Co-amilofruse | | |
| Tinzaparin- 3,500 and 2,500 units | | |
| | | |
| Nebuliser machine | | |
| Cleaning equipment | | |
| Masks | | |
| Tubing | | |
| | | |
| Oxygen | | |
| Tubing | | |
| Venturi masks 24 28 35 | | |
| | | |
| Investigations- routine bloods | | |
| Urea and electrolytes blood vials | | |
| Full blood count vials | | |
| Clotting test blood vials | | |
| Needles | | |
| Syringes | | |
| Sharps box | | |
| Sterile skin prep | | |
| Gloves | | |
| Handwash | | |
| Tourniquet | | |
| Cotton wool/ gauze and tape | | |
| Sputum pots | | |
| | | |
| Arterial Blood Gases | | |
| Arterial Blood Gas syringes | | |
| ABG point of care machine | | |
| ABG machine cartridges | | |
| Ice bag (if ABG machine unavailable) | | |
| | | |
| Observations | | |
| Oxygen saturations (check working) | | |
| Blood pressure- automatic | | |
| Blood pressure- manual | | |
| Stethoscope | | |
| Temperature | | |
| Scales | | |
| Timer (resp rate) | | |
| BMs | | |
| | | |
| Telehealth equipment | | |

Northumbria Healthcare NHS
NHS foundation Trust

**Medication Administration Record-** Medication support provided by social services.

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| OUTCOME OF RISK ASSESSMENT (i. e. Prompt OR Administer): | | | | | | | | | | | | | | | |
| Name: | | | | | | | D.o.B. | | | | | SWIFT / NHS No: | | | |
| GP Details: | | | | | | | Chemist Details: | | | | | | | | |
| Allergies: | | | | | | | Start Dates: | | | | | | | | |
| Medication Details (including name, strength, dose, route and directions) | Signature | | | | | | | | | | | | | | |
| | Date | | | | | | | | | | | | | | |
| | Morning | | | | | | | | | | | | | | |
| | Lunch | | | | | | | | | | | | | | |
| | Teatime | | | | | | | | | | | | | | |
| | Evening | | | | | | | | | | | | | | |
| | Morning | | | | | | | | | | | | | | |
| | Lunch | | | | | | | | | | | | | | |
| | Teatime | | | | | | | | | | | | | | |
| | Evening | | | | | | | | | | | | | | |
| | Morning | | | | | | | | | | | | | | |
| | Lunch | | | | | | | | | | | | | | |
| | Teatime | | | | | | | | | | | | | | |
| | Evening | | | | | | | | | | | | | | |

| | |
|---|---|
| NOTE:<br>All doses must be signed for, if not given for any reason mark with 'O' and ensure documented in the care plan and reported to Team Supervisor | MAR Chart Completed by.....Date.....<br>19<br>Checked by..... Date..... |

**North East Ambulance Service**

This sheet can be found at XXX

North East Ambulance Service NHS

NHS Foundation Trust

**Hospital at Home for COPD Flag Referral**

The North East Ambulance Service (NEAS) is able to attach a flag to a patient record to identify those who are being treated in Hospital at Home for COPD under North Tyneside and Wansbeck General Hospital. Whilst under Hospital at Home, patients who return to hospital will bypass accident and emergency and go straight to the medical admissions unit/ emergency care unit.

To inform the NEAS of a new patient, to update or remove an existing patient's flag please complete the form below.

| | | | |
|---|---|---|---|
| Patient Status | New: ☐ | Existing: ☐ | Remove: ☐ |
| Surname | | | |
| Forename | | | |
| DOB | | | |
| Telephone No | | | |
| NHS Number | | | |
| Address (inc. postcode) | | | |
| GP Name and Practice | | | |
| Documentation in Place: | All patients at home will have their medical records (**red file and drug kardex**) which must return to hospital with the patient. Patients will be in Hospital at Home for 1 to 2 weeks, during which they time they will be seen at home regularly by hospital staff. They will have 24 hour a day contact to a Respiratory Specialist Nurse, who can arrange return to hospital. In the unlikely event that the patient contacts the ambulance service directly, they ambulance crew should contact the bed manager before returning the patient directly to the medical admissions unit/ emergency care unit. | | |
| Location of Documents in Property (if known) | | | |
| Referrer Name and Contact Details | | | |
| Preferred alternative pathways of care should 999 or 111 be contacted (e.g. known to Palliative Care Team and contact details): | Please provide details if available: | | |
| Other Relevant Information (e.g. specific wishes around admission): | Please add the following information with the red flag: "Hospital at Home for COPD patient. If patient returns to hospital please return medical notes (red file and kardex)" | | |
| Patient consents to sharing of information with NEAS (required for flagging): ☐ | | | |

Please ensure that if a patient no longer requires their record flagged with NEAS that this form is resent using the 'Remove' option in the patient status field.

Once completed please email (preferred) or fax this form to the following:

Secure email: handover.form@nhs.net or Fax: 0191 430 2081

Please note: This document, when completed, contains patient identifiable information. To email this form securely it must be sent from an nhs.net account.

v1.1, Jan 2014

**Consent form for admission notes to return home with the patient**

This sheet can be found at X:\Respiratory\Hospital at Home

| |
|---|
| PARTICIPANT NAME |
| NHS NUMBER |
| DATE OF BIRTH |
| ADDRESS |

I …… consent to my medical notes staying in my home for the duration of my treatment in Hospital at Home. I understand that it is my responsibility to control access to my notes by people not from the hospital, including by family members and friends. I accept that there is a risk that someone may look in my notes without my permission.

I understand that my medical notes are the legal record of the medical assessment and treatment I receive. The attending clinical team will have full access to my records and will return the notes to the hospital at the end of this period of care. Should I become unwell, and need to return to hospital, it is important that these notes are brought back to hospital with me. The notes remain the property of Northumbria Healthcare NHS Foundation Trust.

| | | | | |
|---|---|---|---|---|
| | | DD | MM | YYYY |
| **Patient (PRINT)** | **Signature** | **Date** | | |
| | | DD | MM | YYYY |
| **Witness (PRINT)** | **Signature** | **Date** | | |

## COPD re-admission avoidance checklist

| Intervention | Done |
|---|---|
| Smoking cessation – advice, NRT, referral | ☐ |
| Arrange Long Term Oxygen Therapy assessment if required<br>(pO2 <7.3 kPa; or <8kPa + cor pulmonale* or polycythaemia**) | ☐ |
| Pulmonary rehab assessment and referral. Copy discharge letter to physio. | ☐ |
| Education to patient and carer including self-management | ☐ |
| - Rescue pack issued (check sensitivities from previous sputum) | ☐ |
| - Inhaler technique and concordance | ☐ |
| Annual 'flu vaccination | ☐ |
| Pneumonia vaccination | ☐ |
| Azithromycin in recurrent exacerbators (benefit primarily in nonsmokers) | ☐ |
| Consider supported discharge | ☐ |
| Liaise with other members of MDT (e.g. community matron) | ☐ |
| Contact number – respiratory outreach service | ☐ |
| Follow up appointment | ☐ |
| Consider nebuliser assessment for select patients (full trial by protocol) | ☐ |
| Discuss patient with supervising consultant pre-discharge, focusing on re-admission avoidance | ☐ |

*Echocardiogram showing right ventricular dysfunction

*Clinical signs of right sided heart failure such as ankle oedema

**Raised haemoglobin and/ or haematocrit

## Working with and Managing Psychological Distress in the Hospital at Home project

### *Background*

Patient's experiencing an acute exacerbation of COPD will commonly and understandably experience relatively high level of anxiety, low mood (loss of pleasure/ poor sleep etc) and panicky feelings intertwined with increased levels of breathlessness. (*Maurer et al 2008*). However in most cases this could be expected to reduce over time (both towards the end of a 'hospital' episode and during the first several weeks of discharge and rehabilitation) with the resolution of the exacerbation and gradual return to usual day to day functioning. Taking a bio-psycho-social approach to understanding distress is key is helping people.

### *Levels of help*

Emotional support by front line staff in the hospital at home project (CNS's, physio's etc) is a core requirement in the care of individual patients and their families. Good listening, communication and relationship building skills help patients to feel supported, valued, and understood. Also appropriate psycho-education and information giving will help patients to understand and normalise their distress in the context of their exacerbation.

Front line staff can provide advice and support their patients in basic skills to manage distress e.g. breathing control to manage panic/anxiety, use of distraction, use of relaxation.

Good care management plans that actively involve patients (and family/ carers in the home) and are tailored to their specific needs can go a long way to helping patients feel calmer, more in control and hopeful about improvement through an exacerbation:

- small, gradually increasing mobility goals and help with practice and achieving these as part of rehabilitation plan through the hospital at home period
- gradually increasing independence in self-care throughout the exacerbation/ hospital at home period

- referral onto supported pulmonary discharge and community matron support post hospital at home period
- referral onto rehabilitation at home or in hospital after hospital at home.

Be alert to social triggers to a patients' distress:

- social isolation, need for external carers etc.
    - involvement of social services
- other family members; anxiety, lack of knowledge/ understanding of COPD or lack of confidence in supporting the person with breathlessness
    - Talking with and involving partners/ family carers

Where distress in relation to COPD and its symptoms remains high and persistent, despite these areas being addressed, or the person is struggling to engage in these areas of help, then referral to respiratory clinical psychology can be considered. if felt to be appropriate, this can be considered during the exacerbation (after initial 3-4 days) or at a 6 week post exacerbation review.

***Respiratory Clinical Psychology – potential options of help***

Respiratory clinical psychology can provide:

1. Staff case consultation, discussion and advice
2. Staff training, support and supervision in their own delivery of basic psychological help and support to distressed patients
3. Patient assessment and advice to contribute to multidisciplinary understanding, planning and management of the patient.
4. If appropriate and the patient is willing to engage in and use a psychological approach to the management of their distress, providing a contracted piece of therapeutic work (typically 6-8 sessions, but tailored to individual need).
5. Ongoing liaison with MDT members involved in the care of the patient.

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