Can historical assumptions be used to assess fitness to fly for other respiratory compromised patients? An evaluation of physiological parameters to risk stratify patients planning air travel

Ian James Cliff

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Faculty of Science & Engineering, School of Life Science Manchester Metropolitan University in collaboration with the University Hospitals of North Midlands NHS Trust

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Contents

1. List of tables, figures, abbreviation, and publication/abstracts

List of tables **Pages**

List of figures **Pages**

List of abbreviations

HCT	Hypoxic Challenge Test
FTF	Fitness to fly
COPD	Chronic Obstructive Pulmonary Disease
ILD	Interstitial Lung Disease
MND	Motor Neurone Disease
Pack/year	Unit for measuring the amount a person has smoked over a period
BMI	Measure of healthy weight
FEV_1	Forced Expiratory Volume in one second (litres)
FVC	Forced Expiratory Volume (litres)
% pred.	Measure against normal value in term of percent (%)
Z-score	Measure against the normal reference range (±1.645)
FEV_1/FVC	Ratio of expelled air in one second against total volume expelled
FEV_1/FVC <70%	Definition of obstruction
TLco	Diffusion capacity for carbon monoxide
Kco	Index of the efficiency of alveolar transfer of carbon monoxide
Va	Alveolar volume
TLC	Total Lung Capacity

RV	Residual Volume
pH	Measure of acidity
PaO_2	Partial pressure of oxygen
$PaCO_2$	Partial pressure of carbon dioxide
HCO_3	Bicarbonate/Intermediate form in the deprotonation of carbonic acid
BE	The amount of acid required to return pH to 7.4 at 37^oC and a $CaCO_2$ of 5.3 kPa
SpO2	Oxygen saturation within the blood
tHb	Total amount of haemoglobin within the blood
FiO_2	Fraction of inspired oxygen
6MWT	Six Minute Walking Test
SNIP	Sniff nasal inspiratory pressure
LLN	Lower limits of normal

Publication/abstracts

Abstracts submitted to the British Thoracic Society Winter Meeting from the data within this thesis (20th August 2020).

Can historical assumptions be used to assess fitness to fly for MND and ILD patients? An evaluation of physiological parameters to risk stratify patients planning air travel

Ian Cliff, Dr Helen Stone, Charlotte Hurst, Dr Emma Crawford & Dr Naveed Mustfa

Introduction
The risk associated with commercial flight for respiratory compromised patients is well known. Many of the assumptions are based on studies that have included patients with Chronic Obstructive Pulmonary Disease (COPD) and have often been extended to other respiratory and non-respiratory disorders. This study aimed to examine differences in physiological parameters and Hypoxic Challenge Test (HCT) outcome in patients with Motor Neurone Disease (MND), Interstitial Lung Disease (ILD) and COPD.

Methods
Respiratory patients who were referred into a fitness to fly service (n=225) with COPD (n=51), MND (n=118) and ILD (n=56) completed baseline lung function and a HCT as part of a risk stratification for planned air travel. Statistical analysis was performed using one-way ANOVA, Kruskal-Wallis, and Chi-Squared tests, as appropriate.

Results
Demographic data relating to age, smoking history and BMI were significantly different between the patient groups. Spirometric data showed significant differences in Forced Expiratory Volume in one second (FEV_1) absolute, percent predicted and standardised residuals, however there was no significant difference in Forced Vital Capacity (FVC) absolute, or percent predicted. Resting capillary blood gases (CBGs) (FiO_2 21%) showed significant differences between patient groups in all parameters except for pH. Responses to the hypoxic mix during the HCT (FiO_2 15%) showed differences in all CBG values apart from pH. This was also mirrored in the corrective values (FiO_2 28%). The difference between the PaO2 at rest (21%) and during the HCT (15%) is higher in the MND and ILD groups (2.66and 2.74 kPa respectively) versus the COPD group (2.2kPa). The HCT fail rate was greatest for the COPD group (Table).

Conclusions
In this retrospective, exploratory examination, the physiological data supports significant differences between the disorders for most data. The assumptions and algorithms based on the study of COPD patients cannot be assumed for MND or ILD, and these groups need to be specifically studied to better understand their response to the commercial cabin environment.

Table. Descriptive statistics for physiological parameters by condition, including indications of statistical significance.

	MND		ILD		COPD		
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p value**
Age	63	12.99	69.5	7.05	66	9.24	0.001
FEV_1 (L)	1.94	0.85	1.91	0.65	1.13	0.61	0.001
FEV_1 %	65.93	25.72	76.1	19.19	44.76	25.55	0.001
FVC (L)	2.46	1.05	2.54	0.84	2.62	0.95	0.676
FVC %	64.59	24.35	70.8	18.11	74.24	23.13	0.059
PaO_2 21%	10.12	0.12	9.46	1.05	8.68	1.01	0.001
PaO_2 15%	7.46	1.01	6.72	0.75	6.48	0.92	0.001
PaO_2 28%	11.7	2.56	11	2.56	8.94	2.25	0.002
% HCT Fail	20.34		51.79		62.75		0.001

Can existing routine clinical data be used to predict hypoxaemia for MND patients undertaking commercial flight?

Ian Cliff, Dr Helen Stone, Charlotte Hurst, Dr Emma Crawford & Dr Naveed Mustfa

Introduction
Pre-COVID-19, the total number of passengers traveling by commercial airlines rose to 4.3 billion, with Europe amounting to a 7.2% increase. The risks of respiratory compromised patients developing hypoxaemia during flight is well documented. Assessment of these patients is time consuming and often requires specialised equipment. Furthermore, most of the evidence is based on research into patients with Chronic Obstructive Pulmonary Disease (COPD). The aim of this study is to investigate potential predictive biomarkers relating to the development of hypoxaemia during flight in patients with Motor Neurone Disease (MND).

Methods
118 MND patients referred into a fitness to fly service (n=118) completed baseline lung function and a Hypoxic Challenge Test (HCT) as part of a risk stratification for planned air travel (77 male). Data from patients requiring in-flight oxygen was compared to patients who did not, in accordance with the British Thoracic Society recommendations 2011: Managing passengers with stable respiratory disease planning air travel. Statistical analysis was performed using one-way ANOVA, Kruskal-Wallis, and Chi-Squared tests, as appropriate.

Results
There was no significant difference between the pass (n=94) and fail (n=24) groups for age, gender, smoking history or BMI. There was a significant difference for all spirometry data (FEV_1, FVC and FEV_1/FVC ratio – absolute, percent predicted and standardised residuals). Moreover, the resting blood gases (FiO_2 21%) data showed significant difference for all parameters except for pH (<0.001). The regression analysis showed limited predictive value of spirometry and/or resting blood gas data apart from $PaCO_2$ and base excess (BE).

Conclusions
The predictive value of spirometric paraments and resting blood gases are limited in assessing hypoxaemia during commercial flight in MND patients, except for parameters relating to respiratory failure. Despite the significant difference between the two groups, routine physiological data was limited in the predictive regression equations. We recommend that the safest approach in managing this group of patients is to perform an HCT in all patients intending to use air travel until more evidence-based data is available.

Table. Descriptive statistics for physiological parameters by condition, including indications of statistical significance.

	MND		
Variable	**Pass**	**Fail**	**p value**
Age	61.5 (12.67)	66 (14.18)	0.076
FEV_1	2.12 (0.80)	1.25 (0.71)	0.001
FEV_1 %	70 (24.43)	45 (21.04)	0.001
FVC	2.61 (1.02)	1.74 (0.88)	0.003
FVC %	68 (24.09)	49 (19.68)	0.004
PaO_2 21%	10.30 (1.14)	9.045 (1.18)	0.001
PaO_2 15%	7.60 (1.147)	6.39 (0.25)	0.001
$PaCO_2$ 21%	5.28 (0.75)	6.24 (0.86)	0.001
BE 21%	2.35 (2.37)	5.70 (3.34)	0.001

Is routine clinical data useful in predicting hypoxaemia in ILD patients undertaking commercial flight?

Ian Cliff, Dr Naveed Mustfa, Charlotte Hurst & Dr Helen Stone

Introduction
The British Thoracic Society guidelines on air travel in patients with respiratory disease advocate an individual risk assessment, with the respiratory physician being the central referral point. A hypoxic challenge test (HCT) can identify patients that would benefit from in-flight oxygen, but evidence as to which patients should be referred for this test is lacking.

Methods
We aimed to identify parameters that might predict the outcome of an HCT in patients with interstitial lung disease (ILD) the majority of whom had idiopathic pulmonary fibrosis (IPF). 56 consecutive HCTs were reviewed. Data from patients requiring in-flight oxygen according to the HCT was compared to data from patients who did not. Routine clinical data for spirometry, static lung volumes, transfer factor and six-minute walking test (6MWT) was also obtained. Statistical analysis was performed using one-way ANOVA, Kruskal-Wallis, and Chi-Squared tests, as appropriate.

Results
Demographic data relating to age, gender, smoking history and BMI were comparable. Spirometric data showed differences in per cent predicted for Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC). There was no difference in any of the parameters relating to static lung volumes, transfer factor or 6MWT. Furthermore, there was no difference between the group for resting blood gases (21%). The regression analysis showed limited predictive value for spirometry

Conclusions
The data showed that the physiological parameters have limited predictive ability in identifying patients who are at risk of developing hypoxaemia during commercial flights. We have excluded patients on high flow rate oxygen at sea level from our study due commercial airlines limiting flow rate to 4 l/min at altitude. We recommend that the safest approach is to refer all patients with ILD for HCT assessment until more evidence-based data is available, which is the current practice at this regional centre.

Table. Descriptive statistics for physiological parameters by condition, including indications of statistical significance.

	ILD		
Variable	**Pass**	**Fail**	**P Value**
Age	72 (6.95)	68 (6.82)	0.063
FEV_1 %	84 (19.26)	67.56 (15.20)	0.001
FVC %	2.74 (0.95)	2.32 (0.67)	0.002
TLco	3.66 (3.88)	3.86 (0.78)	0.966
TLC	4.14 (1.19)	3.41 (1.23)	0.345
PaO_2 21%	9.64 (1.05)	9.28 (1.04)	0.203
PaO_2 15%	7.34 (0.66)	6.41 (0.36)	0.001
6MWT % Dist.	74.38 (25.61)	61.59 (24.67)	0.196
6MWT Destat.	-6.5 (4.14)	-9.0 (3.78)	0.743

2. Abstract

Can historical assumptions be used to assess fitness to fly for other respiratory compromised patients? An evaluation of physiological parameters to risk stratify patients planning air travel

Introduction

The risks associated with commercial flight for respiratory compromised patients is well known. Many of the assumptions are based on studies that have included patients with Chronic Obstructive Pulmonary Disease (COPD) and have often been extended to other respiratory and non-respiratory disorders. The primary aim of this thesis is to examine the differences in physiological parameters and Hypoxic Challenge Test (HCT) outcomes in patients with Motor Neurone Disease (MND), Interstitial Lung Disease (ILD) and COPD. The secondary outcome is to investigate whether physiological parameters can predict HCT pass or failure in ILD, MND and COPD patient groups.

Methods

Respiratory patients who were referred into a 'fitness to fly' service (n=225) with COPD (n=51), MND (n=118) and ILD (n=56) completed baseline lung function and an HCT as part of risk stratification for planned air travel. Descriptive statistics were obtained, and analysis was performed using one-way ANOVA, Kruskal-Wallis, and Chi-Squared tests, as appropriate.

Data from patients requiring in-flight oxygen was compared to patients who did not, per the British Thoracic Society recommendations 2011 (Ahmedzai et al., 2011). Univariate analysis and logistic regression were performed to evaluate independent physiological parameters for HCT failure.

Results

Demographic data relating to age, smoking history and BMI were significantly different between the patient groups. Spirometric data showed significant differences in Forced Expiratory Volume in one second (FEV_1) absolute, per cent predicted and standardised residuals, however, there was no significant difference in Forced Vital Capacity (FVC) absolute or per cent predicted. Resting capillary blood gases (CBGs) (FiO_2 21%) showed significant differences between patient groups in all parameters except for pH. Responses to the hypoxic mix during the HCT (FiO_2 15%) showed differences in all CBG values except pH. This was also mirrored in the corrective values (FiO_2 28%). The difference between the PaO_2 at rest (21%) and during the HCT (15%) is higher in the MND and ILD groups (2.66 and 2.74 kPa respectively) versus the COPD group (2.2kPa). The HCT fail rate was greatest for the COPD group.

In the MND group there was no significant difference between the pass (n=94) and fail (n=24) groups for age, gender, smoking history, or BMI. There was a significant difference for all spirometry data (Forced Expiratory Volume in one second - FEV_1, FVC - Forced Vital Capacity and FEV_1/FVC ratio – absolute, per cent predicted and standardised residuals).

Moreover, the resting blood gases (FiO_2 21%) data showed a significant difference for all parameters except pH (<0.001). The Regression analysis showed limited predictive value of spirometry and/or resting blood gas data except for $PaCO_2$ and base excess (BE).

In the ILD group, demographic data relating to age, gender, smoking history, and BMI were comparable. Spirometric data showed differences in per cent predicted for FEV_1 and FVC. There was no difference in any of the parameters relating to static lung volumes, transfer factor or 6MWT. Furthermore, there was no difference between the group for resting blood gases (21%). The Regression analysis showed limited predictive value for spirometry.

Conclusions

In this exploratory examination, the physiological data supports significant differences between the disorders for most data. The assumptions and algorithms based on the study of COPD patients cannot be assumed for MND or ILD, and these groups need to be specifically studied to better understand their response to the commercial cabin environment.

The predictive value of spirometic paraments and resting blood gases are limited in assessing hypoxaemia during a commercial flight in MND and ILD patients, except for parameters relating to respiratory failure. Despite the significant difference between the two groups, routine physiological data was limited in the predictive regression equations.

The recommended safest approach in managing these groups of patients is to perform an HCT in all patients intending to use air travel, until more evidence-based data is available.

3. Introduction

A medical emergency occurs in 1 of 604 commercial flights equating to 1 in 30,000 passengers' (Vohra and Klocke, 1993; Spurling et al., 2011). Of these emergencies, respiratory symptoms account for approximately 12% with others including syncope (37%), cardiac symptoms (8%), stroke (2%) and cardiac arrest (0.3%). In a recent study of 1260 healthy volunteers, no significant changes in pulse oximetry (SpO_2) was observed during a simulated 8 hour flight at a cruising altitude of 8000 ft (2438 m) (Lee et al., 2017). However, if an aircraft's cabin pressure exceeds 10,000 ft (3048 m), hypoxaemia becomes more apparent and SpO_2 falls to approximately 89% in healthy individuals (Humphreys et al., 2005). Most commercial aircraft cruise at an altitude of 38,000 ft (11,582 m) with the internal cabin pressurised to equate approximately 8,000 ft (2438 m).

Other potential risk factors associated with commercial air travel include low relative humidity and altitude related expansion of gases within the thoracic area, which include enclosed pulmonary parenchymal spaces (Boyles's law). At the normal cabin altitude of 8000 ft (2438 m), this equates to a 38% expansion of humidified gas (Gong Jr et al., 1984).

There are many other conditions that can contribute to high altitude hypoxaemia leading to inflight complications, which include, obstructive sleep apnoea, pulmonary hypertension, pneumothorax and cystic fibrosis (Nicholson and Sznajder, 2014). Even at rest, hypoxaemia can be present, resulting in respiratory symptoms and critical end organ dysfunction, such as arrhythmia or syncope (Berg et al., 1993). Moreover, patients with cardiovascular

disease, may be unable to adequately increase cardiac output, which would further exacerbate hypoxaemia and impair end organ hypoxia.

As the population ages and our ability to manage respiratory disorders improves, an increased number of patients with underlying respiratory diseases are utilising air travel. With this increased age, there is a possibility of significant underlying comorbidities (Ahmedzai et al., 2011). There is no established process for quantifying in-flight medical emergencies, however adverse incident reporting has been utilised as a means of measuring the problem (Sand et al., 2009). A service was set up in North America offering radio link assistance for in-flight medical emergencies (MedAire Inc, 2020). This facility logged over 17,000 calls a year, with respiratory events accounting for between 10 and 12%, which was the third most frequent cause of medical diversion. Other studies have suggested that the figure is as high as 44,000 per year, with respiratory symptoms being the second most common emergency to syncope (Peterson et al., 2013).

It is important that clinicians who manage patients with respiratory and cardiovascular disorders are aware of the potential effects of the commercial cabin environment. Expert consensus based on literature reviews, date back to 2002 (British Thoracic Society Standards of Care Committee, 2002; Ahmedzai et al., 2011). These were developed in response to the need to better understand the implications of air travel on respiratory compromised patients and to understand how best to manage this group (Coker and Partridge, 2000).

The assessment of fitness to fly in patients with respiratory disorders has predominately centred around chronic obstructive pulmonary disease (COPD), however there are a number of small studies that have looked at restrictive ventilatory disorders, motor neurone disease (MND) and cystic fibrosis (CF) (Christensen et al., 2000; Christensen et al., 2002; Mestry et al., 2009; Fischer et al., 2005). MND encompasses several different conditions whose common feature is the premature degeneration of the motor nerves. Although not recognised as a specific respiratory disorder, much of the management is provided by specialist respiratory centres that treat the dysphagia and breathing difficulties. These come in the form of percutaneous endoscopic gastrostomy (PEG) and non-invasive ventilation (NIV), and this is the reason for respiratory classification.

Pre-flight assessment of adult respiratory patients focuses on their underlying condition and comorbidities, which include cardiovascular disease or immunosuppressant therapy. If there is any doubt regarding their fitness to fly, an assessment is recommended. In general, the patient should be stable, free from exacerbations prior to traveling and have a SpO_2 >92% with no risk factors (table 1). For individuals with the following conditions, assessment is recommended in terms of clinical history and physical examination as a minimum (Ahmedzai et al., 2011). Previous air travel intolerance with significant respiratory symptoms, COPD or asthma, bullous lung disease, severe restrictive disease (intra and extra thoracic), cystic fibrosis, conditions worsened by hypoxaemia (cerebrovascular disease cardiac disease or pulmonary hypertension), pulmonary tuberculosis, 6-weeks post hospital

discharge, recent pneumothorax, previous venous thromboembolism, and individuals requiring oxygen, Continuous Positive Airway Pressure (CPAP) or ventilator support.

Contraindication to commercial air travel include infectious tuberculosis, ongoing pneumothorax with persistent air leak, major haemoptysis and oxygen therapy at flowrates exceeding 4 l/min.

Screening result	**Recommendation**
Sea level SpO_2 >95%	Oxygen not required
Sea level SpO_2 92-95% and no risk factors*	Oxygen not required
Sea level SpO_2 92-95% with additional risk factors*	Perform HCT
Sea level SpO_2 <92%	Inflight oxygen
Receiving supplemental oxygen at sea level	Increase flow while at altitude
*Additional risk factors: hypercapnia; FEV_1 <50% predicted; lung cancer; restrictive lung disease involving the parenchyma (fibrosis,) chest wall (kyphoscoliosis) or respiratory muscles; ventilator support; cerebrovascular or cardiac disease; within 6 weeks of discharge for an exacerbation of chronic lung or cardiac disease.	

Table 1. Results of initial assessments (British Thoracic Society Standards of Care Committee, 2002)

There are a number of methods that can be utilised for the assessment of hypoxia during air travel, which include sea level measurement of PaO_2 and SpO_2, regression equations to predict hypoxaemia at altitude and the hypoxic challenge test (HCT) (British Thoracic Society Standards of Care Committee, 2002; Martin et al., 2007). An SpO_2 of 92-95% without risk factors or an SpO_2 >95% was identified as an indicator that an individual was fit to fly and no further testing warranted (British Thoracic Society Standards of Care Committee, 2002). However, the use of SpO_2 at sea level to risk stratify patients of hypoxia has been shown to be a poor predictor of in-flight SpO_2 (Ahmedzai et al., 2011). Furthermore, it has been

shown that patients who have a SpO_2 >96% at sea level can develop significant hypoxaemia during commercial flights which necessitate the need for in-flight supplemental oxygen when tested by HCT (Coker et al., 2007). Moreover, Akerø et al studied over 100 patients with COPD who were risk stratified using the 2002 BTS algorithm who underwent pulse oximetry and an HCT. The sensitivity and specificity for the oximetry measurement thresholds were 59% and 72% respectively (Akerø et al., 2008), indicating that than lower normal SpO_2 in the absence of significant risk factors, is no longer considered sufficiently robust to screen patients prior to commercial flights.

Regression equations have also been explored to estimate the risk of in-flight hypoxaemia. These incorporate sea level measurements of PaO_2 and spirometric parameters including forced expiratory volume in one second (FEV_1) (Dillard et al., 1989; Gong Jr et al., 1984). However, the predictive equations do not compare favourably with HCT in identifying patients with COPD, interstitial lung disease or cystic fibrosis that are at increased risk of developing hypoxaemia at altitude (Martin et al., 2007). The response to hypobaric hypoxia is variable and dependant on several factors, which include cardiac and respiratory status, anaemia, sea level blood gases, carboxyhaemoglobin, and age. These complex relationships are unlikely to be described by these regression equations. Furthermore, many of these equations regularly overestimate the need for in-flight supplemental oxygen.

The HCT is the preferred method for the assessment of patient in-flight oxygen needs. Initially, the availability of this assessment was limited, however over recent years it has

become more readily available with many specialist departments offering this facility (Nicholson and Sznajder, 2014). Furthermore, its ability to correlate well with air travel has given rise to its popularity (Coker et al., 2007). It uses a reduced fraction of inspired oxygen (FiO_2) to simulate the hypoxic conditions at altitude by several methods and has the additional benefit of titrating supplement oxygen to correct the hypoxaemia. Results of this investigation have been compared to actual in-flight conditions, which has shown good correlation within COPD patients (Kelly et al., 2008). A limitation of the HCT is that is does not replicate the hypobaric conditions experienced during flight, therefore its physiological effect is unclear. The hypobaric effect has been shown to reduce both the FEV_1 and forced vital capacity (FVC) and to increase the residual volume (RV), functional residual capacity (FRC) and total lung capacity (TLC) (Dillard et al., 1998; Coates et al., 1979). Therefore, the HCT may underestimate risk because of its inability to replicate the hypobaric hypoxic environment. However, clinical detection of hyperinflation may be relevant in patients with obstructive airway disease and consideration would be prudent as part of the fitness to fly assessment.

The clinical assessment of fitness to fly is facilitated through either a GP and consultant appointment, with no provision to directly request from a patient or travellers' perspective. The number of individuals travelling via commercial flights who are not adequately assessed is unknown, however with increased awareness by both clinicians and travel insurance companies, this number is thought to be reducing (European Lung Foundation, 2020).

The BTS guidelines (2011) articulate the framework regarding the thresholds for the prescription of in-flight supplemental oxygen therapy (table 2). Following the administration of a 15% FiO_2 for a period of 20 minutes, a PaO_2 >6.60 kPa (50 mmHg) or a SpO_2 >85% suggests that in-flight oxygen is not required. However, blood gas or oximetry values less than these thresholds, necessitates supplemental oxygen via nasal cannula for the duration of the flight.

HCT result	Recommendation
PaO_2 >7.4 kPa (>55 mmHg)	Oxygen not required
PaO_2 6.6 - 7.4 kPa (50 - 55 mmHg)	Borderline: a walk test may be helpful
PaO_2 >6.6 kPa (<50 mmHg)	Inflight oxygen (2 l/min)

Table 2. Results of hypoxic challenge test - 15% FiO_2 for 20 minutes (British Thoracic Society Standards of Care Committee, 2002)

Travellers who require supplemental oxygen during flight are accommodated by many airlines, however adequate precautions must be taken prior to travel. Patients are often allowed to take their own small lightweight cylinders or portable oxygen concentrators (POC) on board, if prior agreement has been made with the airline. Unfortunately, there is a significant disparity regarding policies and procedures amongst the airlines, with some companies stipulating all oxygen needs are met by the airline itself, which come with a cost (European Lung Foundation, 2020). Furthermore, many have their own medical forms that require completion and approval prior to flying.

There are disease specific guidelines with regards to the assessment of fitness to fly that are based on evidence grades ranging from C to D (Harbour and Miller, 2001). This evidence is

taken from well-constructed case control or cohort studies with minimal bias and moderate probability of a causal relationship. However, most of the evidence is based on suggestions from extrapolated data or from recognised best practice as deemed by the BTS Air Travel Working Party (Ahmedzai et al., 2011).

Patients with neuromuscular or chest wall disease should all undergo a HCT as standard. For individuals with interstitial or restrictive lung disease, a detailed assessment should be performed consisting of a physical examination and clinical history to ensure careful assessment of the patient. Furthermore, if high altitude destinations are being considered, supplemental oxygen should be advised. It is also recommended that the patient should have a course of oral corticosteroids and antibiotics in the event of an acute exacerbation of their disease. Patients with COPD require consideration with regards to acute exacerbation during the flight and the severity of disease by spirometry with a FEV_1 < 30% predicted highlighting concern. Moreover, patients are advised to carry their own bronchodilator therapy and have an emergency course of prednisolone (British Thoracic Society Standards of Care Committee, 2002; Ahmedzai et al., 2011).

Certain patients with pulmonary disease should be advised not to fly because of the severity of their disorder and the risk involved to others. These include those who pose an infective risk or with active infectious disease (tuberculosis or influenza). Furthermore, all those where air travel would pose a risk to themselves, which includes haemoptysis, unresolved pneumothorax, and the need for supplemental oxygen more than 4 L/min at sea level.

Other important areas that need to be considered when assessing patients for air travel include.

- The different types of commercial aircraft specifications regarding cabin altitude, which can range from 5400 to 8000 ft (Cottrell, 1988). In addition, aircraft may also vary their cruising altitude several times during the flight, which again can alter cabin pressure.
- Respiratory symptoms may still occur even though a robust pre-flight assessment has been completed. One study found that 18% of COPD patients who travelled by commercial airline developed respiratory symptoms despite passing a pre-fight evaluation (Edvardsen et al., 2012).
- With the increase in long haul flights, the length of time flying is an important factor to consider. Longer flights are associated with increased symptoms that can last in excess of 3 hours (Muhm et al., 2007).
- Levels of activity should also be considered. Patients with COPD and restrictive lung disease show a significant worsening of hypoxaemia at altitude with increased levels of activity (Christensen et al., 2000; Christensen et al., 2002). This should be balanced against the risk of developing Deep Vein Thrombosis (DVT), which actively encourages walking during the flight.

Although there is increased awareness of the potential problems for respiratory compromised patients undertaking commercial flights (Ahmedzai et al., 2011; Nicholson and Sznajder, 2014), the number of centres capable of risk stratifying these patients, and who

have available resources to objectively measure the effects of the hypoxic cabin environment are lacking. The HCT is a specialised assessment and limited to dedicated centres, which can be problematic in adequately assessing individuals planning air travel.

As part of ongoing clinical management, there is a plethora of information gathered to manage their disorder, which may give an insight into how they may response to a hypoxic environment. There have been a number of studies that have looked into utilising surrogate markers as a way of predicting hypoxaemia during commercial flights, which include pulmonary function tests (spirometry, static lung volumes, transfer factor) and functional status (Edvardsen et al., 2011; Ling et al., 2013), which require further consideration.

The thesis sets out to initially investigate if the historical assumption regarding fitness to fly based on the COPD population can be extended to other respiratory disorders (MND and ILD). Secondly, it studies the usefulness of routine clinical investigations and their ability to predict HCT outcomes.

In summary, patients with acute and chronic pulmonary disease have the potential risk of becoming hypoxic during commercial flights, which is due to the cabin pressure environment being equivalent to 8000 ft (2438 m), reducing the FiO_2 to 15%. Respiratory compromised patients with and without significant comorbidities are at risk of developing complications in the hypoxic environment. Failure to engage compensatory mechanisms, which relate to ventilation and cardiac output can further worsen this risk. Currently

patients who are deemed at risk require risk stratification through careful clinical evaluation and physiological assessment.

4. Literature review

A literature search strategy was developed by defining words and synonyms for hypoxic challenge test methodologies that included fitness to fly, hypobaric chamber, normobaric hypoxic chamber, pre-mixed 15% O_2 gas supply using the Boolean operator "or". These terms were then followed with "respiratory", "physiology", "motor neurone disease" (MND), "COPD" (chronic obstructive pulmonary disease) and "fibrosis" using the "and" operation. Several search engines were utilised which included British Nursing Index, Medscape, ProQuest, Medline, PubMed and Google Scholar. Also, individual journals were searched which included Thorax, European Respiratory Journal, Chest, New England Journal of Medicine and Journal of Applied Physiology.

The search criteria returned a significant number of articles (438), which consisted of database searching and additional records identified through other sources. The PRISIMA approach was adopted, which looked at duplications, records screened, eligibility and studies included (Moher et al., 2009). The review of the title and abstract was undertaken initially to ensure that the subject matter was related to respiratory compromised patients and/or there was an association with air travel. The assessment methodologies used within these articles were either based on respiratory disorder, physiological response to hypoxic environment or a combination of both. The included articles were published in peer-reviewed journals to certify that the information used was of an academic standard and appropriate for inclusion in the review. Following this process, the included articles totalled 96.

According to the International Civil Aviation Organisation (ICAO), the total number of passengers traveling by commercial airlines rose to 4.3 billion in 2018, which was an increase of 6.4% from the previous year (ICAO, 2018). During the same period, the number of departures totalled 37.8 million, an increase of 3.5%. Furthermore, the passenger traffic as measured by the total scheduled revenue passenger-kilometres performed (RPKs) increased by 7.1%, which equates to 8,258 billion RPKs. The largest increases were seen in Asia/Pacific (9.5%), which is responsible for 34.8% of the worlds air travel, and Europe demonstrating a 7.2% increase and contributing to 26.3% of the total world traffic. This increase is also seen domestically with the largest increases in Africa (21.9%) and Asia/Pacific (10.6%).

Most commercial aircraft cruise at an altitude of 38,000 ft (11,582 m) with the internal cabin pressurised to equate approximately 8,000 ft (2438 m). The United States Federal aviation regulations specify this criteria and will only recommend deviation in an emergency (FAA, 2020). If there is a need to exceed this initial standard altitude, it must not surpass 10,000 ft (3048 m) (ICAO, 2018). The reasoning behind the arbitrary value of 8000 ft (2438 m) was based on the oxy-haemoglobin dissociation curve, which demonstrates that up to this level arterial oxygen saturation (SpO_2) remain above 90% in an healthy individual free from disease (Aerospace Medical Association, 2008). The aircraft cabin is pressurised by utilising the atmosphere, which is drawn in by the aircraft engines and controlled by the rate of air intake and output, through a regulative exhaust valve. Other factors include the aircraft type and cruising altitude. Up to 50% of the aircrafts cabin environment is removed from

the plane with the remainder being filtered and diluted, which is associated to 20-30 air exchanges/hour (ACH) (Rayman, 2002). As aircraft ascend, the decreased cabin pressure causes gas expansion within body cavities, which is related to the ear “popping” sensation experienced by many of the passengers caused by air escaping from the middle ear via the eustachian tube. At 8000 ft (2438 m), the reduced barometric pressure and decreased partial pressure of oxygen, produces an environment that is equivalent to breathing air of 15% oxygen at sea level. In a healthy individual who has a normal partial pressure of arterial oxygen (PaO_2) of approximately 13.33 to 14.00 kPa, it is of little physiological consequence. This is because the compensatory mechanisms of increased ventilation, heart rate and cardiac output, would reduce the effects on the body (Ahmedzai et al., 2011).

In individuals who are either respiratory or cardiac compromised, the compensatory mechanisms may be less effective resulting in hypoxaemia (Nicholson and Sznajder, 2014; Hammadah et al., 2017). In respiratory patients who have an underlying obstructive ventilatory defect, an increase in minute ventilation may result in hyperventilation, and exacerbate respiratory distress (Tuxen and Lane, 1987; Puente-Maestu et al., 2005). In patients with restrictive ventilatory limitation (e.g. interstitial lung disease, extrathoracic restriction or obesity), an increase in minute ventilation may ensue, however the limitation due to a diffusion abnormality within the lung parenchyma, may attenuate other compensatory mechanisms (Christensen et al., 2002).

i. Pre-flight screening

The British Thoracic Society published original guidance for the management of passengers with stable respiratory disease planning air travel in Thorax in 2002 (British Thoracic Society Standards of Care Committee, 2002). This was updated online in 2004 and then fully reviewed in 2011 (Ahmedzai et al., 2011). These recommendations were one of the first attempts to provide clarity regarding risk stratification for managing respiratory patients planning air travel. These served to provide expert opinion based on literature searches at that time, with the aim of providing consistent practical advice for respiratory specialists, working within secondary care.

Respiratory patients generally tolerate the commercial airline cabin environment with little discomfort when previously assessed by a respiratory specialist (Coker et al., 2007). However, with the significant disruption of flight diversions and the implicated costs due to medical emergencies or the deterioration of a passenger, the judgement in confirming a patient's fitness for air travel must not be taken lightly and is also relevant when visiting high altitude destinations (Ahmedzai et al., 2011). Furthermore, consideration should be given to the flight duration, destination, which not only includes altitude , but also its relation to extreme weather conditions, medications and equipment with the latter's ability to operate effectively and safely at altitude (Nicholson and Sznajder, 2014).

There is limited evidence as to who should have a formal assessment on their suitability for commercial flight, however general expert advice suggests pre-assessment/screening for

the following adult respiratory patients (Ahmedzai et al., 2011; National Institute for Health and Care Excellence, 2010):

a. Those with a respiratory condition with the potential to deteriorate acutely resulting in incapacitation and/or the need for medical intervention. Suggested groups include:
    i. Severe (FEV_1 <50% predicted) or poorly controlled obstructive airways disease as defined by symptoms, oxygen requirements, severe and/or frequent exacerbations.
    ii. Symptomatic restrictive lung or chest wall condition.
    iii. Respiratory muscle weakness causing breathlessness and exercise limitation.
    iv. Pulmonary hypertension.
    v. Comorbidities that would worsen hypoxaemia (cerebrovascular or cardiac disease).
    vi. Recent (< 6 weeks) hospital management for respiratory condition.
    vii. Requirement for CPAP or ventilatory support such as NIV.
    viii. Active cancer with lung involvement.
    ix. Patients already requiring oxygen therapy.
b. Recent pneumothorax.
c. Recent (< 6 weeks) pulmonary embolus for deep venous thrombosis or increased risk of venous thromboembolism.
d. Anyone who has experienced significant symptoms during previous air travel or whose condition is of concern to their physician.

An absolute contraindication to air travel is generally considered in patients with untreated ventilatory failure, untreated pneumothorax, respiratory infections presenting a risk to others and bronchogenic cysts (Tzani et al., 2010). In addition, in-flight oxygen for individuals who have type 2 respiratory failure is contraindicated due to the adverse effect supplemental oxygen would have on the hypercapnia and respiratory acidosis (Spurling et al., 2016). Severe hypoxia and the requirement for >4l/min of supplemental oxygen at sea level were initially considered as absolute contraindications to air travel on the grounds that airlines were unable to provide oxygen greater than 4 l/min (Ahmedzai et al., 2011). However, with the advances in POC, which can deliver oxygen flow rates >5 l/min through continuous and pulsed modalities, the >4l/min threshold would appear to no longer apply.

Clinical assessment of patients who are planning a commercial flight consist of both a clinical history and physical examination, which is initially supported with pulse oximetry as the first screening test (Coker et al., 2007). It is generally accepted that a resting SpO_2 of >95% at sea level would not necessitate the need for inflight supplemental oxygen (British Thoracic Society Standards of Care Committee, 2002; Ahmedzai et al., 2011; Ergan et al., 2018; Edvardsen et al., 2012). Dynamic spirometry is often advised in patients with acute and chronic respiratory disease, specifically relating to the airways as a way of describing the severity of the disorder (Nicholson and Sznajder, 2014). Interestingly, respiratory physiology parameters, which include lung function are often poor at predicting hypoxaemia or complications (Christensen et al., 2000; Ling et al., 2013).

Historically those who have been able to walk 50 m on the flat or who are able to climb 10 to 12 stair runs without distress, have been considered to have sufficient cardiopulmonary reserve to fly without the need for supplemental oxygen (International Air Transport Association, 2014). The ability of the six minute walk test (6MWT) has also been explored in pre-flight estimation because of its assessment of functional capacity and exercise induced hypoxaemia in both COPD (Ergan et al., 2018; Brown and Wise, 2007) and interstitial lung disease (ILD) (Lancaster, 2018).

At present the evidence suggests that the 50 m walk is an insensitive assessment for assessing suitability for commercial flights (Bradi et al., 2009), however it is still referenced by both airlines and aviation authorities (International Air Transport Association, 2014; European Lung Foundation, 2020). There have been numerous studies that have shown no correlation between distanced walked and HCT outcome in several disease categories (Bradi et al., 2009; Edvardsen et al., 2011; Chetta et al., 2007). Furthermore, this would also seem apparent for exertional dyspnoea (Chetta et al., 2007). The 50 m walking test would appear to add little in the assessment of an individual's risk of hypoxia and fitness to fly.

The 6MWT and paced shuttle walking tests (SWT) have been used as measures for predictive outcome of the HCT but have been shown to have limited ability in reliably assessing potential hypoxaemia in several respiratory conditions (Coker et al., 2007; Edvardsen et al., 2011; Edvardsen et al., 2012). However, measures that are made as part of the investigations, which include desaturation as measured by the SpO_2, show some association with the HCT outcome in several respiratory disorders. The change in SpO_2 is

unable to specify the corrective oxygen flow rate during flight but could be used as a marker for screening or the requirement of further assessment (Edvardsen et al., 2012; Chetta et al., 2007; Bandyopadhyay et al., 2010; Edvardsen et al., 2011).

ii. Hypoxic Challenge Tests

There are several methodologies utilised in the delivery of HCT's, which have a variety of advantages and disadvantages. Most methods manipulate the FiO_2 of the supplied gas and this is contrary to the actual cabin environment, which involves exposure to a hypobaric environment. A hypobaric chamber is the only method that exposes individuals to the same factors as during air travel, which is achieved through reducing the barometric pressure, and therefore the partial pressure of oxygen. For many individuals, breathing a FiO_2 of 15% will induce a comparable decline in the PaO_2 that is representative of a cruising altitude of 8000 ft (2438 m). However, in this situation, gas in non-ventilated regions of the lung (bullae) will expand by around 38% according to Boyle's law (Gong Jr et al., 1984). This expansion within the lung can significantly impair ventilation of the communicating regions and further reduce an individual's PaO_2. This wouldn't be replicated by methods that utilise a FiO_2 of 15% at normobaric pressure.

Although the hypobaric chamber provides the most accurate method for the assessment of hypoxaemia during air travel, It is not routinely available for use in a healthcare setting due to cost, space, the need for highly trained staff to oversee their use and the significant health and safety (Mellor, 2011). Due to these reasons, the development of alternative

normobaric methods was needed using the manipulation of the FiO_2 to create the hypoxic environment.

An alternative approach to creating conditions similar to cabin pressure (8000 ft/2438 m) is to use a normobaric chamber (body plethysmographs) that are readily available within many respiratory physiology laboratories (The Association for Respiratory Technology & Physiology, 2012). This method uses nitrogen as the driving gas, which is fed into a plethysmograph (figure 1), which has the effect of diluting the atmosphere within the chamber to the required level (FiO_2 15%) (Cramer et al., 1996). Certain models of plethysmographs have small access ports through which the nitrogen can be entrained. These access ports are necessary for the passing through of sensors for pulse oximetry and/or transcutaneous monitor and are important for the measurement of FiO_2 for monitoring and adjustment to ensure both patient safety and accuracy of the simulation of air travel conditions. Furthermore, supplemental oxygen can be administered with this method for titration and corrective intervention.

Figure 1. Body Plethysmograph

Venturi masks are used in clinical practice for increasing the FiO_2 as part of the management of acute and chronic respiratory disorders (Corrado et al., 2016; Hardinge et al., 2015). This mask utilises the Bernoulli principle where 100% oxygen is driven through a small orifice within the mask causing the pressure lateral to the jet to become sub-atmospheric. Room air is subsequently drawn into the mask and mixed with the oxygen, which can be controlled though various valves to ensure the required FiO_2 is achieved. This technique can be adapted by substituting the 100% oxygen with 100% nitrogen and using a 40% valve to deliver an hypoxic mix that is close to an FiO_2 of 15% (Vohra and Klocke, 1993).

In Vohra and Klocke's seminal paper describing the Venturi mask method, it was reported that the oxygen concentration delivered by two different batches of the same model of commercially available Venturi mask was significantly different. Moreover, the second batch produced a significantly lower FiO_2 of approximately 14% which corresponds to an altitude of 10,000 ft.

Other problems have been reported with this methodology. If the total flow of the Venturi jet is less than the patient's inspiratory flow, then additional air will be drawn into the mask to satisfy the deficit. Venturi masks do not seal well and have large expiratory ports, ideally placed for entraining room air, and this coupled with nitrogen being 14% less dense than oxygen, promotes reduced ventilation leading to inaccuracies for FiO_2 (Johns et al., 1983).

In contrast to the previous HCT methods where the gas composite is produced through a device and flow arrangement, premixed 15% oxygen cylinder can be used through a Douglas bag and one-way valve configuration to provide a hypoxic environment to the subject (Gong Jr et al., 1984). This arrangement ensures that the FiO_2 is maintained at 15% considering the negligible degree of re-breathing due to the dead space within the mouthpiece. However, there several limitations with this method of assessment which include mouthpiece discomfort for the users, inducements of saliva affecting tidal volume (Vt) and ventilation (Ve), the ability to communicate with the patient and the ease at which the corrective supplemental oxygen can be titrated, as is not compatible with a nasal cannula used during air travel.

Hypoxic gas generators are another way of subjecting individuals to a hypoxic environment. This method of induced hypoxaemia is well established within exercise and performance institutes and has shown to increase endurance in the athletic population (Wilber, 2007). It is a relatively low cost system that is commercially available in the form of a hypoxic tent, and has been effectively utilised in performing HCT (Spurling et al., 2011).

iii. Patient prerequisite for HCT

In those patients with stable respiratory disease who have had no previous issues during air travel, the HCT is generally not considered. This is further endorsed by normoxia at sea level and no significant cardiac comorbidities (Ahmedzai et al., 2011). Interestingly, it is also considered unnecessary if an individual has had a previous HCT and assumes a similar outcome will ensue (no inflight oxygen or previous prescribed flow rate) unless their clinical condition has changed, where medical intervention is required. However, it is now becoming common practice for both travel insurance and airline companies to insist on a HCT 2-weeks prior to flight (European Lung Foundation, 2020).

Edvardsen *et al* studied a cohort of COPD patients and suggested that patients who significantly desaturate to below 84% whilst performing exercise, require supplemental oxygen during air travel (Edvardsen et al., 2011). In addition, it was recommended that patients with a resting SpO_2 of >95% with a maintained SpO_2 >84% during a 6MWT, do not require in-flight oxygen. Furthermore, the study suggested that an HCT is not required for patients who have a resting SpO_2 of between 92-95%, and desaturate >84% during exercise,

or who have a resting SpO_2 of <92%, however in-flight oxygen should be made available. All patients within this cohort had COPD with normocapnia and an in-flight oxygen flow rate of 2 l/min was assumed. There was no recommendation with regards to patients with type 1 or 2 respiratory failure.

There are limited data regarding ILD patients in terms of resting and ambulatory measures and the requirement for an HCT. There is poor correlation between in-flight oxygen requirement and resting SpO_2 in patients with extrathoracic restriction (Bandyopadhyay et al., 2010). This is further supported in a study of patients with lung and chest wall restriction (Ling et al., 2013), which advocated that patients with a SpO_2 <95% during moderate exercise would require further assessment by HCT. There is a similar finding for obese patients with hypoventilation syndrome, where resting oxygen values have no predictive value (Ali et al., 2011).

iv. COPD

COPD patients who are planning air travel need to be assessed not only for the respiratory condition, but also because of possible significant comorbidities (Naughton et al., 1995; Nicholson and Sznajder, 2014). The respiratory symptoms experienced during flight in these patients are common, however the HCT does not appear to be able to predict these symptoms in moderate to very severe COPD (Edvardsen et al., 2013). It is suggested that exacerbation of their comorbidities increases risk significantly of severe hypoxaemia, which is often cardiovascular in nature. This is comparable with data from studies that have looked

at both arrythmia and ischemic chest pain in COPD patients who become significantly hypoxic during commercial travel (Gong Jr et al., 1984; Berg et al., 1993). Resting oxygen status utilising PaO_2 and SpO_2 has limited predictive value to HCT outcome (Robson et al., 2008).

Spirometry has been used as a way of improving the predictive reliability of equations for calculation PaO_2 at altitude, however it is of limited benefit (Martin et al., 2007). Furthermore, it is limited in its ability to predict potential complications (Ergan et al., 2018).

v. MND

While MND is not specifically recognised as a respiratory disorder, much of the management is provided by specialist respiratory centres who treat the associated breathing difficulties (breathlessness).

There is limited evidence available in this group of patients, with some studies including both intra and extrapulmonary restriction. It has been suggested that absolute values for both spirometry and blood gases can be used to predict hypoxaemia. There was a limited powered study that looked at 21 kyphoscoliotic and neuromuscular patients undergoing HCTs (Mestry et al., 2009). The authors advocated that those with an FVC <1 litre with normoxia, are likely to significantly desaturate during air travel, requiring supplemental oxygen.

Over the past several years there has been several studies that have looked at parameters that can be used to predict HCT outcomes with MND patients (Crawford et al., 2015; Cliff et al., 2017; Humphreys et al., 2010; Brazzale et al., 2017). In one study looking at 40 MND patients who underwent HCT, the authors' found that parameters relating to respiratory failure (partial pressure of cardon dioxide and base excess) were the only independent predictors of HCT outcome. However, further work was suggested to identify absolute thresholds for patients requiring in-flight supplemental oxygen.

A pilot study of 12 patients with MND concluded that Sniff Nasal Inspiratory Pressure (SNIP), which is a measure of global muscular weakness may accurately predict hypoxaemia during commercial flight (Humphreys et al., 2010). This has been further supported by more recent work, which included resting SpO_2 with SNIP to accurately predict the risk of hypoxaemia at altitude (Brazzale et al., 2017). Interestingly, none of the patients who had a SNIP of >30cmH_2O or SpO_2 >96% failed the HCT (SpO_2 <85%).

vi. ILD

It has been confirmed that SpO_2 measured at sea level and at rest, does not reliably predict the outcome of a HCT in patient with ILD (Seccombe et al., 2004). Furthermore, following light exercise, the oxygen saturation falls significantly under normobaric hypoxia conditions (Christensen et al., 2002). These results are comparable with previous work, which showed that neither spirometry nor SpO_2 values at rest reliably predict significant desaturation at altitude to the level of required supplemental assistance (Coker et al., 2007). In addition, it

has also been reported that ILD patients are more likely to require unscheduled healthcare intervention relating to respiratory episodes, within 4 weeks of air travel. This may be due to these patients not adapting well to hypoxia, that diffusion is disproportionately affected by reduced partial pressure of oxygen at altitude, or that they receive less advice about self-management than patients with COPD.

The developed predictive equations for the calculations of PaO_2 at a FiO_2 of 15% have been used to assess patient with ILD (Martin et al., 2007). The authors found that the equations tended to overestimate the level of hypoxia and subsequent need for inflight oxygen, when compared to COPD or cystic fibrosis patients. This is not surprising considering that these equations have been based on the COPD population, which differs significantly in terms of pathophysiology.

The use of transfer factor for carbon monoxide (TLco) as a predictor of in-flight hypoxaemia for Idiopathic Pulmonary Fibrosis (IPF) patients has been demonstrated by a small study of 19 patients that looked at a number of parameters relating to pulmonary function testing (Cliff et al., 2016). They concluded that a TLco with a standardised residual of $\leq$-3.4 would suggest the need for in-flight oxygen but recognised that further work was required. They also recommend that the safest approach is to refer all patients with IPF for HCT assessment until more evidence-based data is available

More recently, Barratt and colleagues have looked at various physiological parameters for predicting HCT outcomes (Barratt et al., 2018). The two measures of interest centred around TLco and resting PaO_2 at sea level. The authors concluded that by combining the two parameters and using the thresholds of TLco >50% predicted and a PaO_2 >9.42 kPa independently predicted a successful HCT outcome. The proposed pre-flight algorithm for ILD patients suggested a sensitivity and specificity in the region of 86 and 84% respectively. For patients with a TLco of ≤50% predicted and PaO_2 of ≤9.42 kPa at sea level, in-flight supplemental oxygen was recommended without the need of an HCT. For patients whose sea level PaO_2 ≤9.41 kPa and TLco ≥50% predicted, an HCT is recommended.

vii. Future areas for research

In recent years the literature suggests there have been developments in three specific areas, which includes the value and role of the HCT in assessing an individual's need for supplemental oxygen during a commercial flight. Primarily, the research has centred on the accuracy of more readily available physiological parameters (lung function) in predicting hypoxaemia during air travel. There are clear benefits from using existing clinical data in terms of required equipment, consumables, and clinical staff time to perform an HCT. An HCT with a negative outcome will take approximately 30 minutes. This will increase to 60 minutes if there is a need to titrate for in-flight oxygen and up to 90 minutes if modality is to be assessed. However, spirometry requires 20 minutes, a 6MWT 30 minutes and Pulmonary Function Tests (PFT's) 45 to 60 minutes (The Association for Respiratory Technology &

Physiology, 2018). Furthermore, other parameters may be already available as part of the ongoing routine clinical care.

The second development has expanded on previous work that was COPD centric. There has been increased recognition that patients with alternative disorders behave differently in terms of their response to altitude related hypoxaemia. There is limited data regarding this, but there is increasing evidence that a 'one size fits all' approach is no longer supported (Cliff et al., 2016; Cliff et al., 2017).

The final area relates to the equipment used to deliver supplemental oxygen during commercial flights, which has changed considerably over the last decade with the increased availability of portable oxygen concentrators (POC). These devices are often supplied though a leasing arrangement by private means since many UK companies do not normally allow their equipment to be taken out of the country. In addition, prior airline approval is often required before departure (European Lung Foundation, 2020). With the development of technologies there has been a rapid progression in the range of POC available, which deliver varying flow rates and modalities (continuous and pulsed oxygen). As with static and ambulatory oxygen requirements at sea level (Hardinge et al., 2015), not all are suitable for all patients.

5. Aims

The aim of the original research project was to identify patients at increased risk of developing significant hypoxaemia during commercial flights and to assess the management of such hypoxaemia in line with modalities provided by the airlines. Currently individuals whose airline provides pulsed oxygen are not presently assessed for this method and assume continuous flow assessment.

The primary aim of the proposed research was to investigate to what extent in-flight hypoxia affects patients' symptoms and if exposure is detrimental to health.

The secondary aim of the study was to investigate the alternative pulsed method of oxygen delivery against the gold standard (continuous flow) and to offer this alternative method which is in keeping with the modality used by many airlines. In addition, the outcome of the HCT was to compared other physiological measures (e.g., overnight oximetry, supplemental physiological data, and health status questionnaire) and to investigate their predictive ability of HCT outcomes and consequences.

COVID-19

Originating as a cluster of unexplained cases of pneumonia in Wuhan, China, a novel coronavirus disease, officially named as COVID-19 by the World Health Organisation has now reached a pandemic level, which has affected countries across the world. To date (10th August 2020) over 19,845,788 cases and 731,263 confirmed deaths have been reported

(European Centre for Disease Prevention and Control, 2021). In the wake of this global health crisis stringent public health measures have been implemented to curtail the spread of COVID-19 (Adhikari et al., 2020).

One of the characteristics of COVID-19 has been the accelerated geographical spread of the virus from its initial appearance in Asia, and a lagged response in the rest of the world's regions. The majority of airlines tried to operate normal schedules until they were radically affected by travel restrictions, which resulted in a sudden drop of flight numbers from mid-March 2020 onwards (Lau et al., 2020). This was predominantly due to lockdowns and border closures that formed part of the policy across Europe and America.

At a local level, the University Hospitals of North Midlands NHS Trust suspended all recruitment to the studies that it sponsored. This was primarily to address the current potential implications of the COVID-19 outbreak on the patient population that it serves, and to mitigate the impact of COVID-19 sponsored studies.

The resulting effect of the above jeopardised the viability of delivering the initial aims of the research. To this end, alternative arrangements were sought through discussion with Manchester Metropolitan University and the local Trust's Research and Development Department. Therefore, the project would use retrospective data that had been collected from a similar cohort of patients who attended the respiratory physiology service for an HCT.

Revised aim

Primary outcome: To examine differences in physiological and HCT outcomes in patients with ILD, MND and COPD.

Secondary outcome: To investigate whether physiological parameters can predict HCT pass or failure in ILD, MND and COPD patient groups.

6. Methods

a. Design

The respiratory physiology service receives requests for investigation and assessments from both primary and secondary care. This activity is managed within the Trusts patient administration system (PAS). The investigations/assessments are bundled together, which reduces the number of appointments the patient is required to attend. Following the completion of the test, the results are captured on the departments SQL database where they can be interrogated in terms of patient demographics, disease characteristics, physiological measures, assessment, and treatments. Furthermore, this data is captured by the Trusts clinical dashboard (iPortal), which holds all other clinical and non-clinical information.

Patients referred into respiratory physiology from January 2010 to February 2020 for an HCT from either the MND, ILD or COPD services, were included in the study. Variables were selected based on the clinical management of these patient in line with their disease specific pathway. These variables included demographics (age, sex, and BMI), smoking history, pulmonary function (spirometry, static lung volumes, transfer factor), respiratory muscle strength and functional status (6MWT).

Retrospective database analysis was used to identify the patients who performed an HCT within the study period. Other physiological measures were obtained from the same database, which included absolute, percent predicted and standardised residual values.

Patients without a confirmed diagnosis of MND, ILD or COPD were excluded from the study. Individuals who were unable to perform valid technical acceptable manoeuvres or obtain consistent valid results were also removed.

This retrospective observational database study was performed on data obtained during the routine clinical practice and formed part of the patient's ongoing clinical care. As such, the study was deemed exempt from formal ethical approval.

b. Participants

Due to the COVID-19 pandemic and its effect on delivering the original proposed prospective research, the participants were now selected retrospectively from the respiratory physiology database dating back 10 years. The patients must have had a primary diagnosis of either MND, ILD or COPD and attended the department for an HCT as part of their routine clinical care with the appropriate physiological data as dictated by their routine clinical pathways (table 3). The Trust provides specialised commissioned MND and ILD services, which ensures accurate diagnosis for those disorders. Furthermore, the specific COPD clinics confirmed the other studied group.

All the participants in the MND group had muscular degeneration, with extrathoracic patients excluded (kyphoscoliosis and chest wall deformities). The ILD group was predominantly made up of idiopathic pulmonary fibrosis (48/56) with the remainder being usual interstitial pneumonia (UIP). The COPD group had varying levels of obstruction with

many of the referred patients having confirmed emphysema. Due to the homogeneous nature of COPD, this group was the most diverse and lack a standard phenotype.

Disorder	Investigations
MND	HCT, Dynamic Spirometry & SNIP
ILD	HCT, Dynamic Spirometry, Static Lung Volumes, Transfer Factor & 6MWT
COPD	HCT, Dynamic Spirometry, Static Lung Volumes, Transfer Factor, 6MWT & SNIP

Table 3. Investigations as part of routine clinical pathway.

MND and ILD disorders are characterised by a restrictive ventilator defect and presents with a reduced FEV_1 and FVC with a preserved FEV_1/FVC ratio on dynamic spirometry. The restriction in MND is due to a reduced respiratory muscular strength, which is required to overcome the elastic forces of the inward pull of the lung. Conversely, in ILD, the fibrotic nature of the lung reduces the compliance and the lungs' ability to inflate. Both produce the same restrictive pattern, but with completely different pathophysiology (figure 2 – a). The COPD patient presents with airflow limitation cause by a narrowing the bronchial airways, which manifests as an obstructive defect (reduced FEV_1, FEV_1/FVC ratio and preserved FVC) (figure 2 – b). These pathophysiological abnormalities are often confirmed with static lung volumes. Both MND and ILD showing reduced values and COPD with increased/hyperinflation.

a b

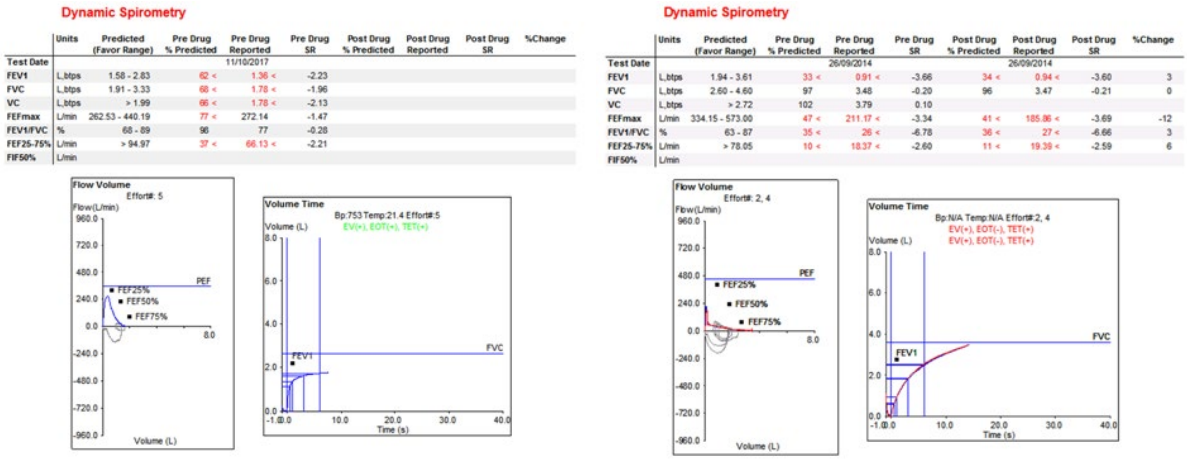

Figure 2. Spirometric traces and representation for (a) restriction and (b) obstruction

c. Investigations

HCT

The HCT assumes that breathing hypoxic gas mixtures at sea level (normobaric hypoxia) equates to the hypobaric hypoxia at altitude. The maximum cabin altitude of 8000 ft (2438 m) can be simulated at sea level with a gas mixture containing 15% oxygen in nitrogen. Subjects are usually asked to breathe the hypoxic gas mixture for 20 minutes or until equilibration. Oxygen saturation (SpO_2) is monitored throughout, and blood gas tensions measured before and on completion. An FiO_2 of 15% oxygen is administered by a Venturi mask and 40% valve with nitrogen as the driving gas. The entrained air dilutes the oxygen producing a 14–15% mixture. A subject is usually judged to require in-flight oxygen if the PaO_2 falls below 6.6 kPa or SpO_2 falls below 85%. These figures appear purely arbitrary with

no supporting evidence, but many physicians have adopted them as a reasonable compromise. Hypoxic challenge testing is the pre-flight test of choice for patients with hypercapnia.

Procedure

The patient is seated with all relevant details obtained. A vasodilator is then applied to the earlobe and a blood gas taken 15 minutes after or when the earlobe becomes sufficiently perfused. If the patients' PaO_2 is below 7.3 kPa or they are currently receiving long-term supplementary oxygen the patient is to be directly assessed for in-flight oxygen requirements by oxygen titration utilising a nasal cannula and the equipment arrangement below.

The patient is fitted with a pulse oximeter and the equipment prepared for assessment (mask, valve, and cylinder). They are connected to the 100% nitrogen via the venturi mask/40% valve (red) for a period of 20 minutes (figure 3). Both SpO_2 and heart rate are monitored during the period with blood gases taken at the end. However, if SpO_2 drops below 85% a blood gas is taken, and the assessment terminated.

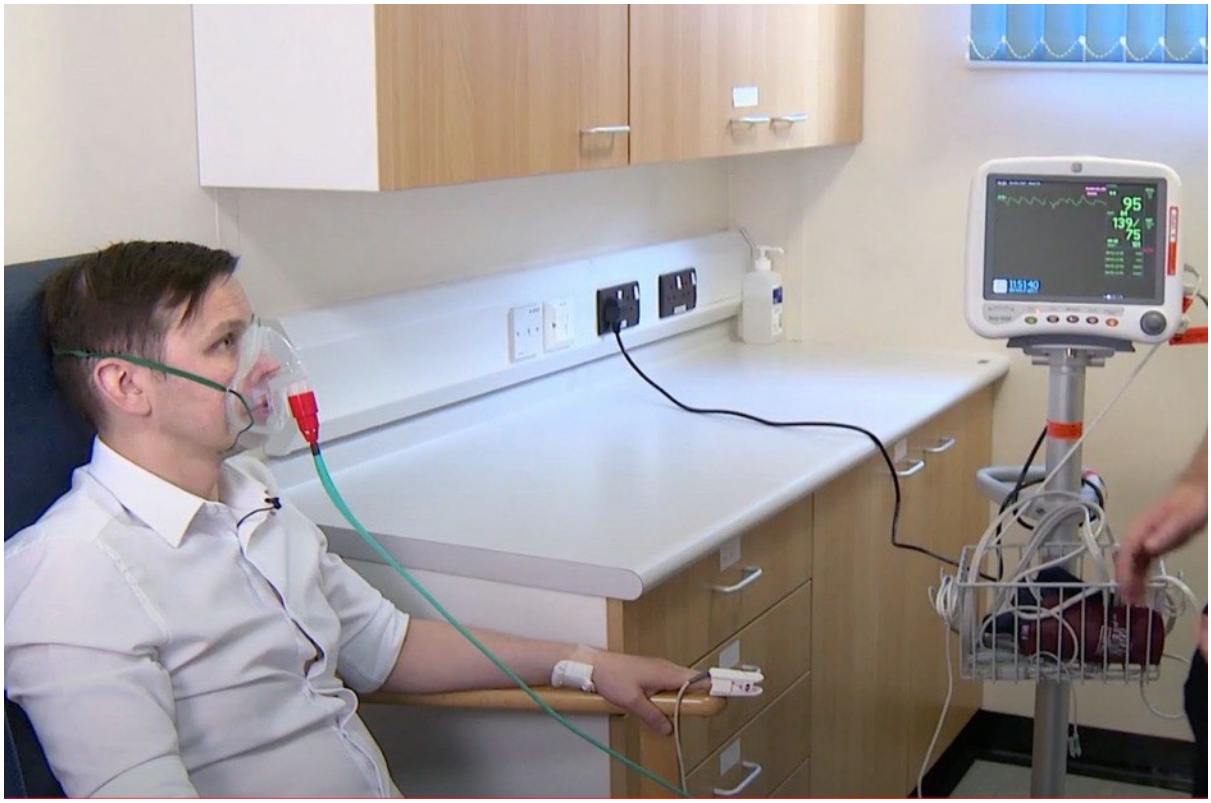

Figure 3. Patient undergoing a HCT (European Lung Foundation, 2020). Reproduced with permission from the European Lung Foundation.

If the patients' PaO_2 is maintained above 6.6 kPa, they would be deemed fit to fly. However, if the PaO_2 drops below 6.6 kPa, the assessment would be repeated with the patient using a nasal cannula set at 2 litres/min for the duration of assessment. The objective of titration is to maintain a PaO_2 above 8.0 kPa. If a PaO_2 of 8.0 kPa or above is not achieved, the assessment would be repeated setting the flow rate to 4 litres/min via nasal cannula.

As previously discussed, there are several advantages and disadvantages between the methodologies in performing an HCT. The 'gold standard' hypobaric chamber is expensive and generally inaccessible within clinical practice. The Venturi mask driven by 100% nitrogen

can be variable and is dependent on ventilation and tidal volume, which are inherently altered by the wearing of a mask. However, this method was chosen due to its ease of use, tolerated well by the patient, ability to titrate corrective oxygen and is routine practice within the respiratory physiology service.

Dynamic spirometry

Dynamic spirometry is a physiological test that is predominately used to investigate airway obstruction within the lung (figure 4). It is an essential tool in the screening of general respiratory health, assisting in diagnosis and the monitoring of many respiratory diseases. In addition, it is embedded within numerous patient pathways (National Institute for Health and Care Excellence, 2010; National Institute for Health and Care Excellence, 2015) and its uses can also be extended to both intra and extrathoracic abnormalities, which present as restrictive pattern (National Institute for Health and Care Excellence, 2013; Godfrey and Jankowich, 2016; National Institute for Health Care Excellence, 2016).

Figure 4. Patient undergoing spirometry testing (British Lung Foundation, 2020). Reproduced with permission from the British Lung Foundation

The primary signal is flow, which is measured when a patient forcefully blows into the spirometer. The signal is then mathematically modelled (integration) to calculate volume. Conversely, when volume is the initial measure, differentiation is used to calculate the flow. However, the latter is generally considered outdated due to the advances in technology, which has made flow measuring devices more stable, accurate and cost effective (Graham et al., 2019). The equipment used for this study were flow measuring devices that had the capability of calculating volume.

Procedure

The patient is seated in an upright chair (arms) with their feet flat on the floor with legs uncrossed. Any tight fitting clothing is loosened and dentures left *in situ* to maintain structure (Moore, 2012).

Encouragement is essential at the initial phase of the blow, and more importantly at the end of the manoeuvre. The patient needs to keep blowing until the volume-time trace reaches a plateau with <50 mls been exhaled in two seconds.

SNIP

SNIP is a non-invasive assessment of inspiratory muscle strength that requires a patient to perform a short, sharp sniff manoeuvre (figure 5). A bung is inserted into one of the nostrils and connected to a pressure transducer via a catheter, which is able to measure nasal inspiratory pressure (Heritier et al., 1994). The nasal cavity acts like a starling resistor with flow remaining relatively low through the un-occluded nostril irrespective of the driving pressure. The pressure measured at the nostril relates to intrathoracic pressure and subsequently inspiratory muscle strength (Sylvester et al., 2020). SNIP is volitional that requires the patient to be both cooperative and motivated. When competently performed, it is a useful tool for the exclusion of respiratory muscle weakness when pressures are within the normal reference range. Although reduced values are indicative of muscle weakness, poor test performance could also be a contributing factor that if used in isolation, could over diagnose muscle weakness (Steier et al., 2007).

There are reference ranges to assist in defining respiratory muscle weakness, which are based on gender and age (table 4). However, it is common practice to consider a value <-60 cmH_2O is consistent with respiratory muscle weakness (Celli, 1989).

	Mean (cmH_2O)	Lower limits of normal (LLN)
Male	(-42 x age) + 126.8	23.8 x 1.645
Female	(-22 x age) + 94.9	17.1 x 1.645

Table 4. Mean reference values and LLM for SNIP (Uldry and Fitting, 1995)

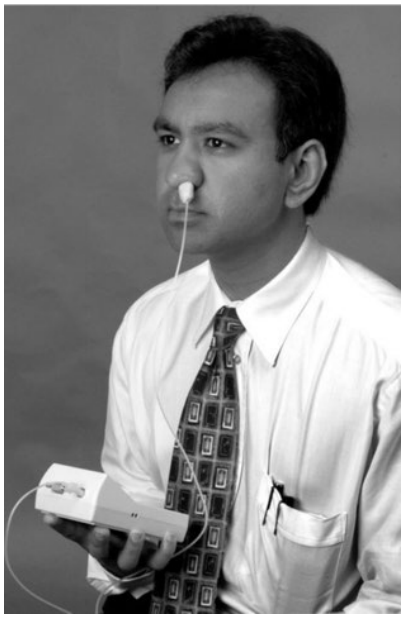

Figure 5. Patient performing SNIP (Mustfa and Moxham, 2001). Reproduced with permission from the author.

Procedure

Prior to performing the investigation, information is sought regarding nasal patency and possible upper airway obstruction. The patient is asked to blow their nose to clear any congestion as this will improve the accuracy of the test. The subject is seated, and the bung

wedged firmly in the patient's nostril. They are instructed to take a short, sharp maximal sniff starting from the end tidal position (Functional Residual Volume), with the maximum achievable peak pressure measured, which is within 0.5 seconds in duration. Due to the familiarity of the manoeuvre, patients usually obtain reproducible results within 10 attempts, however at least 3 additional attempts are performed if the last measurement is the largest.

Static lung volumes

The volumes of the lungs (figure 6) are measured directly through spirometry, however many of the indices of the breathing cycle require alternative methods to calculate parameters such as residual volume (RV), functional residual capacity (FRC) and total lung capacity (TLC). The measurement of these subdivisions is useful in differentiating between obstructive and restrictive ventilatory defect, and also essential in defining hyperinflation (Walker et al., 2014). There are several methods of measuring static lung volumes (SLV), which include whole body plethysmography, helium dilution and nitrogen washout. For this study, nitrogen washout was the technique of choice due to its routine use in clinical practice.

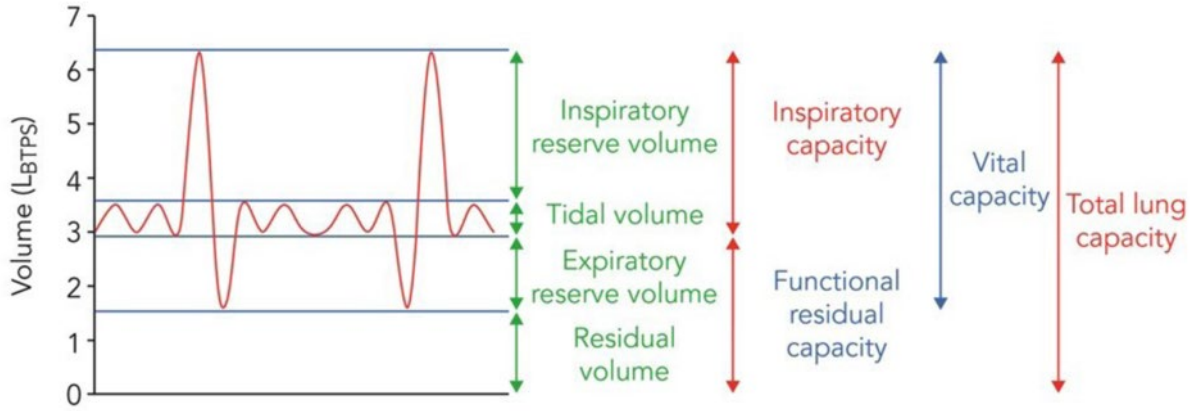

Figure 6. Static lung volumes shown on a spiromogram (Sylvester et al., 2020).

Body plethysmography

The gold standard for the measurement of SLV is whole body plethysmography, which is based on Boyles law, which states that at a constant temperature, the volume (V) of a given mass of an inert gas is inversely proportional to its pressure (P), PV = K. K is a constant that is proportional to the mass of the gas and it's absolute temperature (Miller et al., 2005). This method measures the total gas volume (TGV) within the thoracic area by treating the lungs as a closed compartment, and simultaneously measuring alveolar pressure and changes in volume. The main advantage of this method is that it can measure unventilated areas within the lungs such as bullae.

Procedure

The patient is placed in a body plethysmograph sitting upright with their head in the neutral position wearing nose clips. The door is closed, and sufficient time allowed for thermal equilibrium prior to commencement of the test. The patient is asked to breathe normally on

a flanged mouthpiece with the flat of their hands placed against their cheeks. The shutter is then closed at the end tidal expiration with the patient being asked to pant gently against the occlusion at one breath per second. The measurement and subsequent plot of ΔP_{mouth} verses ΔP_{box} is displayed. Once the shutter is released the patient performs a relaxed vital capacity. This is repeated at least three times to ensure reproducible results are obtained (within 5%). These values are then used to calculate volumes and capacities of the breathing cycle.

Nitrogen washout

The routine alternative method is nitrogen washout. At end-tidal expiration the volume within the lungs is unknown, however it is acknowledged that the gas within this volume contains approximately 79% nitrogen and by measuring this volume of nitrogen, the FRC can be determined. Nitrogen washout was the method of choice within the study, with whole body plethysmograph used if the dilution method was not obtainable.

Procedure

The patient is connected to the equipment via a mouthpiece whilst wearing a nose clip. Once stable tidal breathing is obtained, the subject is switch into to 100% oxygen at the end of tidal expiration. Continuous breathing of the 100% oxygen mix ensues until the concentration of nitrogen falls below 1.5% for three consecutive breaths. The calculation of FRC can be seen below (figure 7). A minimum of three technically acceptable vital capacity

measurements are taken and used in conjunction with the FRC calculation allowing the remaining capacities and volumes to be determined (Robinson et al., 2013).

$$FRC = \frac{(V_E N_2 - V_t N_2)}{(F_I N_2 - F_t N_2)}$$

$V_E N_2$ = Total cumulative volume of exhaled nitrogen
$V_t N_2$ = Volume of nitrogen excreted from the tissues into the lungs during test
$F_I N_2$ = Initial end tidal nitrogen concentration
$F_t N_2$ = Final end tidal of exhaled nitrogen

Figure 7. Calculation of FRC.

Transfer factor

The primary role of the lungs is to upload oxygen and offload CO_2 between the atmosphere and the pulmonary circulation. The ability of the lungs to exchange gas across the alveolar capillary membrane is determined by lung volume, membrane thickness, surface area and the capillary blood volume. Functionally, it is influenced by the ventilation and perfusion of the lung, chemical reaction rate with haemoglobin, blood transit time and **alveolar** capillary membrane characteristics. Within respiratory physiology services the assessment of these processes is by utilising the transfer factor technique. Carbon monoxide (CO) is used as a surrogate for oxygen due to its similar diffusion coefficients and rate of reaction with haemoglobin. In addition, CO has an increased affinity for haemoglobin (>210 times), which

means that the PaO_2 remains in the physiological state and does not influence the measurement.

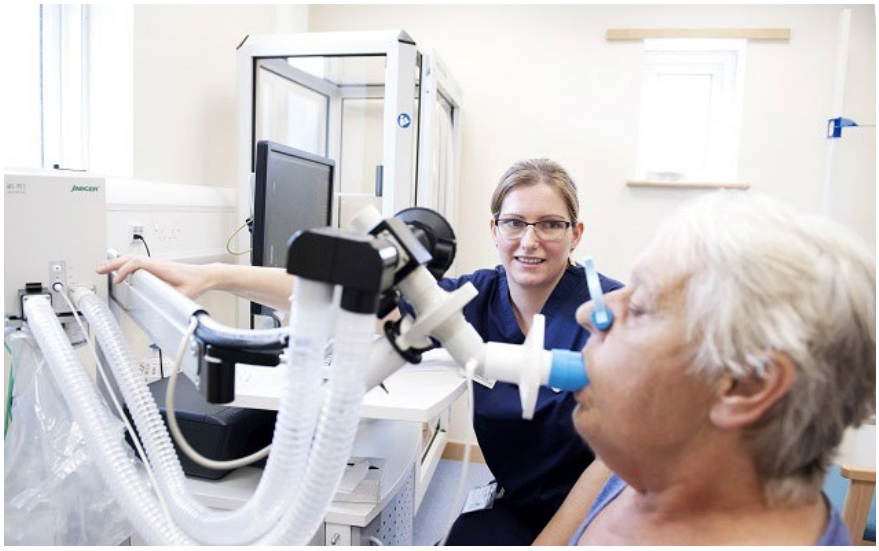

Figure 8. Patient undergoing pulmonary function tests (spirometry, static lung volumes & transfer factor (Royal Papworth NHS Trust, 2020). Reproduced with permission from Royal Papworth NHS Trust

Gas transfer is based on Fick's law of diffusion which states that 'the rate of transfer of the gas through a membrane of constant thickness is proportional to the surface area (A) and the difference in gas partial pressure between the two sides ($P_1 – P_2$), and inversely proportional to the membrane thickness (t)'. Therefore, TLco is the product of the rate of CO uptake (Kco) and the alveolar volume (V_a) (Pellegrino et al., 2005). V_a is measured by utilising an inert gas, which is either helium or methane. Review of Kco and V_a individually provides information on disease pathology.

Procedure

The patient is connected to a pneumotach and rapid gas analysers by a mouthpiece (figure 8). They are asked to exhale maximally to residual volume and then asked to inspire maximally to TLC, which is when the trace and inert gases are administered. A breath hold of approximately 10 seconds is performed to allow a standard time for gas diffusion and interaction with the haemaglobin. This is then followed by a complete exhalation where the initial sample is discarded due to its relation to the conducting section of the lungs (airways). After the dead space gas is discarded, a sample representing the respiratory zone of the lungs (alveolar) is obtained for analysis, which consists of between 500 and 1000 ml. The remainder is then superfluous and discarded. The equations in figure 9 is then used to calculate the parameters.

$$V_A = (V_{IN} - V_D) \times \frac{F_1 Tr_1}{F_A Tr_2} \times BTPS$$

$$\mathrm{T_{LCO}=V_A x \left(\frac{1}{t\ x Pb^{*}} x \ln \left[\frac{F_A CO_0}{F_A CO_t} \right] \right)}$$

Figure 9. TLco and Va calculations (Sylvester et al., 2020).

6 Minute Walking Test

The 6MWT is part of a group of tests that come under the heading of field exercise testing. It provides measures of SpO_2 and heart rate, distance and the subjective measures of breathlessness and fatigue (Enright, 2003; Borg, 1998). It is a useful assessment of functional status and is key in the monitoring and management of long-term respiratory

conditions. In addition, it is a non-invasive procedure that is generally well tolerated by adults of all ages. The purpose of this test is to monitor physiological measures and symptoms pre, during and post walking for 6 minutes and can determine desaturation on exercise, which may highlight disease progression and the requirement for ambulatory oxygen (Hardinge et al., 2015).

Procedure

The patient has an oximeter placed on their wrist and finger and sufficient time allowed for stable SpO_2 and HR measurements. Furthermore, values for breathlessness and fatigue are obtained pre and post walk using the Borg breathlessness score (Borg, 1998). The following instructions should be relayed to the patient.

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

The patient is then asked to walk back and forth around two cones that are at least 10 meters apart in a corridor or hallway. During the walk the specific encouragement below should be given to the patient (Enright, 2003).

After the 1st minute: “You are doing well. You have 5 minutes to go.”
When the timer shows 4 minutes remaining: “Keep up the good work. You have 4 minutes to go.” When the timer shows 3 minutes remaining: “You are doing well. You are halfway done. When the timer shows 2 minutes remaining: “Keep up the good work. You have only 2 minutes left. When the timer shows 1-minute remaining: “You are doing well. You only have 1 minute to go. With 15 seconds to go: “In a moment I’m going to tell you to stop. When I do, just stop right where you are, and I will come to you.” At 6 minutes: “Stop”. If the participant stops at any time prior, you can say: “You can lean against the wall if you would like; then continue walking whenever you feel able.”

The resting values for SpO_2, HR, breathlessness and fatigue are reported along with changes observed during and post walk. Additional comments are also included which generally relate to rests (occasions and reason/s) and other clinically relevant information.

Regression equations

The respiratory physiological measurements made within this study have been compared to reference values, which are based on ethnicity, sex, age, and height of the subjects. This

comparison gives detail regarding abnormality, along with the severity. Conversely, it also highlights normal function. The two main methods of representing comparison with the reference values is percent predicted, where the means of the reference and measured parameter are expressed in terms of percentage difference, with 100% signifying the same means (measured and predicted). In addition, the use of standardised residuals or z-scores was also included, which describes the values relation to the reference range. A value of ±1.645 defines the upper and lower limits of normal and represents the fifth percentile. The reference ranges used whilst performing spirometry, static lung volumes and transfer factor were based on the European Community for Coal and Steel (Quanjer et al., 1993). However, as part of the data validation, both spirometry and transfer factor values were converted to the Global Lung Initiative (Quanjer et al., 2012; Stanojevic et al., 2017), which are considered more relevant. Unfortunately, the static lung volume set was not available at the time of analysis and the writing of this thesis.

d. Statistics

Descriptive statistics were obtained to summarise participants characteristics. Categorical variables were summarised using number and percentages. Continuous measures were represented using mean ± standard deviation (SD) or median and interquartile range (IQR). Univariate analysis of factors associated with the hypoxic challenge test (pass or fail) where performed. Data screening (including identification of outliers) was carried out prior to univariate analysis. Normality probability plot were used to identify applicable departures from normality, which included the assessment of outliers, skewness, and kurtosis.

Univariate analysis was performed using independent paired T test (parametric), Mann Whitney U test or Kruskal-Wallis (non-parametric) and chi squared test (categorical data) as appropriate. Estimates of the odds ratio (OR) and associated 95% confidence interval (CI) for categorical predictors indicating their relative association with the likelihood of failure to the hypoxic challenge test were derived. Significant variables identified from the univariate analysis were combined for further multivariate analysis using a p-value of <0.05.

Logistic regression was performed to evaluate independent physiological parameters for hypoxic challenge test failure. Predictive variables were included in the regression model using a block wise forced enter method to evaluate estimates of OR's. All statistical analysis was conducted utilising Minitab 19 (Minitab 19 Statistical Software, 2019). A p-value of 0.05 was considered statistically significant.

e. Data confidentiality

Identifiable/personal information was accessed, processed, and stored securely in line with models of trust and confidentiality in accordance with legal requirements and best practice including the Data Protection Act (1998), the Caldicott Principles and the Information Governance Toolkit standards. These requirements were consistent with the University Hospitals of North Midlands NHS Trust Data Protection Policy (IG10).

Confidentiality was safeguarded during and after the study. Individual data was anonymised and given a research code known only to the researcher. No personal data was stored on

computer files, and a master list identifying participants and their subject number recorded as a hard copy and held in a locked filing cabinet (along with the consent form) accessed only by the researcher. All data recorded on paper was stored in a separate locked cabinet accessed only by the researcher. In addition, electronic data was protected by an NHS password computer known only to the researcher.

Physiological measurements requiring the use of a portable laptop had encrypted security, and was password protected. All possible data was uploaded onto a secure server and removed locally on all devices in a timely manner. Authorised persons such as researchers within the team, supervisors, sponsors and for monitoring the quality and for audit purposes, regulatory authorities/NHS Research & Development had access to data (as stated on the consent form).

7. Results

Two hundred and twenty-five patients referred into respiratory physiology for an HCT between January 2010 to February 2020 were incorporated in the study. The included patient groups all had an HCT with the relevant physiological measures as directed by their disease pathway at the time of assessment. The number entered into the study were based solely on the individuals who met the entrance criteria. However, the numbers realised within this thesis represent a significant move forward in terms of the number of participants included when compared to previous research. The power calculation for the different groups 98% (MND), 78% (ILD) and 73% (COPD), demonstrating the results were significantly powerful enough to detect an effect. Of these, 118 had a confirmed diagnosis of MND, 56 of ILD and 51 with COPD. Sixty-nine variables were measured, including demographic and clinical measures for the ILD and COPD groups. The MND group consisted of 17 variables as per clinical practice. The clinical characteristics of the cohorts are shown in table 5, which includes both continuous and categorical data with the p value showing the difference across the groups.

Variable	MND	ILD	COPD	p-value
Patients	118	56	51	
Age years	63.00 (12.99)	69.50 (7.05)	66.00 (9.24)	<0.001
M/F	77/41	41/15	27/24	0.088
Pack/Years	10.00 (13.41)	25.00 (26.69)	28.50 (37.49)	<0.001
BMI kg/m^{-2}	24.97 (5.12)	28.04 (29.77)	26.53 (9.62)	0.010
Spirometry				
FEV1 litres	1.94 (0.85)	1.91 (0.65)	1.13 (0.61)	<0.001
FEV1 z-Score	-2.28 (1.80)	-1.43 (1.14)	-3.36 (1.37)	<0.001
FEV1 % pred.	65.93 (25.72)	76.10 (19.19)	44.76 (25.55)	<0.001
FEV1 <80% pred.	61 (70)	30 (56)	35 (90)	0.001
FEV1 <-1.645	55 (63)	26 (48)	34 (87)	0.001
FVC litres	2.46 (1.05)	2.54 (0.84)	2.62 (0.95)	0.676
FVC z-score	-2.60 (1.95)	-1.87 (1.19)	-1.78 (1.65)	0.011
FVC % pred.	64.59 (24.35)	70.80 (18.11)	74.24 (23.13)	0.059
FVC <80% pred.	64 (74)	37 (69)	23 (59)	0.049
FVC <-1.645	57 (66)	33 (61)	21 (54)	0.384
FEV1/FVC	0.81 (0.11)	0.81 (0.08)	0.48 (0.16)	<0.001
FEV1/FVC <70%	9 (10)	1 (2)	39 (100)	<0.001

Legend

Pack years	Clinical quantification of cigarette smoking (packs/years)
BMI	Body Mass Index (kg/m^{-2})
FEV_1	Forced expiratory volume in one second (litres)
FVC	Forced vital capacity (litres)
FEV_1/FVC	Ratio to define obstructive or restrictive disease
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Categorical data - (Chi-squared test**)**

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	MND	ILD	COPD	p-value
Transfer factor				
TLco mmol/min/kPa		3.66 (1.04)	4.82 (2.15)	0.103
Tlco z-score		-3.74 (1.19)	-2.49 (2.81)	0.379
Tlco % pred.		49.24 (11.72)	64.33 (21.84)	0.043
Tlco <80% pred.		27 (93)	10 (67)	0.010
Tlco <-1.645		26 (90)	10 (67)	0.029
Tlco/Va ml/min/kPa		1.03 (0.30)	0.95 (0.37)	0.207
Tlco/Va z-score		-1.60 (1.39)	-2.63 (2.28)	0.379
Tlco/Va % pred.		76.65 (20.91)	65.72 (26.61)	0.181
Tlco/Va <80% pred.		20 (71)	10 (67)	0.660
Tlco/Va <-1.645		14 (48)	9 (60)	0.608
Lung Volumes				
TLC litres		4.04 (1.20)	6.47 (1.49)	<0.001
TLC z-score		-2.97 (1.83)	0.65 (1.64)	<0.001
TLC % pred.		66.41 (12.97)	98.65 (30.52)	0.001
TLC <80% pred.		25 (86)	1 (6)	0.004
TLC <-1.645		25 (86)	1 (6)	0.004
RV litres		1.09 (0.38)	2.73 (0.79)	<0.001
RV z-score		-3.09 (0.80)	-0.54 (2.22)	<0.001
RV % pred.		50.0 (13.0)	109.0 (42.1)	<0.001
RV <80 Pred.		29 (97)	1 (6)	<0.001
RV <-1.645		29 (97)	1 (6)	<0.001
RV/TLC		30.55 (7.21)	45.88 (7.54)	<0.001
RV/TLC z-score		-2.12 (1.25)	0.48 (1.97)	<0.001
RV/TLC % pred.		70.0 (17.3)	105.5 (32.7)	0.001
RV/TLC <80 pred.		17 (58)	1 (6)	0.251
RV/TLC <-1.645		17 (58)	1 (6)	0.015

Legend

TLco	Transfer factor of the lungs for carbon monoxide (mmol/min/kPa)
TLco/Va	Carbon monoxide coefficient ml/min/kPa). Also known as Kco
TLC	Total lung capacity (litres)
RV	Residual volume (litres)
RV/TLC	Ratio to define hyperinflation
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Categorical data - (Chi-squared test)

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	MND	ILD	COPD	p-value
Patients	118	56	51	
pH (21%)	7.43 (0.03)	7.42 (0.03)	7.43 (0.03)	0.448
$PaCO_2$ (21%) kPa	5.45 (0.85)	5.17 (0.47)	5.22 (0.75)	0.002
PaO_2 (21%) kPa	10.12 (0.12)	9.46 (1.05)	8.68 (1.01)	<0.001
HCO_3 (21%) mmol/l	26.70 (2.72)	25.20 (1.39)	26.20 (1.56)	<0.001
BE (21%) mmol/l	2.80 (2.95)	1.05 (1.74)	2.00 (2.18)	<0.001
SaO_2 (21%) %	95.00 (1.47)	95.00 (2.36)	94.00 (2.55)	<0.001
tHb (21%) g/dl	152.11 (14.48)	154.02 (17.81)	151.41 (16.24)	0.665
pH (15%)	7.44 (0.38)	7.43 (0.03)	7.45 (0.05)	0.118
$PaCO_2$ (15%) kPa	5.22 (0.82)	4.94 (0.43)	5.09 (0.86)	0.018
PaO_2 (15%) kPa	7.46 (1.01)	6.72 (0.75)	6.48 (0.92)	<0.001
HCO_3 (15%) mmol/l	26.50 (2.93)	25.20 (1.27)	26.60 (1.70)	<0.001
BE (15%) mmol/l	2.70 (3.03)	0.80 (1.59)	2.70 (2.27)	<0.001
SaO_2 (15%) %	91.00 (3.43)	88.00 (3.23)	88.00 (4.80)	<0.001
pH (28%)	7.42 (0.36)	7.41 (0.02)	7.42 (0.04)	0.418
$PaCO_2$ (28%) kPa	6.20 (0.87)	5.41 (0.50)	5.58 (0.81)	<0.001
PaO_2 (28%) kPa	11.70 (2.56)	11.38 (2.53)	8.94 (2.25)	0.002
HCO_3 (28%) mmol/l	28.00 (3.77)	25.30 (1.50)	26.60 (1.63)	<0.001
BE (28%) mmol/l	4.15 (3.46)	1.30 (1.93)	2.80 (2.12)	<0.001
SaO_2 (28%) %	97.00 (4.15)	97.00 (2.12)	95.00(2.31)	0.184

Legend

pH	Acidity scale
PaO_2	Partial pressure of oxygen within arterial blood (kPa)
$PaCO_2$	Partial pressure of carbon dioxide within arterial blood (kPa)
HCO_3	Bicarbonate within the blood (mmol/l)
BE	Base excess is the amount of H+ ions required to return blood pH to 7.35 (mmol/l)
tHb	Total haemoglobin within the blood (g/dl)
SaO_2	Oxygen saturation (%)
(21%)	Fractional inspired oxygen (FiO_2) 21%
(15%)	Fractional inspired oxygen (FiO_2) 15%
(28%)	Fractional inspired oxygen (FiO_2) 28%

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	MND	ILD	COPD	p-value
6MWT Distance		341.50 (129.50)	387.00 (136.80)	0.955
6MWT Dis % pred		72.88 (27.13)	77 (29.30)	0.916
6MWT Dis <80 pred		24 (63)	3 (60)	0.756
SaO2 rest		96.24 (1.74)	95.20 (2.86)	0.473
SaO2 Ex		88.97 (4.23)	89.60 (3.85)	0.749
Recover time/sec		60.00 (51.06)	60 (1.58)	0.011
Desaturation diff.		-7.00 (3.98)	-4.00 (3.65)	0.437
Desaturation diff >4		25 (66)	2 (40)	0.333
HCT pass/fail	94/24	27/29	19/32	<0.001
SNIP	-41.34 (25.77)		-63.00 (5.66)	0.133

Legend

6MWT Distance	Distance walked in 6 minutes (m)
6MWT Dis % pred	Percentage waked of predicted distance (%)
SaO_2 (rest)	Oxygen saturation at rest (%)
SaO_2 (ex)	Oxygen saturation during walk/exercise (%)
Recovery time	Time for SaO_2 to returned to basline (rest) value (second)
Desaturation Diff. %	Difference from rest and walk/exercise SaO_2 (%)
HCT pass/fail	Hypoxic challenge test – number who passed vs number who failed
SNIP	Sniff nasal inspiratory pressure (cmH_2O)

Categorical data - (Chi-squared test)
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Table 5. Continuous and categorical data of variables all groups.

All Groups (MND, ILD & COPD)

There were significant differences between disease specific groups for all demographic and lifestyle measures (Table 5), except for male/female ratios. Spirometric data showed significant differences between disease groups for, FEV_1 percent predicted (p = <0.001), FEV_1 z-score (p = <0.001), levels of abnormality by percent predicted (p = 0.001) and z-score (p = 0.001). FVC z-score (p = 0.011), FEV1/FVC ratio (p = <0.001) and the assessment of obstruction were significantly different (FEV1/FVC <70%) (p = <0.001). No significant differences were found in measured FVC and the derived level of abnormality by z-score, however FVC <80% predicted showing a borderline difference (p = 0.049).

When comparing ILD and COPD groups, no significant differences were found in the following transfer factor measures: TLco (p = 0.103); TLco z-score (p = 0.379); Kco (p = 0.207); Kco z-score (p = 0.379); Kco percent predicted (p = 0.181); Kco <81% predicted (p = 0.660); and Kco <1.645 standard deviations (p = 0.608). The assessment of TLco for abnormality using <80% predicted (p = 0.010) and z-score (0.029) demonstrated differences between the two groups. There was significant difference for TLco percent predicted (p = 0.043).

Comparing indices of static lung volume capacities between ILD and COPD groups revealed significant differences, except for RV/TLC ratio <80% predicted (p = 0.251). This was also observed for the 6MWT data apart from recovery time relating to SpO_2 from desaturation (p

= 0.011). The latter is a consequence of the limited number of participants in the COPD group performing the investigation (6MWT).

The blood gas values showed no significant difference for pH on resting (FiO_2 21%) (p = 0.448), whilst breathing hypoxic mix (FiO_2 15%) (p = 0.118), titration (FiO_2 28%) (p = 0.418) and tHb (p = 0.665). There was also no significant difference in response to supplemental oxygen (FiO2 28%) as measured by SpO_2 (p = 0.184) between the three disease groups. All other measures showed significant differences at all levels of the HCT.

The assessment of respiratory muscle strength was not significantly different between the MND and COPD groups. Furthermore, there was a significant difference between the HCT pass/fail ratio between the three disease groups.

MND group

The continuous and categorical data for the MND pass and fail groups is shown in table 6, which compares demographic and physiology data for spirometry, blood gases (different factions of inspired oxygen) and SNIP.

Variable	Pass	Fail	p-value
Patients	94	24	
Age years	61.50 (12.67)	66.00 (14.18)	0.076
M/F	63/31	14/10	0.043
Pack/Years	11.3 (11.91)	16.4 (17.50)	0.670
BMI kg/m^{-2}	24.86 (4.82)	27.13 (5.89)	0.140
Spirometry			
FEV1	2.12 (0.80)	1.25 (0.71)	<0.001
FEV1 z-Score	-2.00 (1.71)	-3.63 (1.60)	0.002
FEV1 % pred	70.4 (24.43)	44.48 (21.04)	<0.001
FEV1 <80% pred	38 (53)	14 (93)	0.004
FEV1 <-1.645	40 (56)	14 (93)	0.006
FVC	2.61 (1.02)	1.74 (0.88)	0.003
FVC z-score	-2.36 (1.90)	-3.72 (1.82)	0.017
FVC % pred	67.83 (24.09)	49.06 (19.68)	0.004
FVC <80% pred	50 (69)	14 (93)	<0.001
FVC <-1.645	44 (56)	14 (93)	0.016
FEV1/FVC	83 (0.10)	0.73 (0.13)	0.011
FEV1/FVC <70%	27 (38)	11 (67)	0.011

Legend

Pack years	Clinical quantification of cigarette smoking (packs/years)
BMI	Body Mass Index (kg/m^{-2})
FEV_1	Forced expiratory volume in one second (litres)
FVC	Forced vital capacity (litres)
FEV_1/FVC	Ratio to define obstructive or restrictive disease
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Categorical data - (Chi-squared test**)**
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
pH (21%)	7.43 (0.03)	7.42 (0.03)	0.311
PaCO2 (21%)	5.28 (0.75)	6.24 (0.863)	<0.001
PaO2 (21%)	10.30 (1.14)	9.045 (1.178)	<0.001
HCO3 (21%)	26.30 (2.01)	28.95 (3.67)	<0.001
BE (21%)	2.35 (2.37)	5.70 (3.34)	<0.001
SaO2 (21%	96.00 (1.30)	94.00 (1.41)	<0.001
tHb (21%)	152.61 (13.77)	150.00 (17.34)	0.516
pH (15%)	7.44 (0.03)	7.44(0.05)	0.279
PaCO2 (15%)	5.10(0.86)	6.010 (0.66)	<0.001
PaO2 (15%)	7.60 (1.17)	6.39 (0.25)	<0.001
HCO3 (15%)	26.35 (3.67)	28.10 (4.40)	0.003
BE (15%)	2.35 (3.34)	4.70 (3.86)	<0.001
SaO2 (15%)	92.00 (1.41)	86.000 (2.20)	<0.001
pH (28%)		7.41 (0.04)	
PaCO2 (28%)		6.26 (0.93)	
PaO2 (28%)		11.97 (2.71)	
HCO3 (28%)		28.60 (4.15)	
BE (28%)		4.88 (3.82)	
SaO2 (28%)		95.66 (4.79)	
SNIP	-41.87 (26.67)	-39.37 (22.72)	0.707

Legend

pH	Acidity scale
PaO_2	Partial pressure of oxygen within arterial blood (kPa)
$PaCO_2$	Partial pressure of carbon dioxide within arterial blood (kPa)
HCO_3	Bicarbonate within the blood (mmol/l)
BE	Base excess is the amount of H+ ions required to return blood pH to 7.35 (mmol/l)
tHb	Total haemoglobin within the blood (g/dl)
SaO_2	Oxygen saturation (%)
(21%)	Fractional inspired oxygen (FiO_2) 21%
(15%)	Fractional inspired oxygen (FiO_2) 15%
(28%)	Fractional inspired oxygen (FiO_2) 28%
SNIP	Sniff nasal inspiratory pressure (cmH_2O)

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Table 6. Continuous and categorical data for the MND pass and fail HCT groups

The mean age of the 118 patients in the MND group was 63 ±12.99 years with a mean pack year history of 10.00 ±13.41 years and an average body mass index of 24.97 ±5.12 kg/m^2 (table 6). The Forty-one (53%) were female. Twenty-four patients (26%) within the MND group failed the HCT.

Dynamic spirometry was available for 87/118 (74%) patients. The cohorts (MND) spirometric means were, FEV_1 of 1.94 ±0.85 litres, FEV_1 percent predicted 65.93% ±25.72 and FEV_1 z-score -2.28 ±1.80. The mean for FVC was 2.46 ±1.05 litres, FVC percent predicted 64.59% ±24.35 and FVC z-score -2.60 ±1.95 respectively. The mean FEV_1/FVC ratio was 0.81 ±0.11. Sixty-one (70%) patients had a clinically reduced FEV_1 using percent predicted to assess clinical normality, contrasting to 55 (63%) when assessing by z-scores. Sixty-four (74%) patients had a clinically reduced FVC using percent predicted (<80% predicted), contrasting to 57 (66%) when assessing by z-scores.

The resting blood gases (FiO_2 of 21%) showed a median for pH of 7.43 ±0.03, partial pressure of carbon dioxide ($PaCO_2$) of 5.45 ±0.85 Kpa, bicarbonate (HCO_3) of 26.70 ±2.72 mmol/l, base excess (BE) of 2.80 ±2.95 mmol/l and an SpO_2 of 95.0% ±1.47. The mean value for PaO_2 was 10.12 ±0.12 kPa with total haemoglobin being 152.11 ±14.48 g/dl.

The blood gases relating to hypoxic mix (FiO_2 of 15%) showed a median for pH of 7.44 ±0.38, $PaCO_2$ of 5.22 ±0.82 kPa, PaO_2 of 7.46 ±1.01 kPa, HCO_3 of 26.50 ±2.93 mmol/l, BE of 2.70 ±3.03 mmol/l and an SpO_2 of 91.0% ±3.43.

The blood gas values whilst administering supplemental oxygen (FiO_2 of 28%) during HCT showed a median for pH of 7.42 ±0.36, mean $PaCO_2$ of 6.20 ±0.87 kPa, a median for PaO_2 of 11.070 ±2.56 kPa, HCO_3 of 28.00 ±3.77 mmol/l, BE of 4.15 ±3.46 mmol/l and an SpO_2 of 97.0% ±4.15.

There was no significant difference between the HCT pass and fail groups with regards to age (p = 0.076), BMI (p = 0.140) and pack year history (p = 0.140). However, the fail group were older (61.5 ±12.67 vs 66.00 ±14.18) (p = 0.076), had a higher pack year history (11.3 ±11.91 vs 12.63 ±17.5) (p = 0.670) and BMI (24.86 ±4.82 vs 27.130 ±5.89) (p = 0.140). There was also no significant difference in the male/female ratio (p = 0.043).

Dynamic spirometry parameters including FEV_1 (p = <0.001), FVC (p = 0.003) and FEV_1/FVC ratio (p = 0.011) showed significant difference between the HCT pass and fail groups. These physiology measures relate to the movement of air into and out the lungs indicating reduced ventilation and increased limitation caused by the disease pathology. However, the direct measure of respiratory muscle strength (SNIP) cmH_2O were not significantly different between the HCT pass and fail groups (p = 0.707).

No significant differences in resting blood gases (FiO_2 on 21%), pH (p = 0.311) or tHb (p = 0.516). There were, however, significant differences in $PaCO_2$, PaO_2, HCO_3, BE and SaO_2 (p = 0.001) respectively. The HCT failure group had lower oxygen values (PaO_2 9.045 ±1.178 vs 10.30 ±1.14 and SpO_2 94.0 ±1.41 vs 96.0 ±1.30) indicating advanced ventilatory decline,

which was supported by the presence of hypercapnia ($PaCO_2$ 6.24 ±0.863 vs 5.28 ±0.75) that is chronic in nature (HCO_3 28.95 ±0.3.67 vs 26.3 ±2.01 and BE 5.70 ±3.34 vs 2.35 ±2.37).

The blood gas results on the hypoxic mix (FiO2 on 15%) showed no significant difference in pH ($p = 0.279$) between HCT past and fail groups. There were, however, significant differences in $PaCO_2$, PaO_2, HCO_3, SaO_2 ($p = 0.001$) and BE ($p = 0.003$) respectively. All the MND patients maintained a PaO_2 >8.00 kPa during oxygen titration with no change in hypercapnia.

A binary logistic regression model analysis was used to examine whether the predictors of resting PaO_2, $PaCO_2$, BE (FiO2 of 21%), FEV_1 percent predicted, and birth sex predicts PaO_2 at altitude (Appendix 1). The analysis of variance indicates that a PaO_2 (FiO_2 of 21%) was the only significant parameter in predicting a failed HCT ($p = 0.027$). The OR suggests that if the PaO_2 is reduced, there is a 4.9 increase to fail the HCT. Furthermore, the model explains approximately 55% of the variance in the test outcome ($r^2 = 54.47$). Additional analysis exploring the relation to normal and abnormal spirometric parameters FEV_1 and FVC, showed that in the presence of a normal FEV_1 the likelihood of passing the HCT almost doubles (OR 1.75). Furthermore, a normal FVC increases the possibility of passing the HCT fivefold (OR 5.27).

Analysis of PaO_2 (FiO_2 of 21%) as a predictive variable in the calculation of PaO_2 at altitude (FiO_2 15%) confirmed the association is statistically significant ($p = 0.001$). However, the

coefficient of determination is low (r^2 = 25), which is problematic on the predictive precision (Figure 10).

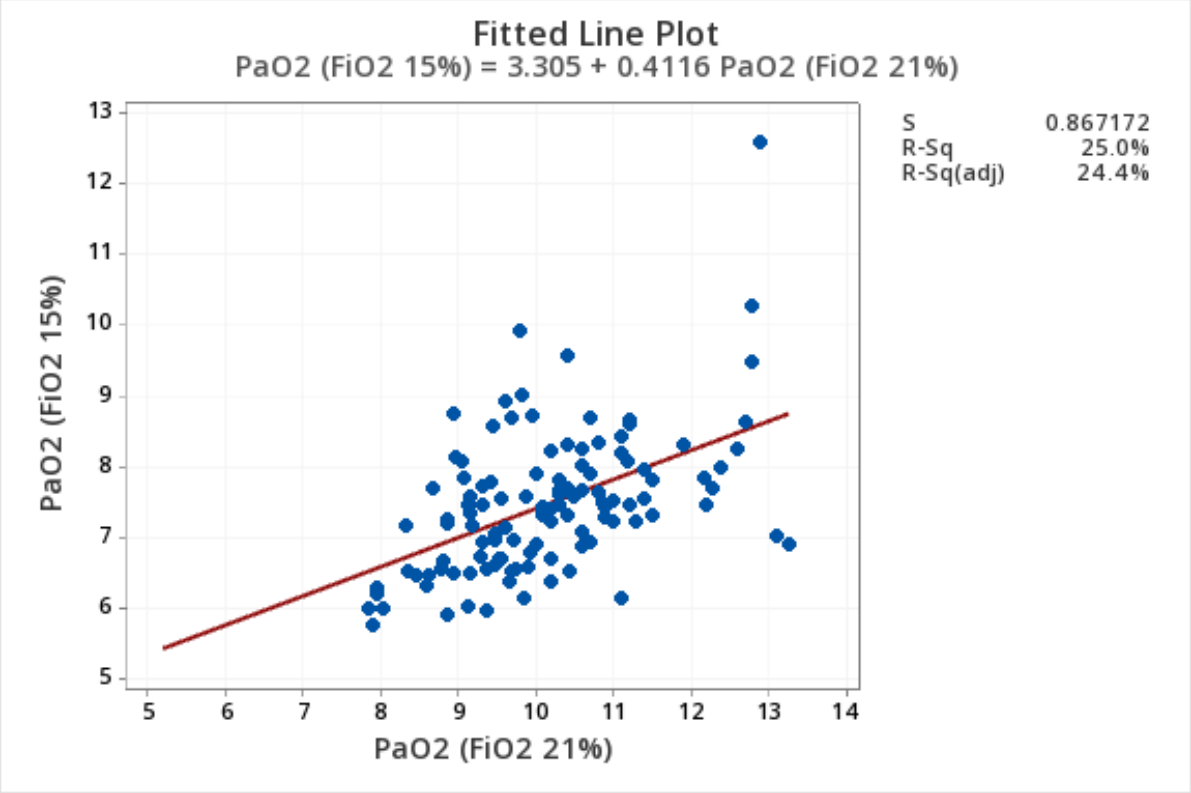

Figure 10. Regression analysis: PaO2 (21%) vs PaO2 (15%).

Regression equation: PaO_2 (15%) = 3.305 + 0.4116 PaO_2 (21%)

The above regression equation suggests that a resting PaO_2 (FiO_2 of 21%) ≤8.00 kPa would be indicative of a requirement for in-flight oxygen. Additional analysis was explored further utilising spirometric parameters to increase the predictive power, however FEV_1 (r^2 = 26.87) and FVC (r^2 = 22.97) did not improve the model's accuracy.

ILD group

The continuous and categorical data for the ILD pass and fail groups is shown in table 7, which compares demographic and physiology data for spirometry, transfer factor, static lung volumes, blood gases (different factions of inspired oxygen) and 6MWT.

Variable	Pass	Fail	p-value
Patients	27	29	
Age years	72.00 (6.95)	68.00 (6.82)	0.063
M/F	18/9	23/6	0.286
Pack/Years	25.00 (17.0)	26.25 (31.44)	0.588
BMI kg/m^{-2}	27.49 (28.13)	28.61 (40.97)	0.258
Spirometry			
FEV1	2.17 (2.24)	1.78 (0.56)	0.081
FEV1 z-Score	-0.94 (1.14)	-1.94 (0.90)	0.001
FEV1 % pred	84.32 (19.26)	67.56 (15.20)	0.001
FEV1 <80% pred	9 (33)	20 (77)	0.002
FEV1 <-1.645	8 (30)	17 (65)	0.010
FVC	2.74 (0.95)	2.32 (0.67)	0.068
FVC z-score	-1.38 (1.17)	-2.38 (0.99)	0.002
FVC % pred	78.00 (18.67)	63.33 (14.33)	0.002
FVC <80% pred	14 (52)	23 (88)	0.030
FVC <-1.645	11 (41)	21 (81)	0.017
FEV1/FVC	0.83 (0.83)	0.81 (0.97)	0.364
FEV1/FVC <70%	0 (0)	1 (4)	0.339

Legend

Pack years	Clinical quantification of cigarette smoking (packs/years)
BMI	Body Mass Index (kg/m^{-2})
FEV_1	Forced expiratory volume in one second (litres)
FVC	Forced vital capacity (litres)
FEV_1/FVC	Ratio to define obstructive or restrictive disease
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Categorical data - (Chi-squared test**)**
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
Tlco			
TLco	3.66 (3.88)	3.86 (0.78)	0.966
Tlco z-score	-3.74 (1.22)	-4.00 (0.97)	0.894
Tlco % pred	49.24 (11.99)	46.14 (9.70)	0.824
Tlco/Va	1.03 (1.07)	1.04 (0.09)	0.966
Tlco/Va z-score	-1.57 (1.44)	-1.87 (0.46)	0.536
Tlco/Va % pred	76.98 (21.65)	72.40 (6.51)	0.517
Lung Volumes			
TLC	4.14 (1.19)	3.41 (1.23)	0.345
TLC z-score	-2.83 (1.90)	-3.83 (1.00)	0.161
TLC % pred	68.08 (12.42)	56.00 (12.99)	0.181
RV	1.08 (0.38)	1.17 (0.311)	0.863
RV z-score	-3.26 (0.76)	-3.72 (1.03)	0.344
RV % pred	48.00 (12.37)	43.50 (13.44)	0.699
RV/TLC	29.78 (6.85)	26.50 (1.21)	0.199
RV/TLC z-score	-2.38 (1.11)	-2.64 (0.01)	0.763
RV/TLC % pred	68.00 (15.33)	65.00 (1.41)	0.606

Legend

TLco	Transfer factor of the lungs for carbon monoxide (mmol/min/kPa)
TLco/Va	Carbon monoxide coefficient ml/min/kPa). Also known as Kco
TLC	Total lung capacity (litres)
RV	Residual volume (litres)
RV/TLC	Ratio to define hyperinflation
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
pH (21%)	7.41 (0.02)	7.43 (0.3)	0.787
PaCO2 (21%)	5.17 (0.40)	5.15 (0.54)	0.787
PaO2 (21%)	9.64 (1.05)	9.28 (1.04)	0.203
HCO3 (21%)	25.10 (1.30)	25.4 (1.48)	0.646
BE (21%)	1.20 (1.61)	0.90 (1.87)	0.652
SaO2 (21%	96.00 (2.47)	95.00 (2.25)	0.041
THb (21%)	151.35 (16.88)	156.41 (15.56)	0.294
pH (15%)	7.43 (0.02)	7.44 (0.03)	0.341
PaCO2 (15%)	4.95 (0.35)	4.92 (0.51)	0.683
PaO2 (15%)	7.34 (0.66)	6.41 (0.36)	<0.001
HCO3 (15%)	25.20 (1.20)	25.20 (1.37)	0.833
BE (15%)	0.80 (1.51)	1.10 (1.70)	0.603
SaO2 (15%)	91.00 (2.39)	86.40 (2.28)	<0.001
pH (28%)	7.42 (0.01)	7.41 (0.03)	0.508
PaCO2 (28%)	5.31 (0.39)	5.42 (0.51)	0.627
PaO2 (28%)	15.45 (3.44)	10.80 (1.93)	0.015
HCO3 (28%)	25.25 (1.71)	25.30 (1.50)	0.978
BE (28%)	0.80 (2.20)	1.30 (1.93)	0.869
SaO2 (28%)	98.30 (0.84)	97.00 (2.11)	0.016

Legend

pH	Acidity scale
PaO_2	Partial pressure of oxygen within arterial blood (kPa)
$PaCO_2$	Partial pressure of carbon dioxide within arterial blood (kPa)
HCO_3	Bicarbonate within the blood (mmol/l)
BE	Base excess is the amount of H+ ions required to return blood pH to 7.35 (mmol/l)
tHb	Total haemoglobin within the blood (g/dl)
SaO_2	Oxygen saturation (%)
(21%)	Fractional inspired oxygen (FiO_2) 21%
(15%)	Fractional inspired oxygen (FiO_2) 15%
(28%)	Fractional inspired oxygen (FiO_2) 28%

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
6MWT Distance	360.0 (126.50)	279.00 (127.60)	0.103
6MWT Dis % pred	74.38 (25.61)	61.59 (24.67)	0.196
6MWT Dis <80 pred	14 (52)	10 (77)	0.130
SaO2 rest	96.20 (2.00)	96.31 (1.18)	0.854
SaO2 Ex	89.00 (4.40)	88.92 (4.05)	0.957
Recover time/sec	60.00 (57.60)	60.00 (35.95)	0.549
Desaturation diff.	-6.50 (4.14)	-9.00 (3.78	0.743
Desaturation diff >4	17 (63)	8 (62)	0.931

Legend

6MWT Distance	Distance walked in 6 minutes (m)
6MWT Dis % pred	Percentage waked of predicted distance (%)
SaO_2 (rest)	Oxygen saturation at rest (%)
SaO_2 (ex)	Oxygen saturation during walk/exercise (%)
Recovery time	Time for SaO_2 to returned to baseline (rest) value (second)
Desaturation Diff. %	Difference from rest and walk/exercise SaO_2 (%)

Categorical data - (Chi-squared test)
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Table 7. Continuous and categorical variables for HCT pass and fail ILD groups

The mean age of patients in the ILD group was 69 (±7.05) years and fifteen (37%) were female. The mean pack year history was 25.00 (±26.69) years, and the mean body mass index was 28.04 (±29.77) kg/m^2 (table 7). Twenty-nine patients (52%) within the ILD group failed the HCT.

Physiology data (ILD patients) was available for dynamic spirometry 53/56 (95%), transfer factor 28/56 (50%) static lung volumes 31/56 (55%) and 6MWT 40/56 (71%). The ILD group had a mean FEV_1 of 1.91 (±0.65) litres, FEV_1 percent predicted of 76.1% (±19.19) and a FEV_1 z-score of -1.43 (±1.14). The mean FVC was 2.54 (±0.84) litres, FVC percent predicted of 70.8% (±18.11) and FVC z-score of -1.87 (±1.19). The mean FEV_1/FVC ratio was 0.81 (±0.08).

Thirty (56%) patients had a clinically reduced FEV_1 using percent predicted to assess clinical normality, opposed to 26 (48%) when assessing by z-scores. Thirty-seven (69%) patients had a clinically reduced FVC using percent predicted, contrasting to 33 (61%) when assessing by z-scores.

The transfer factor showed a mean TLco of 3.66 (±1.04) ml/min/kPa, TLco percent predicted of 49.24% (±11.72) and TLco z-score of -3.74 (±1.19). The mean Kco was 1.03 (±0.30) ml/min/kPa, Kco percent predicted of 76.65% (±20.91) and Kco z-score of -1.60 (±1.39). Twenty-seven (93%) patients had a clinically reduced TLco using percent predicted to assess clinical normality, opposed to 26 (90%) when assessing by z-scores. Twenty (71%) patients had a clinically reduced Kco using percent predicted, contrasting to 14 (48%) when assessing by z-scores.

The static lung volumes showed a mean TLC of 4.04 (±1.20) litres, TLC percent predicted of 66.41% ±13.97 and a mean TLC z-score of -2.97 (±1.83). The mean RV was 1.09 (±0.38) litres, RV percent predicted of 50.0% (±13.0) and RV z-score of -3.09 (±0.80). The mean RV/TLC ratio was 30.55 (±7.21), RV/TLC ratio percent predicted of 70.0% (±17.3) and RV/TLC ratio z-score of -2.12 (±1.25). Twenty-five (86%) patients had a clinically reduced TLC. Twenty-nine (97%) had a reduced RV with 17 (58%) having a low RV/TLC. Normality assessed by percent predicted or z-score resulted with the same outcome.

The median resting blood gases (FiO_2 of 21%) indicate a pH of 7.42 (±0.03) kPa, $PaCO_2$ of 5.17 (±0.48) kPa, HCO_3 of 25.20 (±1.39) mmol/l, BE of 1.05 (±1.74) mmol/l and an SpO_2 of 95.0% (±2.36). The mean value for PaO_2 was 9.46 (±1.05) kPa with total haemoglobin being 154.02 (±17.81) mmol/l.

The blood gases relating to hypoxic mix (FiO_2 of 15%) showed a median of 7.43 (±0.03) for pH, $PaCO_2$ of 4.94 (±0.0.43) kPa, PaO_2 of 6.72 (±0.075) kPa, HCO_3 of 25.20 (±1.27) mmol/l, BE of 0.80 (±1.59) mmol/l and an SpO_2 of 88.0% (±3.23).

The blood gases values whilst administering supplemental oxygen (FiO_2 of 28%) during HCT showed a mean $PaCO_2$ of 5.41 (±0.50) kPa, a median for pH of 7.41 (±0.02), PaO_2 of 11.38 (±2.53) kPa, HCO_3 of 25.30 (±1.50) mmol/l, BE of 1.30 (±1.93) mmol/l and an SpO_2 of 97.0% (±2.12).

The 6MWT showed a median distance of 341.0 (±129.5) metres, percent predicted distance of 72.88% (±27.13), a SpO_2 recovery time 60.0 (±51.06) seconds and a desaturation of -7.00% (±3.98). Mean values for SpO_2 at rest (96.24% ±1.74) and during exercise (88.97% ±4.23) were obtained. Twenty-four (63%) of patients had a reduced exercise tolerance as defined as an achieved distance of <80% predicted. Twenty-five (66%) patients significantly desaturated during the walk (reduction in SpO_2 >4%).

There was no significant difference between the HCT pass and fail groups with regards to age (p = 0.063), BMI (p = 0.258) and pack year history (p = 0.588). However, the fail group were younger (68.0 ±6.82 vs 72.0 ±6.95) (p = 0.63).

Dynamic spirometry parameters including mean FEV_1 (p = <0.081), FVC (p = 0.068) and FEV_1/FVC ratio (p = 0.364) showed no significant difference between the HCT pass and fail groups. However, when assessing for normality against demographics, both FEV_1 (p = 0.001) litres and FVC (p = 0.002) litres showed significant difference for both percent predicted and z-scores. FEV1/FVC ratio was consistent for both groups (p = 0.364).

There was no significant difference between the pass and fail group for transfer factor, static lung volumes or 6MWT, which included assessment of clinical normality. This was also observed in the blood gas values at rest, during the hypoxic challenge and oxygen titrating apart from PaO_2 (p = 0.001) and SpO_2 (p = 0.001) whilst breathing the 15% hypoxic mix.

A binary logistic regression model analysis was used to examine whether the predictors of resting PaO_2, $PaCO_2$, BE (FiO2 of 21%), FEV_1 percent predicted, and birth sex predicts PaO_2 at altitude (Appendix 2). The analysis of variance indicated that a reduced FEV_1 percent predicted was the only significant parameter in predicting a failed HCT (p = 0.005). Furthermore, the model explains approximately 19% of the variance in the response (r^2 = 19.34)

The FEV_1 was used as a predictive variable in the calculation of PaO_2 at altitude (figure 11). The regression analysis confirmed no association between FEV_1 and PaO_2 (FiO2 of 15%), which is consistent with the low coefficient of determination (r^2 = 9.2). Additional analysis explored the relation to normal and abnormal spirometric parameters FEV_1 and FVC, showed that in the presence of a normal FEV_1 the likelihood of passing the HCT increased sixfold (OR 6.49). The FVC showed no significant relationship (p = 0.971).

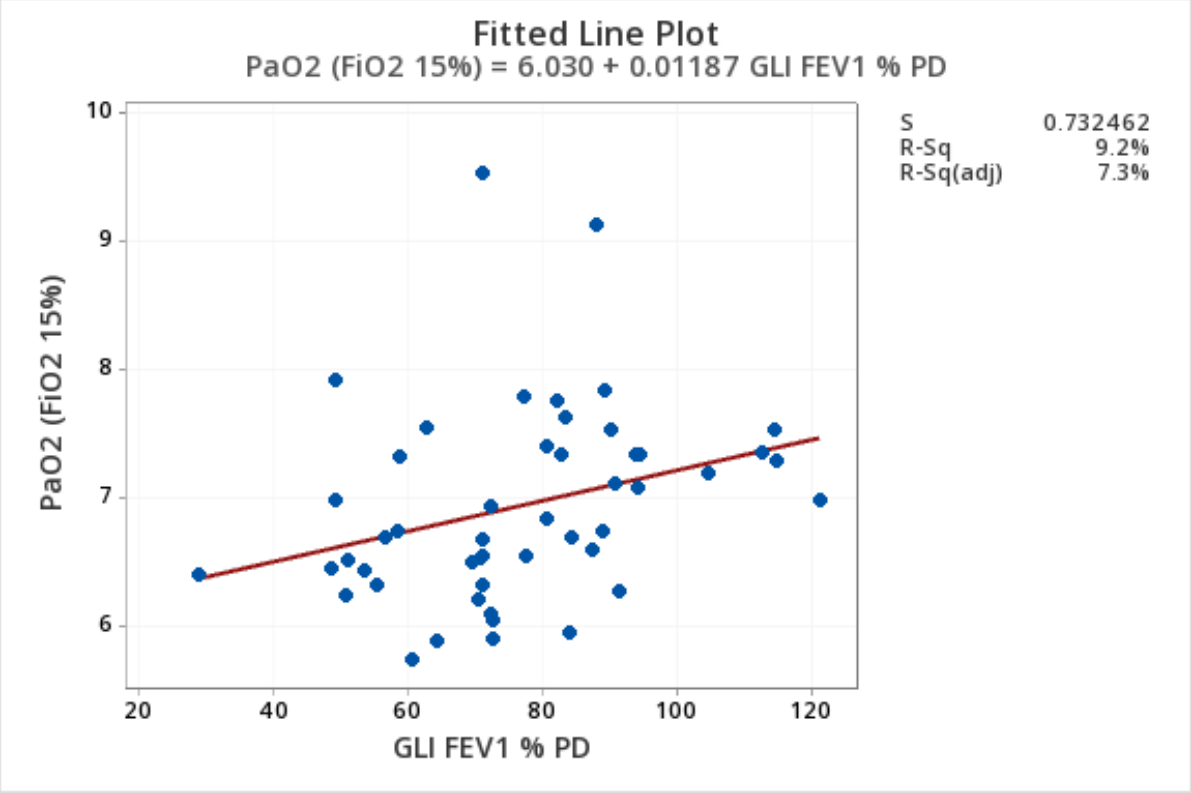

Figure 11. Regression analysis: FEV_1 percent predicted vs PaO2 (15%).

COPD group

The continuous and categorical data for the COPD pass and fail groups is shown in table 8, which compares demographic and physiology data for spirometry, transfer factor, static lung volumes, blood gases (different factions of inspired oxygen) and 6MWT.

Variable	Pass	Fail	p-value
Patients	19	32	
Age years	65.00 (1.19)	66.00 (9.40)	0.755
M/F	10/9	17/15	0.210
Pack/Years	25.00 (25.24)	37.00 (42.82)	0.172
BMI kg/m^{-2}	26.53 (8.40)	26.89 (10.29)	0.647
Spirometry			
FEV1	1.18 (0.773)	1.06 (0.45)	0.339
FEV1 z-Score	-3.11 (1.51)	-3.54 (1.26)	0.366
FEV1 % pred	49.61 (22.87)	41.39 (18.54)	0.311
FEV1 <80% pred	13 (81)	22 (96)	
FEV1 <-1.645	13 (81)	21 (91)	
FVC	2.86 (1.19)	2.45 (0.71)	0.237
FVC z-score	-1.40 (1.74)	-2.04 (1.58)	0.249
FVC % pred	79.62 (25.20)	70.50 (21.34)	0.247
FVC <80% pred	7 (43)	15 (65)	
FVC <-1.645	9 (56)	14 (61)	
FEV1/FVC	49.00 (21.19)	41.00 (15.32)	0.909
FEV1/FVC <70%	17 (100)	23 (100)	

Legend

Pack years	Clinical quantification of cigarette smoking (packs/years)
BMI	Body Mass Index (kg/m^{-2})
FEV_1	Forced expiratory volume in one second (litres)
FVC	Forced vital capacity (litres)
FEV_1/FVC	Ratio to define obstructive or restrictive disease
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Categorical data - (Chi-squared test**)**
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
Tlco			
TLco	4.44 (2.36)	5.40 (2.08)	0.603
Tlco z-score	-3.29 (1.68)	-1.14 (3.89)	0.385
Tlco % pred	56.66 (23.49)	80.74 (26.04)	0.524
Tlco/Va	0.80 (0.33)	0.96 (0.44)	0.695
Tlco/Va z-score	-2.80 (1.82)	-2.44 (2.87)	0.833
Tlco/Va % pred	62.48 (23.49)	69.40 (31.3)	0.64
Lung Volumes			
TLC	6.58 (1.91)	6.37 (1.04)	0.794
TLC z-score	0.67 (1.91)	0.63 (1.38)	0.962
TLC % pred	107.0 (21.87)	107.5 (15.15)	0.958
RV	2.38 (1.06)	2.81 (0.43)	0.270
RV z-score	0.98 (2.68)	1.04 (1.81)	0.495
RV % pred	104.5 (47.4)	117.50 (38.9)	0.462
RV/TLC	44.00 (7.76)	47.75 (7.32)	0.339
RV/TLC z-score	-0.47 (2.17)	0.800 (1.78)	0.189
RV/TLC % pred	94.5 (34.7)	107.50 (31.9)	0.227

Legend

TLco	Transfer factor of the lungs for carbon monoxide (mmol/min/kPa)
TLco/Va	Carbon monoxide coefficient ml/min/kPa). Also known as Kco
TLC	Total lung capacity (litres)
RV	Residual volume (litres)
RV/TLC	Ratio to define hyperinflation
Z-score	Distance from the mean (±1.645 clinical upper and lower limit)
% pred.	Percent from the predicted mean

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Variable	Pass	Fail	p-value
pH (21%)	7.43 (0.04)	7.43 (0.03)	0.185
PaCO2 (21%)	5.07 (0.81)	5.35 (0.70)	0.141
PaO2 (21%)	9.00 (1.13)	8.50 (0.89)	0.108
HCO3 (21%)	25.90 (1.51)	26.20 (1.61)	1.000
BE (21%)	1.40 (2.12)	2.15 (2.24)	0.800
SaO2 (21%	95.00 (2.74)	94.00 (2.35)	0.032
THb (21%)	152.42 (13.79)	150.81 (17.71)	0.720
pH (15%)	7.47 (0.06)	7.45 (0.03)	0.05
PaCO2 (15%)	4.53 (1.00)	5.31 (0.67)	0.002
PaO2 (15%)	7.77 (0.58)	6.00 (0.40)	<0.001
HCO3 (15%)	26.50 (1.65)	26.80 (1.75)	0.853
BE (15%)	0.90 (2.47)	2.85 (2.29)	0.258
SaO2 (15%)	93.00 (2.47)	84.00 (3.43)	<0.001
pH (28%)		7.42 (0.04)	
PaCO2 (28%)		5.58 (0.80)	
PaO2 (28%)		8.94 (2.25)	
HCO3 (28%)		26.60 (1.63)	
BE (28%)		2.80 (2.13)	
SaO2 (28%)		95.00 (2.31)	

Legend

pH	Acidity scale
PaO_2	Partial pressure of oxygen within arterial blood (kPa)
$PaCO_2$	Partial pressure of carbon dioxide within arterial blood (kPa)
HCO_3	Bicarbonate within the blood (mmol/l)
BE	Base excess is the amount of H+ ions required to return blood pH to 7.35 (mmol/l)
tHb	Total haemoglobin within the blood (g/dl)
SaO_2	Oxygen saturation (%)
(21%)	Fractional inspired oxygen (FiO_2) 21%
(15%)	Fractional inspired oxygen (FiO_2) 15%
(28%)	Fractional inspired oxygen (FiO_2) 28%

Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

6MWT Distance	393.5 (157.80)	311	Insuf
6MWT Dis % pred	69.5 (31.3)	84	Insuf
6MWT Dis <80 pred	3 (75)		
SaO2 rest	96.00 (2.58)	92	Insuf
SaO2 Ex	90.25 (4.11)	87	Insuf
Recover time/sec	60.00 (0.00)	60	Insuf
Desaturation diff.	-4.00 (4.19)	-5.00	Insuf
Desaturation diff >4	1 (25)	1 (100)	
SNIP	-67	-59	Insuf

Legend

6MWT Distance	Distance walked in 6 minutes (m)
6MWT Dis % pred	Percentage waked of predicted distance (%)
SaO_2 (rest)	Oxygen saturation at rest (%)
SaO_2 (ex)	Oxygen saturation during walk/exercise (%)
Recovery time	Time for SaO_2 to returned to baseline (rest) value (second)
Desaturation Diff. %	Difference from rest and walk/exercise SaO_2 (%)

Categorical data - (Chi-squared test)
Mean ±SD or median ±IQR or n (%) - (one-way ANOVA, Kruskal-Wallis, or Mann-Whitney Test & Paired T test)

Table 8. Continuous and categorical variables for HCT pass and fail COPD groups

The mean age of the patients in the COPD group was 66 (±9.24) years and twenty-four (47%) were female. The mean pack year history was 28.500 (±37.49) years and patients had a mean body mass index of 26.53 (±9.62) kg/m^2 (Table 8). Thirty-two patients (62%) within the COPD group failed the HCT.

Physiology data was available for dynamic spirometry 23/51 (45%), transfer factor 7/51 (14%) static lung volumes 8/51 (16%) and 6MWT 5/51 (10%). The cohort had a median FEV_1 of 1.13 (±0.61) litres, mean FEV_1 percent predicted of 44.76% (±25.55) and FEV_1 z-score of -3.36 (±1.37). The median FVC was 2.62 (±0.95) litres, mean FVC percent predicted of 74.24% (±23.13) and FVC z-score of -1.78 (±1.65). The median FEV_1/FVC ratio was 0.48 ±0.16. Thirty-

five (90%) patients had a clinically reduced FEV_1 using percent predicted to assess clinical normality, opposed to 34 (87%) when assessing by z-scores. Twenty-three (59%) patients had a clinically reduced FVC using percent predicted, contrasting to 21 (54%) when assessing by z-scores.

The transfer factor showed a median TLco of 4.82 (±2.15) mol/min/kPa, a TLco percent predicted of 64.33% (±21.84) and TLco z-score of -2.49 (±2.81). The median Kco was 0.95 (±0.37) ml/min/kPa, a mean Kco percent predicted of 65.72 (±26.61) and Kco z-score of -2.63 (±2.28). Ten (67%) patients had a clinically reduced TLco using percent predicted to assess clinical normality, which was replicated by z-scores. Ten (67%) patients had a clinically reduced Kco using percent predicted, opposed to 9 (60%) when assessing by z-scores.

The static lung volumes indicated a mean TLC of 6.47 (±1.49) litres, TLC percent predicted of 98.65% (±30.52) and TLC z-score of 0.65 (±1.64). The median RV was 2.73 (±0.79) litres, RV percent predicted of 109.0% (±42.1) and RV z-score of 0.54 (±2.22). The mean RV/TLC ratio was 45.88 (±7.54), with a mean RV/TLC ratio percent predicted of 105.5% (±32.7) and RV/TLC ratio z-score of 0.48 (±1.97). One (6%) patient had a clinically reduced TLC, RV and RV/TLC ratio. Normality assessed by percent predicted and z-score were consistent.

The resting blood gases (FiO_2 of 21%) showed a median for pH of 7.43 (±0.03), $PaCO_2$ of 5.22 (±0.75) kPa, HCO_3 of 26.20 (±1.56) mmol/l, BE of 2.00 (±2.18) mmol/l and an SpO_2 of 94.0%

(±2.55). The mean value for PaO_2 was 8.68 (±1.01) kPa with total haemoglobin being 151.41 (±16.24) g/dL.

The blood gases relating to hypoxic mix (FiO_2 of 15%) showed a median for pH of 7.45 (±0.03), $PaCO_2$ of 5.09 (±0.0.86) kPa, PaO_2 of 6.48 (±0.092) kPa, HCO_3 of 26.60 (±1.70) mmol/l, BE of 2.70 (±2.27) mmol/l and an SpO_2 of 88.0% (±4.80).

The median blood gases values whilst administering supplemental oxygen (FiO_2 of 28%) during HCT were 7.42 (±0.04) for pH, 5.58 (±0.81) kPa for $PaCO_2$, 26.60 (±1.63) mmol/l for HCO_3, 2.80 (±2.12) mmol/l for BE, 95.0% (±2.31) for SpO_2 with a mean PaO_2 of 8.94 (±2.25) kPa.

In the 6MWT, the patients measured a median distance of 387.0 (±136.8) metres, a percent predicted distance of 77% (±29.30), a SpO_2 recovery time 60.0 (±1.58) seconds and a desaturation of -4.00% (±3.65). Mean values for SpO_2 at rest (95.2% ±2.86) and during exercise (89.6% ±3.85) were obtained. Three (60%) of patients had a reduced exercise tolerance as defined as an achieved distance of <80% predicted. Two (40%) patients significantly desaturated during the walk (reduction in SpO_2 >4%).

There was no significant difference between the HCT pass and fail groups with regards to age ($p = 0.755$), BMI ($p = 0.647$) and pack year history ($p = 0.172$).

There was no significant difference between the pass and fail group for dynamic spirometry, transfer factor or static lung volumes (Table 8). This was also observed in the blood gas values at rest, during the hypoxic challenge and whilst titrating apart from SpO_2 at rest (p = 0.032) kPa, PaO_2 (p = 0.002) kPa and SpO_2 (p = 0.001) whilst breathing the 15% hypoxic mix. Due to the limited number of subjects who have performed a 6MWT, there was insufficient data for a meaningful analysis.

A binary logistic regression model analysis was used to examine whether the predictors of resting PaO_2, $PaCO_2$, BE (FiO2 of 21%), FEV_1 percent predicted, and birth sex predicts PaO_2 at altitude (Appendix 3). The analysis of variance indicates that none of the parameters were significant in predicting a failed HCT. Furthermore, the model explains approximately 16% of the deviance in the response (r^2 = 15.78). Further analysis exploring in the relation to normal and abnormal spirometric parameters FEV_1 and FVC, showed no predictive statistical relationship to pass or failure of the HCT (figure 12).

Analysis of Variance

		Wald Test	
Source	DF	Chi-Square	P-Value
Regression	3	4.00	0.262
PaO2	1	2.55	0.110
FEV1 Norm-Abnorm	1	1.52	0.218
FVC Norm-Abnorm	1	0.08	0.777

Figure 12. Analysis of variance: PaO2 (21%) FEV_1 and FVC normal/abnormal.

8. Discussion

Most of the work regarding the assessments of individuals planning commercial flights has been based on COPD patients. Many of these measures and assumptions have been extended to other clinical disorders, which include both respiratory and cardiovascular abnormalities. The hypothesis that other conditions behave in a similar way and demonstrate comparable outcomes in their ability to respond to a hypoxic environment requires further consideration. In this retrospective exploratory examination, the demographic and lifestyle measures (MND, ILD and COPD) were significantly different, and highlights the variance in these disorders on several levels.

HCT performed on patients with these three conditions produced significantly different results at baseline, during hypoxic exposure and in their response to supplemental oxygen (Table 9). The assessment of lung ventilation by spirometry shows significant differences between the disorders and confirms the extent to which ventilation is compromised in terms of restrictive and obstructive elements, along with severity. This is further supported by static lung volumes and describe the pathophysiological differences between the ILD and COPD disorders. These variations in response characteristics suggest that the historical assumptions made regarding the assessment of an individual's fitness to fly based on COPD patients, cannot be extended to the MND or ILD disorders.

Variable	MND	ILD	COPD	p-value
PaO2 (21%) kPa	10.12	9.46	8.68	<0.001
PaO2 (15%) kPa	7.46	6.72	6.48	<0.001
PaO2 (28%) kPa	11.70	11.00	8.94	0.002
FEV1 %PD litres	65.93	76.10	44.76	<0.001
FEV1/FVC	0.81	0.81	0.48	<0.001

Table 9. Summary of the main differences between the disorders for HCT and spirometry

The patients within the MND group who failed the HCT (required supplemental oxygen during commercial flight) had significantly different spirometric and resting blood gas results when compared to patients who did not require in-flight oxygen. The spirometry confirms the relationship between ventilatory capacity and the need for in-flight oxygen and is supplemented by the observed respiratory failure (blood gases). These measures of ventilatory limitation is further evidence of this groups inability to engage compensatory mechanisms to overcome significant hypoxaemia during flight. Interestingly, the measure of respiratory muscle strength (SNIP), which is a major component of MND, showed no difference between the groups and would advocate other mechanisms come into play outside of the respiratory muscle weakness.

The ILD group also showed significant differences between the resulting groups in terms of ventilation, as measured by spirometry. However, there was no significant difference between the pass and fail groups for other measures specific to the pathophysiology of the disorder or functional status. These results would support the hypothesis that ILD patients are unable to engage the compensatory mechanism relating to ventilation and this is a major cause of hypoxaemia during commercial flight. ILD is a group of conditions affecting

the pulmonary parenchyma (interstitial) and/ or alveolar lumen, which have significant consequences for the respiratory zone of the lung. This aspect of the pathophysiology in ILD would appear to have no relationship on an individual's ability to maintain acceptable oxygen levels during commercial flights, nor does the level of fibrosis, which manifests with reduced lung volumes.

The COPD analysis showed similar findings with ventilation being the major difference between the pass and fail groups. No other investigation or related parameter was distinguishable between the patients requiring in-flight oxygen with those that did not. This again would suggest that COPD patients are unable to engage compensatory mechanisms and increase ventilation sufficiently to maintain safe oxygen levels during air travel.

The consequence of these finding has a significant impact on identifying key resting measures that would assist in risk stratifying patients prior to planned air travel, apart from ventilatory assessment. The arbitrary values of oxygen status as measured by resting blood gases appears to be of little value especially within the ILD or COPD patients, however this is not extended to the patients with MND.

The predictive ability of routine clinical measures that form part of the disease specific patient pathway showed limited benefit. The regression analysis demonstrated that even when utilising the measures that showed significant differences between the patients requiring in-flight oxygen against those that did not, there was limited predictive value.

Despite the spirometric evaluation of ventilatory capacity and the indirect association with the ability to engage the compensatory mechanism of increased breathing, the associated parameters (FEV_1, FVC etc.) were poor predictors of a failed HCT and need for inflight oxygen. This was also evident with measures of respiratory failure.

The value of this study has significant consequences for how to clinically risk stratify patients who are planning to travel by commercial airlines. The assumptions made by previous work on patients with COPD cannot be translated to patients with MND or ILD disorders. The plethora of physiological measures as part of the disease specific pathways gives no insight in identifying patients who have increased risk of developing hypoxaemia due to cabin pressure changes seen on commercial flights. Furthermore, their predictive power in identifying individuals whose PaO_2 will drop below 6.6 kPa whist breathing 15% oxygen and subsequently failure of an HCT, is not realised. However, there are various measures that may be helpful in advising and directing patients who are at increased risk of developing significant hypoxaemia during air travel.

In the assessment of fitness to fly with clinical practice, careful consideration is warranted. Reliance on resting routine measures that includes spirometry and blood gas values cannot accurately identify patients that require in-flight oxygen during commercial flight. The assumptions that are based on the study of COPD patients do not extend to other respiratory disorders, and as such, patients must be assessed on a case-by-case basis. The

HCT is the only definitive measure for the assessment of need for in-flight supplement oxygen.

Primary aim: To investigate if historical data based on COPD patients for HCT can be extended to other respiratory compromise patients, irrespective of pathophysiology.

The BTS recommendation for managing passengers with stable respiratory disease planning air travel was a seminal document that laid the foundations for clinical practice when assessing compromised patients prior to commercial flights (British Thoracic Society Standards of Care Committee, 2002). The update in 2011 provided recommendations based on current evidence and expert opinion with the view of both increasing awareness within specialist respiratory centres and providing consistent practical advice (Ahmedzai et al., 2011). However, there has been a significant number of years since the publication of these documents, and the information within should be considered outdated. There is an understanding within the BTS that there is a need to review the recommendations and in 2018 commissioned a review to produce a new clinical statement within this field, which remains unpublished at the time of this thesis write up.

Although much of the information within the documents are outdated, many of the statements within remain true. There is an acknowledgement that air travel for respiratory compromised patients is generally safe if relevant factors have been considered as part of a review by a respiratory specialist. Nonetheless, a clinical opinion endorsing a patient's

suitability for commercial flight cannot be taken lightly. This is further complicated by comorbidities that can adversely affect the individual's ability to maintain adequate oxygenation during the hypoxic environment caused by the pressurisation of the aircraft cabin to 8,000 ft (FiO2 15%).

There is no quality evidence to determine who should formally be assessed prior to air travel, which is a concern not only for the patients, but also compromises the healthcare professionals whose role it is to advise and answer the increased concerns by the patient, insurance companies and airlines themselves (European Lung Foundation, 2020). The identification of patients who are fit to fly against those who are not would appear to be straight forward. Patients presenting with early disease with limited physiological consequence or need for medical intervention would generally be considered suitable to travel. Conversely, those with conditions or disease with the potential to become acutely unwell resulting in medical intervention would be a concern.

The advances in medical management and integrated care have seen better patient outcomes and improved quality of life that has allowed a more active and enhanced lifestyle for patients (Flanagan et al., 2017). This coupled with increased amounts of expendable money has fuelled the rapid rise seen in tourism and air travel alike (Kharas, 2017). This has created a group of patients that have significant underlying conditions that are well managed by both their care providers and themselves, who wish to live a full and active life. This is supported by the National Health Service (NHS), which is committed to improving

patients' lives and is a cornerstone of the NHS constitution (England NHS, 2013). This has created an intermediate group that have significant disease that are not straightforward. On one hand there is sufficient disease to cause concern, but on the other, one would want to give them the best opportunity to travel and fulfil many of their ambitions.

The previous recommendations centre around severity of airway obstruction, with an FEV_1 <50% predicted as an arbitrary threshold for concern. This points directly to the patient group that has historically been used in the risk stratification of air travel and the identification of hypoxaemia during flight. The COPD population has made a significant contribution to our understanding and subsequent management of patients planning air travel, which resulted in the last BTS recommendations (Ahmedzai et al., 2011). This is a trend that we have continued to see in the following years from this publication, which has contributed to our understanding in terms of COPD, but this has come at the cost to other relevant respiratory disorders. The proposed recommendations in figure 1, clearly give a roadmap of how to manage patients presenting with varying levels of oxygen status and comorbidities, but at the time of publication there was little or no evidence for lung cancer, restrictive lung disease, chest wall or diseases affecting muscle function. In the absence of significant evidence, it would appear the best approach would be to err on the side of caution.

Screening result	Recommendation
Sea level SpO_2 >95%	Oxygen not required
Sea level SpO_2 92-95% and no risk factors*	Oxygen not required
Sea level SpO_2 92-95% with additional risk factors*	Perform HCT
Sea level SpO_2 <92%	Inflight oxygen
Receiving supplemental oxygen at sea level	Increase flow while at altitude
*Additional risk factors: hypercapnia; FEV_1 <50% predicted; lung cancer; restrictive lung disease involving the parenchyma (fibrosis,) chest wall (kyphoscoliosis) or respiratory muscles; ventilator support; cerebrovascular or cardiac disease; within 6 weeks of discharge for an exacerbation of chronic lung or cardiac disease.	

Table 1. Results of initial assessments (British Thoracic Society Standards of Care Committee, 2002)

The data from this study shows that for the population investigated, there were significant differences in age, smoking history and BMI. The variances reflect the disparities in the diseases in terms of onset, cause, and other related factors.

MND

The onset of MND often occurs between 60 to 70 years of age, which is supported by the data from this study (mean 63 years). MND is a severely life-limiting condition for the majority of people, with life expectancy of around 3 years from initial symptoms for 50% of patients (Palange and Rohde, 2019). Due to the aggressive nature of the disease and the age range associated with onset, experience has shown that this group of patients are entering a time in their life where many of their ambitions are to be realised, which is a goal often set within their working life. The realisation is that they have limited time and numerous objectives to achieve, with many relating to travel. Lifestyle choices have often meant they have led a healthy lifestyle, which is supported by the data (significant lower smoking history and BMI). Interestingly, this group of patients had the worst values related to

spirometry when corrected for demographical variance but were able to maintain relatively higher PaO_2 during exposure to hypoxic mix than the ILD or COPD groups. This could reflect lung health, which is unaffected by the pathophysiology of this condition. Furthermore, this group was also the youngest and suggests that they are not negatively impacted by the progressive degeneration of tissues, structure and function of vital organs associated with ageing (MacNee et al., 2014). In addition, the MND group had the best response in terms of corrective supplemental oxygen to the induced hypoxaemia by the HCT. The patients studied within the MND group showed that 70% were deemed fit to fly without the need for in-flight oxygen, which would suggest the initial assessments, as proposed by the BTS do not accurately risk stratify patient with this disorder. Due to the recommendations advocating unnecessary assessments that are both time consuming and costly for both the patients and speciality service.

ILD

Interstitial lung disease is a term used to describe more than 200 different conditions that cause fibrosis (scarring) of the lung, which results in reduced lung volume and thickening of the interstitial tissue. The average survival for the most common form (idiopathic pulmonary fibrosis) is between 3 to 5 years, and describes the aggressive nature of the disorder that significantly shortens life-expectancy (Palange and Rohde, 2019). Like MND, many of these patients have ambitions to travel and visit regions of the world before their disease progresses to the state where ill health prevents. This group within the study was the oldest and possibly disadvantaged by the development of age-related disorders.

However, they were the least limited by ventilation, which was displayed by the spirometry. When corrected for demographical variance, the ILD patients had the best result in terms of FEV_1. Despite this, the reduction in PaO_2 during HCT was significantly lower than the MND group, and more akin to the COPD group. Unlike the MND patients, the pathophysiology of ILD affects alveolar performance, which would contribute to the greater reduction in PaO_2. Interestingly, of the ILD patient's assessment for in-flight oxygen, 52% were identified as not requiring supplemental oxygen during the flight, which was significantly more than those of the MND group.

COPD

COPD is a smoking related disorder that includes chronic bronchitis caused by long-term inflammation of the airways, and in its advanced form, emphysema as a result of protease and oxidants leading to the destruction of the alveoli (Walker et al., 2014). It is estimated that more than 80 million people worldwide suffer from moderate to severe disease, and it is predicted to be the third largest cause of death worldwide by the end of 2020 (NICE: Guideline Updates Team UK, 2018). The onset of COPD is generally considered to be from the age of forty onwards, however evidence is growing to suggest it can start considerably earlier, due to the significant problem of smoking through pregnancy (Bagdonas et al., 2015). The spirometric values for this group demonstrate the poorest FEV_1 with a similar mean FVC result to the MND and ILD groups. However, the pattern of limitation is completely different to the other disorders, which is obstructive in nature and validate the inability to engage the compensatory mechanism of ventilation to minimise hypoxaemia.

The COPD group had the lowest recorded PaO_2 during the HCT with 63% of the patients assessed deemed to require supplemental oxygen during commercial flights.

The demographic, spirometry and HCT data demonstrate significant differences between the disorders and express the pathophysiology, physiological and response to hypoxia during commercial flight. The development of the HCT, which is a fundamental part of the fitness to fly assessment was biased towards COPD patients. Furthermore, much of the screening and recommendations (figure 1) was based on Edvardsen and colleagues work, which was also COPD centric (Edvardsen et al., 2011; Edvardsen et al., 2012). The primary aim of this study was to investigate if these historical assumptions can be extended to other respiratory compromised patients, which on the evidence included within this work, would suggest not. Patients with respiratory limitation should be assessed on an individual basis until further work has been completed that describes the most appropriate approach to risk stratifying for their specific disorder.

Secondary aim: To examine the outcome of the HCT and compare to other physiological measurements, and to explore their predicted ability of HCT outcomes and consequences

Routine clinical care provides a plethora of data that is utilised to ensure optimum management of the patient's condition and to ensure the best prognostic outcome. Many respiratory physiology tests are used to risk stratify patients, which include preoperative assessment for major surgery, suitability for treatment (Pirfenidone and Nintedanib) or

when to initiate management (Older et al., 1999; National Institute for Health and Care Excellence, 2013; National Institute for Health and Care Excellence, 2016). The HCT has a clear threshold that is used to either confirm the patient is fit to fly without the need for supplemental oxygen or not. This binary approach (oxygen or not) would be best served by results already in the clinical domain and would provide a real step forward in ensuring the advice given to patients is both correct, evidence based and consistent.

MND

The MND group showed no difference with regards to age, smoking history or BMI in the pass and failed sets, however the fail group (require in-flight oxygen) were generally older and biased towards women. The spirometer data showed promise because many of the measures of this assessment showed significant difference, which would indicate a disparity that can be used to predict an outcome. The FEV_1 absolute, percent predicted, and z-scores were around 42% lower in the group that required in-flight oxygen suggesting this limitation in ventilation and subsequent inability to recruit compensatory mechanisms would help in identifying those at risk of hypoxaemia during flight. However, the analysis of variance through the binary logistic model signified limited relationship with the outcome of the HCT. The resting blood gas data also showed significant differences between the pass and fail groups for most measures, with similar findings. Nonetheless, if a patient has moderate to severely reduced spirometric values, and blood gases indicating respiratory failure, there is a fourfold increase in the need for in-flight oxygen, which is an important finding that can be translated into clinical practice. The resting PaO_2 and SpO_2 showed limited predictive value

to HCT outcome, which confirmed that the assessment and recommendations within the BTS guidance on managing patients planning air travel are unconvinced (Ahmedzai et al., 2011). Furthermore, numerous patients had PaO_2 >11.0 kPa and/ or SaO_2 >95% and went on to require in-flight oxygen as deemed by the HCT. Remarkably, the direct measure of respiratory muscle strength was comparable for both groups and offered no value in the evaluation of HCT outcomes.

These findings have significant consequences for clinical practice and challenge our understanding to date. Resting normoxia (sea level) and unremarkable spirometry do not translate to preserved oxygen status during commercial flight and requires a fundamental shift in our understanding in the assessment of fitness to fly in the MND patient population. This further supports the need to assess patients on an individual basis and highlights the importance of direct challenge to the hypoxic environment to ensure the correct management and prescription.

The use of predictive equations has been explored previously using resting oxygen status and spirometric values as predictors of HCT outcome (Martin et al., 2007). The study consisted of 45 patients made up of COPD (n = 15), ILD (n = 15) and cystic fibrosis (n = 15), which was significantly less than the patient numbers within this thesis. They concluded that predictive equations considerably overestimate the need for in-flight oxygen compared to the HCT. Interestingly, the regression equations produced from the MND data disagrees with this finding and describes the opposite. Furthermore, the proposed inclusion of

spirometry indices did not increase the equation accuracy in predicting in-flight hypoxaemia.

ILD

Within the ILD group, there was a significant increase in the number of patients who failed the HCT to the number who were investigated (52%) when compared to the MND group. This gives an insight into the clinical management of these 2 groups of patients and could indicate that we are over cautious with the latter. Conversely, it could suggest that there is increased risk of hypoxaemia during commercial flights for ILD patients. If the latter, it would support the view that historical assumptions cannot be extended to this group of patients.

Like the MND group, the spirometric data highlighted the majority difference between the pass and fail groups for ILD. The FEV_1 was approximately 18% lower for the fail group with FVC 16% respectively, confirming the difference in terms of ventilation capacity. However, this was to a lesser degree for FVC, which showed no significant difference ($p = 0.68$) and confirmed that it was rate related rather than volume. This suggests that increasing the frequency of ventilation is more important than the volume breathed in or out. Surprisingly, many of the investigations that are used in clinical practice to track the progression of the disease (transfer factor, static lung volumes, blood gases and 6MWT) showed no difference. These tests are specific to the pathophysiology of the disorder and chosen because of their physiological consequence. Both groups (pass and fail) had a reduction of over 50% in the

ability to transfer oxygen into the body, which reduce to 25% when corrected for reduced lung volume and is a direct measure of the alveolar/capillary membrane interaction. Static lung volumes were reduced for both groups, but approximately 18% more in the failed group. This was mirrored in the functional status measure (6MWT) by around 22%.

Although there was no significant difference between the pass and fail groups apart from dynamic spirometry, PaO_2 and SpO_2 during hypoxic mix, the patients who did require in-flight supplemental oxygen had physiological values that were between 16% to 25% lower than patients who did not require in-flight supportive oxygen. Further investigation of the spirometric data showed that there was a relationship between failing an HCT and FEV_1 corrected for demographics (FEV_1 % predicted), however this was weak (r^2 = 9.2%). The subsequent regression equation indicated that if you had a FEV_1 < 50% predicted, you would require in-flight oxygen. This would have incorrectly predicted a requirement for in-flight oxygen in 85% of the ILD HCT pass group. Even when you use resting PaO_2 and FEV_1 percent predicted the equation is still weak (r^2 = 13.7). This further demonstrates the inconsistences of predictive equations for calculating the need for in-flight oxygen and highlights the dangers of using other physiological data to risk stratify outcomes.

COPD

The COPD group showed a worryingly high proportion of patients that required in-flight oxygen compared to the overall number in the group (59%). The management of COPD is predominately primary and intermediate care based, with acute exacerbations through

accident and emergency portals to secondary care (Wedzicha et al., 2017). If these findings are extended to the wider population, there is the question of who is assessing this patient populace, and risk stratifying with regards to their ability to fly on commercial airlines? All COPD passengers should be appraised for risk of flying and every intervention should be reviewed to minimise risk and prevent adverse events from occurring (Ergan et al., 2018). This includes medical history, comorbidities, ongoing treatments, and clinical assessments. In addition, discussions about flying and previous symptoms during travel should be discussed with the patient to ensure they are part of the assessment process. Furthermore, optimisation of treatment, risk for in-flight hypoxaemia and oxygen need are key. General practitioners (GP's) are often the first healthcare provider prior to air travel and should be actively involved in assessment and educating the patients. All referrals into this study have come from disease specific services and general respiratory clinics within a tertiary centre. Within North Staffordshire, there are no referral pathways for GPs to obtain clinical support to assess risk of hypoxaemia during air travel, nor oxygen need. This is clearly a concern and creates a potential situation where numerous COPD patients are planning and undertaking air travel, which is not adequately assessed. Using the pass to fail ratio within this study, it could be argued that there is a large portion of COPD patients who are undertaking air travel without any formal assessment and are at significant risk of hypoxaemia and adverse events. However, this would require further investigation to understand the extent of the problem.

The spirometry results within the failure group demonstrated increased level of severity with regards to obstruction, which was supported by the static lung volumes in terms of hyperinflation and air trapping. Conversely, they exhibited better results for transfer factor. Unfortunately, the number of patients that had available pulmonary function tests was restricted and is a limitation within this study group, which resulted as insufficient data for valid comparison for the 6MWT (functional status) and SNIP (respiratory muscle strength). However, eleven of the thirty-two patients in the fail group had $SaO_2 \geq 95\%$, which questions the initial assessment as set out by the BTS (Ahmedzai et al., 2011).

Limitations

There are several limitations to the study, with the primary limitation being the retrospective design. Therefore, caution must be exercised as patient selection, data and information cannot be controlled. However, the risk of any bias is likely to be low since the investigated variables were recorded as part of the clinical pathway.

Investigated variables were based on available information obtained through routine clinical patient care and equated to the relevant literature to date. While this approach is appropriate for the ongoing management of the patient's condition, other physiological parameters relating to pathophysiology may not have been considered, including confounding variables. All the patients included in the study were managed in a tertiary centre due to the level of expertise required for ongoing management. Unfortunately, patients from the community were not included and this would advocate further research

within this setting to gain an understanding of the potential problems within this location. Due to this, the results of the study may only be reflective of secondary care and may not be extended to the primary care setting. However, this is a snapshot that is specific to the University Hospitals of North Midlands NHS Trust, which is real world clinical care that can further advance the previous research for better patient care.

Although the overall sample size is good for the MND group, the ILD and COPD groups were significantly less. This coupled with incomplete or missing data, may have affected the outcomes in the regression analysis. There are no static lung volumes, transfer factor or 6MWT data for the MND group as per clinical guidance. Furthermore, twenty-three ILD patients also did not have static lung volumes or transfer factor results, and 15 no 6MWT data. For the COPD group, nine had no spirometric data, twenty-three had no static lung volume or transfer factor results and only five patients had a 6MWT assessment. However, the populations studied within this thesis were significantly more than many of the research studies included in the literature review, especially for the MND and ILD groups. Complete data and additional participants would be required to increase the sample sizes and overcome the limitation in patient numbers.

To improve the design of this retrospective study the following suggestions should be considered. A prospective study should be conducted, which would allow additional variables to be included that are outside the routine clinical care of the studied patient groups. This would also address the issue of missing data and would improve the quality of

the statistics. Increasing the patient numbers would help in the development of tools which could accurately predict the risk of hypoxaemia during air travel.

Clinical application

The findings of this thesis confirm that there are significant differences in the way that patients tolerate the hypoxic setting during commercial air travel. Their ability to respond to this environment is largely based on the pathophysiology of their disorder and the ability to recruit compensation mechanisms to reduce hypoxaemia. Many of the recommendations and guidelines for the assessment and management of patients planning air travel are based on COPD populations with limited data for other respiratory conditions. The understanding and recommendations endorsed by these documents to safely risk-stratify patients planning air travel has been challenged and questions the current guidance in the clinical assessment of fitness to fly (British Thoracic Society Standards of Care Committee, 2002; Ahmedzai et al., 2011). The thresholds recognised in these documents must be treated with caution as it is clear from the data that normoxia does not advocate that an individual will not develop hypoxaemia during a commercial flight. Furthermore, physiological assessments which are used to complement the measure of resting oxygen status can also be misleading and cannot accurately predict in-flight oxygen needs.

Currently, clinicians base their advice on the BTS recommendations (Ahmedzai et al., 2011), which suggest a SpO2 >95% (sea level) indicates that a patient does not require in-flight oxygen. Furthermore, if the SpO2 is between 92% to 95% with no risk factors (hypercapnia,

FEV_1 <50% predicted, lung cancer, restrictive lung disease involving the parenchyma (fibrosis,) chest wall (kyphoscoliosis) or respiratory muscles, ventilator support, cerebrovascular or cardiac disease, within 6 weeks of discharge for an exacerbation of chronic lung or cardiac disease) there is still no requirement for in-flight oxygen. The same criteria with risk factors advocate the need for an HCT to determine in-flight oxygen need. If the patients SpO_2 <92% or those who received oxygen therapy as part of their ongoing management, require in-flight oxygen. However, there are still discrepancies regarding which patient requires a referral before air travel and what is the gold standard test for assessment of hypoxaemia (Ergan et al., 2018). Generally, patients who present with poor physiological indices (FEV1 <1.5 litres or FEV1 <30% predicted) with significant comorbidities that may exacerbate hypoxaemia and have previously had symptoms during air travel, are considered high risk and require further evaluation (International Air Transport Association, 2014), but this is based predominately on COPD patients and cannot be extended to other respiratory diseases.

The clinical practice should consist of an assessment of general wellbeing, evaluation of symptoms with a full clinical history that questions recent exacerbation and ongoing treatments/management for all patients planning a flight. This should also be supplemented by a full physical examination. Historically, the investigations used for pre-flight assessment were oxygen saturation (96%), pulmonary function (95%), HCT (45%) and walk test (10%) (Coker et al., 2007). However, the result from this thesis has questioned the definitive value of resting oxygen saturation and pulmonary function, and therefore advocates the increased

use of HCT in the assessment of in-flight hypoxaemia, which will be challenging moving forward due to availability. This is further supported by the data which confirms different response characteristics of other respiratory disorders and supports the development of the disease specific guidelines rather than one single recommendation. Finally, the clinician should also ensure that the patient is receiving optimate medical treatment according to their disease severity and that they are in a stable period, which should be at least 6-week without any recent exacerbations.

Future research

The originally proposed research for this thesis was to be a prospective study that looked at three specific aspects of respiratory compromised patients undertaking air travel. The initial aim of the research was to look at patients' previous experience of air travel and comparing this with the result of an HCT. The second aim of the study was to investigate the modalities in which oxygen is supplied during a flight (continuous or pulsed oxygen). The final aim was to investigate the outcomes of the HCT and compare this to other physiological measures to explore their predictive ability of HCT outcomes and consequences.

Awareness of the problems associated with air travel for patients who are compromised by their disorder come from airline adverse incident reports or organisations responsible for overseeing aviation standards (ICAO, 2018; Peterson et al., 2013). This represents a biased view of the problems and only identifies those who experience difficulties due to the hypoxic environment. Prior understanding of their underlying condition and comorbidities is

not known and how they compare to the recognised pre-flight assessment of oxygen status, risk factors and response to the pressurised cabin environment. This information would have been obtained through a questionnaire that is completed by the individual following a previous flight (Appendix 4). The questionnaire was designed to obtain the following information.

I. Indicated main health problem
II. Time since last flight
III. Destination and duration of the flight
IV. If symptoms were experienced (shortness of breath, chest pain, cough, faint, wheeze, infection, phlegm or other)
V. When the symptoms occurred (outbound, during visit/holiday or return flight)
VI. Treatment received and if so, what? (Inhalers, steroids, antibiotics, pain relief, nebulisation, or oxygen)
VII. Did they sleep at any time during the flights?
VIII. Obtain information about their understanding of the problems associated with air travel (rescued oxygen, expansion of gas, infections, or deep vein thrombosis (DVT)
IX. Had they had a previous HCT?
X. Where did they obtain their information?
XI. Did this impact their decision to fly?

The information regarding condition, symptoms and medication received from the questionnaire could be compared to the outcome of the HCT and physiological measure to appraise the current guidance set out by the BTS (Ahmedzai et al., 2011) in terms of resting oxygen status, spirometry, and comorbidities. The questionnaire would give an insight into the effect of flight duration, which equates to the period of exposure to the hypoxic environment along with the patients understanding of the risks associated with air travel. This would enable the targeting of key areas both within the patient and clinical domains to increased knowledge and understanding and to ensure consistent information and advice is maintained. The questionnaire was developed through both clinical and patient involvement to assess readability and clinical relevance.

There is currently a plethora of airlines carrying passengers all over the world. These airlines adhere to their own policies for the provision of on-board oxygen for patients who potentially become hypoxaemic during the flight. These policies range from airline provision for in-flight oxygen to allowing passengers to provide their own oxygen modality. The airline providing oxygen is generally in the continuous form by either 2 or 4 litres/min. However, many are moving to a pulsed system, which delivers a pulse of oxygen to the user during inspiration (European Lung Foundation, 2020). The benefit of this is that there is a reduced demand for oxygen during the flight and can demonstrate significant financial benefit. When assessing patient suitability before air travel, the correct modality must be identified so that the appropriate oxygen titration, during an HCT can be performed. Currently, many centres providing fitness to fly assessment with HCT only use the continuous method

irrespective of planned modality for the future flight (The Association for Respiratory Technology & Physiology, 2012). Furthermore, disorders that adversely affect respiratory muscle function or tidal volume, often are unable to trigger the device for pulsed oxygen due to insufficient negative pressure on inspiration (Palwai et al., 2010). This discrepancy could lead to the passenger having incorrectly prescribed oxygen leading to an increased risk of hypoxaemia.

Further research is required to investigate the extent to which this difference in modality can make with regards to supplemental oxygen response during flight. Patients attending for a fitness to fly assessment whose HCT indicated the need for in-flight oxygen would be titrated using both modalities (continuous and pulsed) to explore the differences in maintaining normoxia. This analysis could also contribute to our understanding of the way specific diseases respond and help in the management of these individual groups. Furthermore, this could be extended to the assessment of portable oxygen concentrators, which is an accepted method of self-administered oxygen provision during a commercial flight for some airlines (Nicholson and Sznajder, 2014; European Lung Foundation, 2020).

The ability to predict the outcome of an HCT and subsequent passenger oxygen requirements during a commercial flight has enormous benefits for clinical practice. Ongoing care and management of patients produce a significant amount of physiological data which describes the pathophysiology of the disease. The aim of this thesis was to

explore the predictive ability of this data to foresee the outcome of the HCT and therefore, in-flight oxygen need.

Due to the retrospective nature of the thesis, some of the data was incomplete and subsequently affected the quality. Furthermore, because of the specific patient pathways, there was an inconsistency between the studied populations with promising predictive investigations or results not realised. A prospective study would address this issue and allow the inclusion of other potential predictive markers of HCT outcome. These would include full pulmonary function tests (dynamic spirometry, static lung volumes, transfer factor) and 6MWT. The use of questionnaires within respiratory medicine is significant and forms a vital part of the management of many respiratory conditions by providing relevant clinical information regarding disease progression, signs and symptoms, impact on daily activities and prognostic outcomes (Yohannes et al., 2000; Pitta et al., 2006). This form of clinical data could be included in future research to explore the effects of specific diseases on the activities of daily living, and how this correlates with response to a hypoxic environment (cabin).

Many clinical conditions within respiratory and cardiovascular specialities can result in nocturnal oxygen desaturation. The extent of this problem has been investigated extensively (Davies et al., 1991; Plywaczewski et al., 2000; Nisbet et al., 2006), however its relation to in-flight hypoxaemia less so. A hypothesis that many patients who are assessed as part of a fitness to fly service experience nocturnal desaturation most nights due to their

underlying condition. The predictive merits of overnight oximetry could be considered and investigated in terms of its relation to in-flight hypoxaemia by comparing overnight oximetry with HCT outcome.

The previously suggested questionnaire to obtain retrospective information regarding prior flight experience could be problematic because it relies on the individual to accurately document their observations, facts, or events. A prospective questionnaire completed during or immediately following a planned commercial flight would be more robust and accurate. The questionnaire in appendix 5 was developed as part of the original thesis and was an academic, ethical, clinical, and patient collaborative.

Future research considerations concerning risk stratification of respiratory compromised patients wishing to undertake air travel stem from the preliminary work which formed part of the original proposal for this thesis. The primary aim of the proposed research was to investigate to what extent in-flight hypoxia affects patients' symptoms and if exposure is detrimental.

The secondary aim of the study was to investigate the alternative pulsed method of oxygen delivery against the gold standard (continuous flow) and to offer this alternative method which is in keeping with the modality used by many airlines. Also, the outcome of the HCT will be compared to other physiological measures (e.g., overnight oximetry, supplemental physiological data, and health status questionnaire) to investigate their predictive ability of

HCT outcomes and consequences. To address these aims, a protocol was developed and is summarised below (figure 13). Many of the investigations and procedures were outside of routine clinical practice, which necessitated the need for ethical consideration and approval (Appendix 6). The flowchart describes the process and the patient journey from recruitment to exit of the study. Unfortunately, COVID-19 had a significant impact on all research and therefore the hosting organisation stopped all ongoing studies including the original thesis proposal.

An application is currently being considered by the research and development department at the University Hospitals of North Midlands NHS Trust, to restart the study that has successfully recruited and exited fifteen participants to date. Furthermore, the process of extending the research past its original completion date is currently being reviewed by the regional ethics committee. Once approval has been achieved, the original research will commence with the view of publication of results which could form the basis of future guidelines for patients wishing to undertake air travel.

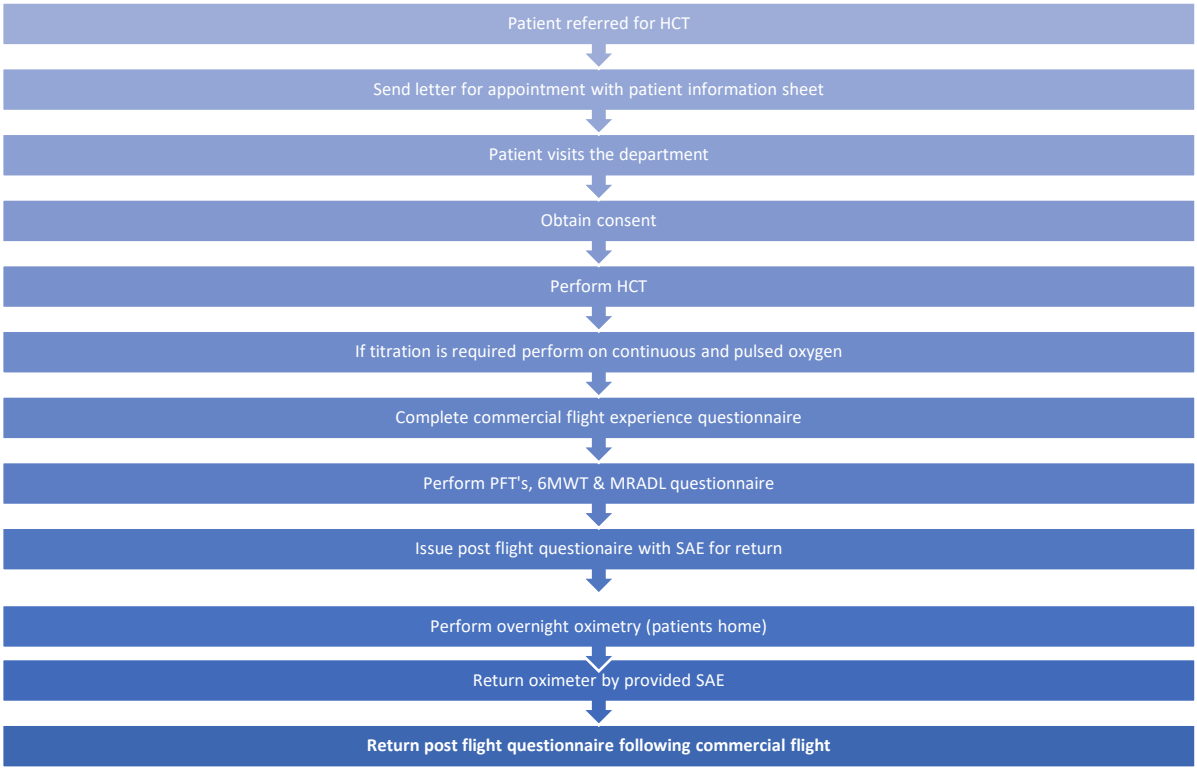

Figure 13. Trial flowchart

9. Conclusion

In respiratory compromised patients, there is a significant risk of hypoxemia during air travel. The pressurisation of the aircraft cabin to 8000 ft (2438 m) maintains FiO_2 at a reduced level of approximately 15%. The historical evidence has predominately included COPD patients and accepted that other disorders respond in a similar physiological manner. This retrospective observational study explored the effect of a hypoxic environment on MND and ILD patients and compared this to accepted recommendations and guidelines based on the COPD population. The analysis demonstrated that both MND and ILD patients differ significantly in their physiological responses to a hypoxic environment than COPD patients. Furthermore, there were differences between all the studied groups.

The clinical evaluation of patients undertaking air travel by utilising resting physiological parameters was limited. The data had a low predictive value in identifying patients at risk of becoming hypoxic during a commercial flight. The current recommendations are based mainly on a patient's ability to maintain normoxia at sea level. However, the data within the thesis showed that typical PaO_2 values could not assume an individual did not require in-flight oxygen. The use of spirometric parameters was unable to enhance predictive power.

The observation within this thesis illustrates that assumptions of guidelines and recommendations clinically used to risk-stratify patients planning air travel do not adequately appreciate the pathophysiology of other respiratory disorders. An individual's ability to recruit compensatory mechanisms as a response to a hypoxic environment

requires an appropriate clinical assessment consisting of a full clinical history, physical examination, and a hypoxic challenge test.

The research has highlighted the need for further work specifically around disease types. There is currently ethical approval to research the groups studied within this thesis in terms of further exploration of differences, predictive factors and the development of disease-specific guidelines and recommendations.

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Appendix 1 Binary logistic regression MND: HCT outcome vs PaO2. PaCO2. BE. FEV1 PD & birth sex

WORKSHEET 2

Binary Logistic Regression: Passed versus PaO2, PaCO2, BE, GLI FEV1 % PD, Gender

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	85
Rows unused	33
Test set fraction	30.6%

Response Information

Variable	Value	Training Count	Test Count
Passed	Fail	12	3 (Event)
	Pass	47	23
	Total	59	26

Regression Equation

P(Fail) = exp(Y')/(1 + exp(Y'))

Gender	
F	Y' = 3.836 - 1.376 PaO2 + 1.452 PaCO2 + 0.3539 BE - 0.006752 GLI FEV1 % PD
M	Y' = 2.540 - 1.376 PaO2 + 1.452 PaCO2 + 0.3539 BE - 0.006752 GLI FEV1 % PD

Coefficients

Term	Coef	SE Coef	Z-Value	P-Value	VIF
Constant	3.84	7.68	0.50	0.617	
PaO2	-1.376	0.621	-2.22	0.027	1.31
PaCO2	1.45	1.42	1.02	0.306	2.99
BE	0.354	0.364	0.97	0.332	2.61
GLI FEV1 % PD	-0.0068	0.0263	-0.26	0.798	1.40
Gender					
M	-1.30	1.09	-1.19	0.236	1.16

Odds Ratios for Continuous Predictors

	Odds Ratio	95% CI
PaO2	0.2527	(0.0749, 0.8528)
PaCO2	4.2695	(0.2649, 68.8272)
BE	1.4247	(0.6974, 2.9105)
GLI FEV1 % PD	0.9933	(0.9433, 1.0459)

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Gender			
M	F	0.2735	(0.0321, 2.3312)

Odds ratio for level A relative to level B

Model Summary

Deviance R-sq	Deviance R-sq(adj)	AIC	AICc	BIC	Area Under ROC Curve	Test Deviance R-sq	Test Area Under ROC Curve
54.47%	46.08%	39.13	40.75	51.60	0.9433	27.94%	1.0000

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	53	27.13	0.999
Pearson	53	35.66	0.968
Hosmer-Lemeshow	8	6.65	0.575

Analysis of Variance

Source	DF	Wald Test Chi-Square	P-Value
Regression	5	10.90	0.053
PaO2	1	4.91	0.027
PaCO2	1	1.05	0.306
BE	1	0.94	0.332
GLI FEV1 % PD	1	0.07	0.798
Gender	1	1.41	0.236

Fits and Diagnostics for Unusual Observations

Training Set

Obs	Observed Probability	Fit	Resid	Std Resid	
57	0.000	0.504	-1.185	-1.58	X
68	0.000	0.545	-1.255	-1.64	X
96	1.000	0.178	1.857	2.02	R
106	1.000	0.701	0.844	1.05	X
108	1.000	0.053	2.425	2.62	R

R Large residual
X Unusual

Fits and Diagnostics for Unusual Observations

Test Set

Obs	Observed Probability	Fit	Resid	Std Resid	
25	0.000	0.509	-1.193	-0.95	X
59	0.000	0.535	-1.238	-0.93	X
63	0.000	0.821	-1.855	-1.36	X

X Unusual X

Appendix 2 Binary logistic regression ILD: HCT outcome vs PaO2. PaCO2. BE. FEV1 PD & birth sex

WORKSHEET 1

Binary Logistic Regression: Passed versus PaO2, PaCO2, BE, GLI FEV1 % PD, Gender

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	53
Rows unused	3

Response Information

Variable	Value	Count
Passed	Fail	26 (Event)
	Pass	27
	Total	53

Regression Equation

P(Fail) = exp(Y')/(1 + exp(Y'))

Gender

Female Y' = 3.661 - 0.1019 PaO2 + 0.2420 PaCO2 - 0.04996 BE - 0.06183 GLI FEV1 % PD

Male Y' = 4.687 - 0.1019 PaO2 + 0.2420 PaCO2 - 0.04996 BE - 0.06183 GLI FEV1 % PD

Coefficients

Term	Coef	SE Coef	Z-Value	P-Value	VIF
Constant	3.66	6.20	0.59	0.555	
PaO2	-0.102	0.310	-0.33	0.742	1.13
PaCO2	0.242	0.951	0.25	0.799	1.81
BE	-0.050	0.245	-0.20	0.839	1.73
GLI FEV1 % PD	-0.0618	0.0219	-2.82	0.005	1.11
Gender					
Male	1.026	0.730	1.40	0.160	1.08

Odds Ratios for Continuous Predictors

	Odds Ratio	95% CI
PaO2	0.9032	(0.4920, 1.6580)
PaCO2	1.2738	(0.1974, 8.2194)
BE	0.9513	(0.5883, 1.5382)
GLI FEV1 % PD	0.9400	(0.9005, 0.9813)

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Gender			
Male	Female	2.7901	(0.6667, 11.6754)

Odds ratio for level A relative to level B

Model Summary

Deviance R-sq	Deviance R-sq(adj)	AIC	AICc	BIC	Area Under ROC Curve
19.34%	12.53%	71.25	73.08	83.07	0.7892

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	47	59.25	0.108
Pearson	47	53.38	0.242
Hosmer-Lemeshow	8	4.39	0.820

Analysis of Variance

		Wald Test	
Source	DF	Chi-Square	P-Value
Regression	5	9.84	0.080
PaO2	1	0.11	0.742
PaCO2	1	0.06	0.799
BE	1	0.04	0.839
GLI FEV1 % PD	1	7.96	0.005
Gender	1	1.97	0.160

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
13	0.000	0.883	-2.071	-2.14	R
14	0.000	0.758	-1.686	-2.04	R
32	1.000	0.129	2.022	2.13	R

R Large residual

Appendix 3 Binary logistic regression COPD: HCT outcome vs PaO2. PaCO2. BE. FEV1 PD & birth sex

WORKSHEET 1

Binary Logistic Regression: Passed versus PaO2, PaCO2, BE, GLI FEV1 % PD, Gender

Method

Link function	Logit
Categorical predictor coding	(1, 0)
Rows used	39
Rows unused	12

Response Information

Variable	Value	Count
Passed	Pass	16 (Event)
	Fail	23
	Total	39

Regression Equation

P(Pass) = exp(Y')/(1 + exp(Y'))

Gender	
Female	Y' = -2.645 + 0.7423 PaO2 - 0.8837 PaCO2 + 0.3024 BE + 0.01501 GLI FEV1 % PD
Male	Y' = -4.051 + 0.7423 PaO2 - 0.8837 PaCO2 + 0.3024 BE + 0.01501 GLI FEV1 % PD

Coefficients

Term	Coef	SE Coef	Z-Value	P-Value	VIF
Constant	-2.65	7.19	-0.37	0.713	
PaO2	0.742	0.487	1.52	0.127	1.66
PaCO2	-0.88	1.02	-0.87	0.384	3.50
BE	0.302	0.352	0.86	0.390	3.51
GLI FEV1 % PD	0.0150	0.0199	0.75	0.450	1.21
Gender					
Male	-1.405	0.884	-1.59	0.112	1.46

Odds Ratios for Continuous Predictors

	Odds Ratio	95% CI
PaO2	2.1008	(0.8090, 5.4552)
PaCO2	0.4132	(0.0564, 3.0268)
BE	1.3531	(0.6790, 2.6965)
GLI FEV1 % PD	1.0151	(0.9763, 1.0555)

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI
Gender			
Male	Female	0.2453	(0.0433, 1.3881)

Odds ratio for level A relative to level B

Model Summary

Deviance R-sq	Deviance R-sq(adj)	AIC	AICc	BIC	Area Under ROC Curve
15.78%	6.32%	56.47	59.09	66.45	0.7582

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	33	44.47	0.088
Pearson	33	41.24	0.154
Hosmer-Lemeshow	8	9.23	0.324

Analysis of Variance

		Wald Test	
Source	DF	Chi-Square	P-Value
Regression	5	5.78	0.328
PaO2	1	2.32	0.127
PaCO2	1	0.76	0.384
BE	1	0.74	0.390
GLI FEV1 % PD	1	0.57	0.450
Gender	1	2.53	0.112

Fits and Diagnostics for Unusual Observations

Obs	Observed Probability	Fit	Resid	Std Resid	
41	1.000	0.081	2.243	2.40	R

R Large residual

Appendix 4 Commercial flight experience questionnaire

Study No: _____

Commercial Flight Experience Questionnaire

1. Could you indicate your main health problem?

- ☐ N/A
- ☐ COPD
- ☐ MND
- ☐ ILD
- ☐ Other .....

2. How long has it been since you went on a commercial flight? (Choose one option).

- ☐ <1 month
- ☐ 1-3 months
- ☐ 4-5 months
- ☐ 6-12 months
- ☐ >12 months
- ☐ N/A (Go to question 8)

3. Could indicate the destination and approximate duration of the flight in hours?

	Duration/Hr
☐ Europe	_____
☐ America	_____
☐ Australasia	_____
☐ Africa	_____
☐ Asia	_____

4. Did you have any symptoms or problems below during any of the flights?

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Short of breath	☐	☐	☐	☐	☐
Chest pain	☐	☐	☐	☐	☐
Cough	☐	☐	☐	☐	☐
Faint (Light headed)	☐	☐	☐	☐	☐
Wheeze	☐	☐	☐	☐	☐
Infection	☐	☐	☐	☐	☐
Phlegm	☐	☐	☐	☐	☐

Other (please state) .....

5. When did these symptoms or problems occur?

Out-bound
During holiday/visit aboard
Return flight
Both
☐ N/A (Go to question 8)

6. Which treatment, if any, did you receive? (Select all that apply)

☐ Use of inhaler/s
☐ Steroids
☐ Antibiotics
☐ Paracetamol or Ibuprofen
☐ Use of nebuliser
☐ Oxygen
☐ No treatment required

7. Did you sleep during any of the flights?

☐ Yes, during the outboand flight only
☐ Yes, During the return flight only
☐ Yes, during both the outbound and return flight
☐ No, I did not sleep on either flight

8. Do you understand the associated problems with flying?

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Reduced Oxygen	☐	☐	☐	☐	☐
Expansion of gases (ear popping)	☐	☐	☐	☐	☐
Spread of infection	☐	☐	☐	☐	☐
Blood clots (DVT)	☐	☐	☐	☐	☐

9. Did you know you can have a flight assessment to check your oxygen level before travelling?

☐ Yes
☐ No

10. If yes, where did you obtain this information from?

GP
Hospital Doctor
Clinical Nurse Specialist
Internet
Information Leaflets
Other, please state .....

11. Did the information from your previous flight assessment give you confidence to fly?

Yes
No

Thank you for your help in completing this questionnaire

Appendix 5 Post commercial flight experience questionnaire

Study No: _____

Commercial Flight Experience Questionnaire

To be completed upon return from travels

1. Could indicate the destination and approximate duration of the flight in hours?

	Duration/Hr
☐ Europe	_____
☐ America	_____
☐ Australasia	_____
☐ Africa	_____
☐ Asia	_____

2. Did you sleep during the flight?

☐ Yes, during the outboand flight only
☐ Yes, During the return flight only
☐ Yes, during both the outbound and return flight
☐ No, I did not sleep on either flight

3. Did you have any symptoms or problems below during your current flight?

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Short of breath	☐	☐	☐	☐	☐
Chest pain	☐	☐	☐	☐	☐
Cough	☐	☐	☐	☐	☐
Faint (Light headed)	☐	☐	☐	☐	☐
Wheeze	☐	☐	☐	☐	☐
Infection	☐	☐	☐	☐	☐
Phlegm	☐	☐	☐	☐	☐

Other (please state) .....

When did these symptoms occur?

☐ Out-bound
☐ During holiday/visit aboard
☐ Return
☐ Both
☐ N/A

Could you please return this questionnaire **within 2 week** of returning and thank you for your help in participating in the research

Version 3

Appendix 6 Ethical committee approval letter

Health Research Authority

South Central - Oxford B Research Ethics Committee
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol
BS1 2NT
Telephone: 020 7104 8049

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

23 July 2019

Mr Ian Cliff
Clinical Scientist
University Hospitals of North Midlands
Respiratory Physiology
Heart & Lung Clinic
Main Building
ST4 6QG

Dear Mr Cliff

Study title:	**Is the perceived risk of hypoxia during commercial aircraft travel a relevant risk for individuals who are respiratory compromised, and are we assessing appropriately or are there more effective methods to ensure normoxia?**
REC reference:	**19/SC/0315**
Protocol number:	**2455[##IfProtocolRef##]**
IRAS project ID:	**251944**

Thank you for your letter of 17th July 2019, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Recommendation:

The Committee noted that there was a typographical error in the revision to the invitation letter. "Influence and fitness-to-fly" should read "influence any fitness-to-fly". They suggested this be corrected but that the Committee did not need to see revised documentation.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

It is a condition of the REC favourable opinion that all clinical trials are registered on a publicly accessible database. For this purpose, clinical trials are defined as the first four project categories in IRAS project filter question 2. For clinical trials of investigational medicinal products (CTIMPs), other than adult phase I trials, registration is a legal requirement.

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [HRA REC cover letter Hypoxic Challenge Test 09.05.2019]		09 May 2019
GP/consultant information sheets or letters [HCT Role in Flight Assessment GP Letter V1.0 09.07.2019]	v1.0	09 July 2019
IRAS Application Form [IRAS_Form_09052019]		09 May 2019
IRAS Checklist XML [Checklist_17072019]		17 July 2019
Letter from sponsor [R&D Sponsorship Approval Letter Cliff, Ian]		03 January 2019

Letters of invitation to participant [HCT Role in Flight Assessment Participant Invite Letter v1.1 09072019 IRAS 251944]	v1.1	09 July 2019
Letters of invitation to participant [HCT Role in Flight Assessment Participant Invite Letter v1.1 09072019 IRAS 251944 TC]	1.1	09 July 2019
Non-validated questionnaire [Baseline commercial flight experience questionnaire v1.1 10072019]	v1.1	10 July 2019
Non-validated questionnaire [Follow Up Commercial Flight experience Questionnaire v1.1 10072019]	v1.1	10 July 2019
Other [Peer Review Approval for DClinSci Research Project Proposal Proforma (Physiological Sciences)]		20 August 2018
Other [HCT Role in Flight Assessment Protocol v1.1 09072019 IRAS 251944 TC]	v1.1	09 July 2019
Other [CV Academic Supervisor 260619]		26 June 2019
Other [Statement form Academic Supervisor 260619]		26 June 2019
Other [Follow- Up Commercial Flight experience Questionnaire v1.1 1072019 TC]	v1.1	10 July 2019
Other [Baseline commercial flight experience questionnaire v1.1 10072019 TC]	v1.1	10 July 2019
Other [HRA and Ethics cover letter 17.07.2019]		17 July 2019
Participant consent form [HCT Role in Flight Assessment Consent Form v2.0 09072019 IRAS 251944]	2.0	09 July 2019
Participant consent form [HCT Role in Flight Assessment Consent Form v2.0 09072019 IRAS 251944 TC]	2.0	09 July 2019
Participant information sheet (PIS) [HCT Role in Flight Assessment PIS v2.0 09072019 IRAS 251944]	v2.0	09 July 2019
Participant information sheet (PIS) [HCT Role in Flight Assessment PIS v2.0 09072019 IRAS 251944 TC]	v2.0	09 July 2019
Research protocol or project proposal [HCT Role in Flight Assessment Protocol v1.1 09072019 IRAS 251944]	v1.1	09 July 2019
Summary CV for Chief Investigator (CI) [Ian Cliff CV February 2018]		14 February 2018
Validated questionnaire [MRADL]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/SC/0315	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely
PP

Mr Chris Foy
Chair

Email:nrescommittee.southcentral-oxfordb@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Ms Heather Reidy, University Hospitals of North Midlands