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Title:
Understanding the clinical course and progression of non-malignant pleural disease

implications for future interventions

Understanding the clinical course and progression of non-malignant pleural disease: implications for future interventions

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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Health Sciences

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March 2020

Word count: 42,172

ABSTRACT

Introduction

Pleural disease secondary to non-malignant processes is a significant cause of morbidity and mortality. There is currently sparse literature detailing the clinical course and progression of this patient cohort.

The two populations of interest are patients with transudative pleural effusions and patients with pneumothorax secondary to underlying lung disease (secondary spontaneous pneumothorax).

This thesis seeks to expand the understanding of the disease course in these patient populations and examine whether ambulatory management would improve outcomes. The hypothesis of this thesis is 'ambulatory management of non-malignant pleural disease will lead to improved patient-related outcomes and shorter length of hospitalisation'.

Methods

Part A: Ambulatory management of transudative pleural effusion

Analysis of 782 patients, including 356 with non-malignant pleural effusions, demonstrated a high 1-year mortality in patients with transudative effusions. Analysis of 105 patients with cardiogenic pleural effusions found a high rate of symptomatic re-accumulation, with nearly a quarter of patients requiring further therapeutic pleural procedures. To investigate the optimal method of managing symptomatic, refractory transudative pleural effusions, this thesis details the REDUCE trial, a randomised controlled trial in this patient cohort, allocating participants to indwelling pleural catheters or therapeutic aspiration.

Part B: Ambulatory management of pneumothorax

In order to investigate the disease course of pneumothoraces, this thesis conducted a systematic review on the rate of recurrence in patients with a primary spontaneous pneumothorax, demonstrating a 32% recurrence rate. A further study examined conservative management in patients with traumatic pneumothoraces, demonstrating a role for expectant management. The final study, the Hi-SPEC trial, is a randomised controlled trial examining the role of ambulatory management of secondary spontaneous pneumothorax, allocating participants to ambulatory Heimlich valve or standard care.

Discussion

This thesis adds to our understanding of the prognosis and outcomes of patients with transudative pleural effusions. The results from the REDUCE trial will inform on the use of ambulatory management in this patient cohort.

This thesis adds to our understanding of the natural history of pneumothoraces. The results from the Hi-SPEC trial will inform on the use of ambulatory management in patients with secondary spontaneous pneumothorax.

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author

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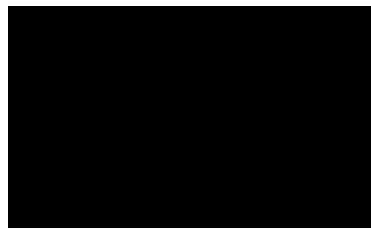
DATE: 2nd April 2020

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

A&E	Accident & emergency
ACE-inhibitor	Angiotensin-converting enzyme inhibitor
AE	Adverse events
AF	Atrial fibrillation
ARB	Angiotensin II receptor blocker
ATLS	Advanced trauma life support
ATS	American thoracic Society
BAPE	Benign asbestos pleural thickening
BMI	Body mass index
BPM	Beats per minute
BTS	British thoracic society
CA-125	Cancer antigen 125
CABG	Coronary artery bypass graft
CAG	Confidentiality advisory Group
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Clinical record form
CRP	C-reactive protein
CRT	Cardiac-resynchronization therapy

CT	Computerised tomography
Cx	Conservative
CXR	Chest x-ray
DMC	Data monitoring committee
DPT	Diffuse pleural thickening
DSS	Dystrophic severity score
ECOG	Eastern cooperative oncology group
ED	Emergency Department
ELC	Emphysema-like changes
EQ-5D-5L	EuroQol - 5 dimensions - 5 Levels
FDA	Food and drug Administration
Fr	French
GA	General anaesthetic
GCP	Good clinical practice
GCS	Glasgow coma scale
H20	Dihydrogen monoxide
HAS	Human albumin solution
HDU	High dependency unit
Hi-SPEC	Heimlich valves in secondary spontaneous pneumothorax: enhancing care
HR	Hazard ratio
HRA	Health research authority
HRCT	High-resolution computer tomography

HV	Heimlich valve
HVCD	Heimlich valve chest drain
ILD	Interstitial lung disease
ICD	Intercostal drain
ICD-10	International classification of diseases
ICU	Intensive care unit
IPC	Indwelling pleural catheter
IPPV	Intermittent positive pressure ventilation
IQR	inter-quartile range
ISS	Injury severity score
LAM	Lymphangioleiomyomatosis
LDH	Lactate dehydrogenase
LENT	LDH; ECOG performance score; NLR, Tumour type
LV	Left ventricular
MCT	Mini-chest tube
MD	Median
MELD	Model for end-stage liver disease
MID	Minimal important difference
MN	Mean
MPE	Malignant pleural effusion
MTC	Major trauma centre
NA	Needle aspiration

NA	Not applicable
NHS	National health service
NLR	Neutrophil lymphocyte ratio
NMPD	Non-malignant pleural disease
NMPE	Non-malignant pleural effusion
NRES	National research ethics service
NS	Not stated
NYHA	New York heart association
O2	Oxygen
OR	Odd ratio
PA	Posterior-anterior
PD	Peritoneal dialysis
PE	Pulmonary embolism
PICD	Paracentesis-induced circulatory dysfunction
PICO	Population intervention comparator outcome
PO	Per oral
PIS	Patient information sheet
PPV	Positive pressure ventilation
PRA	Plasma renin activity
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMISE	survival and PleuRodesis response Markers in malignant plEural effuSion
PSP	Primary spontaneous pneumothorax

QoL	Quality of life
R&I	Research and innovation
RAPID	Renal, Age, Purulence, Infection source, and Dietary factors
RCT	Randomised control trial
REDUCE	Randomised controlled trial evaluating the Efficacy of inDwelling pleUral Catheters in persistent non-malignant symptomatic pleural Effusions
SAE	Serious adverse events
SBP	Systolic blood pressure
SD	Standard deviation
SE	Subcutaneous emphysema
SPAP	systolic pulmonary artery pressure
SOP	Standard operating procedure
SSA	Site specific assessment
SSP	Secondary spontaneous pneumothorax
TARN	Trauma audit and research network
TB	Tuberculous
TIPS	Transjugular intrahepatic portosystemic shunt
TSC	Trial steering committee
TTE	Transthoracic echocardiogram
TUS	Thoracic ultrasound
UK	United Kingdom
US	United States
VAS	Visual analogue scale

VASD   Visual analogue scale for dyspneoa

VATS   Video-assisted thoracoscopic surgery

WHO   World health organisation

CHAPTER 1.   INTRODUCTION

Pleural disease can lead to accumulation of fluid or air into the pleural space. This can be caused by either malignant processes, usually due to cancerous micro-metastasis to the pleural membrane, or non-malignant processes. In the last 10 years, the malignant pleural effusion (MPE) has been extensively investigated, leading to increased understanding of the pathophysiology, as well as its management and prognostication, allowing for a personalised approach to the patient(1). This bench to bedside data is not available in non-malignant pleural disease (NMPD), with little high-grade evidence on the clinical course in these patients.

An area of particular research interest in MPE is the outpatient ambulatory pathway, so as to avoid lengthy inpatient stays, maximise mobilisation and minimise the complications associated with prolonged bedrest(2-5). With trials demonstrating improvements in patient-centred outcomes with this pathway, particularly using the indwelling pleural catheter (IPC) for ambulatory drainage, pleural medicine has moved away from an inpatient speciality, to one where patients can be managed in the community.

The aim of this PhD is to improve the understanding of the clinical course and progression of non-malignant pleural disease, specifically looking at two patient populations: the pleural effusion secondary to the refractory transudative effusions and in patients with secondary spontaneous pneumothoraces.

1.1.   The refractory transudative effusion

"The customary division of transudates from exudates at the specific gravity of 1.016 has been found to be true only in certain diseases" Paddock, 1940(6)

The history of extravascular fluid analysis is one of correctly identifying the exudate, originally to diagnose pleural effusions from tuberculous (TB), and more recently, to identify malignant pleural effusions. Since the early 19th century, extravascular fluids have been classified based on either protein content or specific gravity into either a transudate or an exudate(6). Transudates, with low protein, were felt to result from increased intravascular fluid pressures or diminished colloid oncotic forces, typically as a consequence of cardiac dysfunction. Exudates with higher protein levels resulted from vessel alteration during inflammation, usually either due to infection or malignancy. The search for a differentiating test between the two states focused on establishing cut-off values for the biochemical properties, such as specific gravity, protein or LDH. Paddock, in

a paper published in the 1940s determined from an analysis of 1300 fluids, that using specific gravity cut-off of 1.016 misclassed 10% of cardiac effusions and tuberculous effusion, and over 30% of non-tuberculous infected pleural fluids and 40% of malignant fluids(6). Similarly, no singular pleural protein content value, either by itself, or compared to serum protein as a ratio, could be found to accurately differentiate exudates from transudates (6-8). The measurement of a metabolic enzyme, lactate dehydrogenase (LDH) demonstrated a positive correlation with exudative effusions, however it again lacked diagnostic accuracy by itself (9, 10).

Dr Richard Light proposed simultaneous use of both protein and LDH pleural-serum ratio to discriminate between pleural transudates and exudates(11). With the three-part Light's Criteria, an effusion is an exudate when any one of the following findings is present: a ratio of pleural fluid protein to serum protein higher than 0.5, a ratio of pleural fluid LDH level to serum LDH level higher than 0.6, or a pleural fluid LDH level higher than 200 IU per litre (or >67% of the upper limit of the normal range for serum LDH level). This criterion has become the standard approach to the initial characterisation of the pleural effusion and has demonstrated high sensitivity in diagnosing exudates (98%). The combination of multiple tests in an 'or' rule, leads to this increased sensitivity, but at the expense of an increased likelihood of false-positive findings. This results in an over-diagnoses of transudates as exudates(12), with approximately 25% of transudates misclassified (13). Additionally, from as early as the 1930s it was appreciated, that along with decreasing the effusion volume, diuretics altered the pleural biochemistry(14), with more recent studies demonstrating both protein and LDH increase progressively during diuretic therapy(13). This alteration of the pleural biochemical components further increases the rate misclassification of transudates as an exudate (pseudoexudate). It has been suggested in these patients that calculating the gradient between serum and pleural protein or albumin is more accurate in differentiating transudates from exudates whilst on diuretics, as the gradient appears to increase less than the ratio whilst on diuretics. NT-proBNP, a hormone produced by cardiomyocytes in response to parietal stress in heart failure, has been found to be highly sensitive and specific (94%) in differentiating cardiac from non-cardiac effusions(15) and can also be helpful in identifying pseudoexudates (16)

This weighting towards sensitivity in identifying exudative processes was not accidental, as it was felt that exudates represented the more serious pathologies such as malignancy and infection, as opposed to the transudative processes of heart and liver failure(12). This may have contributed to the perception that transudates are of less consequence, reinforced by their nomenclature of 'benign pleural effusions '.

The division of pleural effusion into exudates and transudates forms the initial part of the British Thoracic Society (BTS) diagnostic algorithm(17). It advises that patients with a transudative effusion be managed with medication to optimise existing organ dysfunction, either presumptively   when the clinical picture is suggestive of a transudate or if pleural analysis confirms this.

However, it is increasingly recognised that a proportion of transudative effusions do not respond to optimisation of their underlying organ dysfunction and these patients may require invasive therapeutic interventions. There has been little research of the outcomes of these transudates which are refractory to medical management, or how best to manage them. Any management approaches are extrapolated from research in malignant pleural effusion (MPE). One of these management approaches is the use of a tunnelled silicone-coated indwelling pleural catheter (IPC) to manage pleural effusions as an outpatient. Whilst these are well established in MPE, there has been little research in the role of ambulatory care in patients with transudative effusion, with no randomised studies on the use of IPCs in transudative pleural effusions.

1.1.1.   Congestive Heart Failure

Congestive Heart Failure (CHF) has a prevalence of over 5.8 million in the USA, and over 23 million worldwide(18). It is the leading cause of pleural effusions, with an estimated annual incidence in the US of 500,000(19), with up to 70% of patients with heart failure thought to develop a pleural effusion during their disease course and 87% of patients with acute decompensated heart failure demonstrating an effusion on CT imaging(20, 21).

Normal pleural fluid is both produced and absorbed primarily from the parietal surface and typically originates from the systemic capillaries of the pleura (22, 23). However, in patients with CHF there's debate about whether pulmonary or systemic pressure elevation causes pleural effusions(23). Elevated systemic pressure could lead to pleural effusion formation by increasing filtration across the systemic circulation of the parietal pleura and by decreasing lymphatic flow through increases in the downstream venous pressure. Conversely, elevated pulmonary pressure elevation could result in pleural effusion formation by increasing filtration across the pulmonary circulation of the visceral pleura (23). The resultant increased cardiac pressures are transmitted back, leading to increased pulmonary venous hypertension. This increase in pulmonary venous pressure that leads to alveolar oedema increases the interstitial pressure in the subpleural regions, with the resultant fluid leaking from the visceral pleural surface, increasing the rate of fluid accumulation(24). This has been demonstrated in experimental work and clinical studies. Studies on anaesthetised sheep found that fluid leaks directly from the oedematous sheep's lung,

via the visceral pleural, into the pleural space (25). A prospective study of 37 patients on a Coronary Care Unit (CCU), with CHF supported these findings. In the 19 (57%) patients with pleural effusions, the pulmonary capillary wedge pressure was significantly higher than those without effusions (24.1±1.3 vs 17.2±1.5mmHg) (26).

Elevated systemic venous pressures can result from transmitted left elevated atrial pressures via the right heart or from isolated right heart failure. The increase in systemic venous pressure could produce a net increase of pleural fluid by increasing filtration of fluid from the parietal capillaries and by decreasing lymphatic drainage by increasing the outflow pressure in the thoracic duct(24). Despite this plausible mechanism, it is felt that pleural effusions are unusual in patients with isolated right heart failure (RHF). A small study of 18 patients with severe pulmonary hypertension (50±5mmHg), with significant raised right atrial pressures (11±2mmHg) and normal mean pulmonary capillary wedge pressures, found no evidence of pleural effusion on x-ray or ultrasound(27). A more recent study has challenged this, examining 147 patients with isolated RHF, 128 of which had patients had IPAH (idiopathic pulmonary arterial hypertension). In this study thirty-one of 147 patients (21.1%) had evidence of pleural effusions. These effusions were generally small, with nearly two thirds of the pleural effusions described as trace to small in size. Of the 3 patients with massive effusions, two had ascites, suggesting that translocation from ascites might be the possible mechanism. The majority of the effusions were unilateral right sided effusions (58%), compared to bilateral (26%). This study was limited by its retrospective nature, and that most of the effusions were not sampled, with the authors postulating alternate causes of the pleural effusions other that RHF in ten patients(28).

A large retrospective review of 3245 consecutive patients with acute decompensated heart failure (ADHF) looked at the factors which predisposed patients to forming pleural effusion. Pleural effusions were detected in 1504 (46%) patients, and with male gender, higher systolic pulmonary artery pressure (sPAP), hypoabluminaemia and higher NT proBNP independent predictors of pleural effusion development(29).

The first line treatment of pleural effusion secondary to heart failure is optimisation of medical therapy with diuretics therapy, low-salt diet and reducing afterload. These measures improve pleural effusions in the majority of patients. One prospective study of 60 consecutive patients hospitalised with CHF, 52 (87%) of which had pleural effusions. At a median follow-up of 16.2 ± 4.5 days (range 10 to 30 days), 41 of 46 patients (89%) with pleural effusion had complete resolution of their pleural effusion during the follow-up period. The remaining patients also had partial resolution(20). Sufficient follow-up data were not obtained in 6 patients because they deteriorated during the follow-up period. The management regime consisted of treatment with a

combination of oxygen, digoxin, nitrates, diuretics, sympathomimetic agents, and synthetic human atrial natriuretic peptide(20). Most of these patients were NYHA class IV (40%) with 28% and 32% class III and II respectively. This study had several limitations which affects its generalisability to all patients with CHF. It is was a small study, at a single centre, with no CCU. The commonest cause of CHF in this patient cohort was degenerative valvular heart disease (26/60), with ischaemic cardiomyopathy only accounting for 9/60 of the patients. This was felt to be due to patients with IHD preferentially referred to other hospital with CCUs. As mentioned, follow data was also incomplete.

There is limited literature on patients with CHF in whom the effusion is unresponsive to medical optimisation. Devices such as cardiac-resynchronization therapy (CRT) can help optimise cardiac function with dyssynchronous left ventricular contraction, and has been shown to increase functional capacity, improve quality of life and decrease mortality in selected patients (30). There is no literature available on the effect of CRT on pleural effusions and pleural effusions are not an indication for their use.

1.1.2.   Hepatic Failure

Patients with liver failure can develop a pleural effusion, known as a hepatic hydrothorax. Liver cirrhosis is the commonest underlying liver pathology, with between 5-10% of cirrhotic patients developing a pleural effusion (31). Hepatic hydrothorax are typically right sided unilateral effusions (73%), although they can be left (17%) or bilaterally (10%)(32). They are often large, with one series defining 71% of pleural effusions as large(32). Whilst often associated with ascites, up to 10% will not have neither clinically nor radiologically detectable ascites(32).

There are several proposed underlying mechanisms, including azygous vein hypertension from collateral anastomoses between portal and azygous systems, hypoalbuminemia from impaired hepatic function, passage of ascitic fluid via transdiaphragmatic fenestrations and possibly lymphatic leakage from the thoracic duct(33). Among these, the direct passage of ascitic fluid through defects within the diaphragm appears the most plausible (33). The defects originate from fluid filled pleuroperitoneal blebs as of result of increased intra-abdominal pressure. This increased pressure from ascites then causes the blebs to rupture, resulting in diaphragmatic fenestrations. These diaphragmatic defects have been demonstrated both microscopically at post-mortem(31) and macroscopically at thoracoscopy(34). Radiological studies have also demonstrated transfer of CO_2 and radioisotopes from the peritoneal to the pleural cavity(35).

The other postulated mechanisms are less convincing in isolation. There appears to be no association between low serum albumin and hepatic hydrothorax, and is unlikely to be a cause in isolation (36). In a study of 200 cirrhotic patients with ascites, mean albumin levels were nearly identical in the group with ascites alone and the group with ascites and HH(37). Collateral anastomoses between the portal and azygos system leads to hypertension in the azygous vein system and leakage from this system is a suggested causative mechanism. However, this should result in bilateral pleural effusions, which is rare in HH, and so is not generally felt to be a causative factor(38, 39). Cirrhosis and ascites causes increased lymph flow in the thoracic duct(40) and it has been suggested that resultant lymphatic leakage from the thoracic duct leads to HH formation. However, as increased thoracic flow is common in cirrhosis, whilst effusion formation rare, it is felt that this is unlikely to have a significant effect in isolation (38).

The first line management of hepatic hydrothorax is the same for ascites and comprises alcohol abstinence, management of underlying liver disease if possible, restriction of sodium intake to 2 g/day, avoidance of medications which decrease systemic blood pressure and/or impair renal perfusion (ACE-inhibitors, ARBs & NSAIDs), and the use of oral diuretics (spironolactone and furosemide in a ratio of 100 : 40mg daily, titrated up as required) (41). However, approximately 25% of patients with hepatic hydrothorax have effusions refractory to salt restriction and diuretics(41)

There are a number of invasive interventions for cirrhotic patients which can be used to treat hepatic hydrothorax(41). The transjugular intrahepatic portosystemic shunt (TIPS) is an image-guided procedure which connects the portal vein to the hepatic vein in the liver, creating a porto-systemic shunt, with the aim of decreasing portal hypertension, and subsequent decrease in effusion and ascitic fluid formation. In one series of 24 patients, 58% of patients had complete relief of symptoms and did not require further thoracentesis and a further 21% were reported as requiring fewer thoracentesis, although there was no comparator arm (42). However, there are significant side effects, with 38% developing transient hepatic encephalopathy and a 25% mortality rate within 45 days, with one patient dying from procedural complications. These findings are limited by the lack of comparator.

Liver transplant is the only treatment which confers a survival benefit, improving median survival in patients with a hepatic hydrothorax from 1896 days to 321 days(32) However, there are strict criteria for transplantation and a significant waiting time for patients which varies by country. In the US the median waiting time is 18.5 months(43) and in the UK it is 4.7 months, with 19% dying before a transplant organ was available or being removed from the elective list, primarily because they became too unwell(44).

Human albumin solution (HAS) is a sterile aqueous solution for intravenous use, mainly consisting of the albumin component of human plasma. It is used routinely during paracentesis of ascitic fluid to prevent paracentesis-induced circulatory dysfunction (PICD). PICD is characterised by impairment of circulatory function and occurs in 80% of cases where paracentesis isn't performed with plasma volume expansion(45). The vasoactive and neurohumoral changes in PCID appear to have an immediate phase in the first hours, which are predominately beneficially, and later phase, which is detrimental and associated with worse outcomes if not corrected. The immediate haemodynamic changes are marked decreased in right atrial, pulmonary and mean arterial pressure and an increased in cardiac output and systemic vasodilation, with a reduction of plasma renin activity (PRA) and aldosterone levels (46). This can occur after removal of a little as 250ml if ascitic fluid. These initial changes are predominately beneficial but are typically only transient if paracentesis is not followed by plasma expansion. Otherwise in the following 24 hours, cardiac output decreases and PRA and aldosterone concentrations increase(46, 47). PICD is associated with worsening renal function, ascites re-accumulation and poorer prognosis(48). Intravenous HAS administration, at 8g/L of ascites drained, has been shown to be the optimal plasma expander in preventing PICD and the administration appears to prevent the resultant hypovolaemic state in the majority of patients(49). More recently a half-dose of 4g/L has been shown to be equally effective(48). There is little information on the use of HAS in hepatic hydrothorax drainages via IPC, and practice is usually guided by local hepatologist. A retrospective review of patients who have undergone IPC placement for hepatic hydrothorax examined the baseline and follow-up (mean 29.6 days; range, 1-122 days) albumin levels(50). It found a small downward trend, with a decrease of 0.3 g/dL, which is of uncertain clinical significance(50)

1.1.3.   Renal failure

Pleural effusion secondary to renal impairment is typically an indicator of severe disease and can be demonstrated in 20% of patients on haemodialysis(51). There have been several case-series examining patients on haemodialysis with pleural effusions(51-53). The studies were retrospective and relied mostly on clinical evaluation, with the thoracentesis rate in the two earlier studies less than 30%(51, 52). The later study by Rashid-Farokhi et al was the only study to use echocardiographic criteria for heart failure, and had a higher thoracentesis rate of 87%(53). Cardiovascular disease is common in patients with end-stage renal disease (ESRD)(54) and most case-series found that fluid overload, either due to heart failure, or due to another mechanism, was the leading cause. Other potential causes of fluid overload in patients with ESRD, aside for cardiac dysfunction, are pulmonary over-hydration secondary to water and solute retention; hypoproteinemia; high-output arteriovenous fistula or injury of the alveolo-capillary membrane

secondary to toxic-lesional factors (55). The study by Jarratt and colleagues found that 46% of cases were due to heart failure(52), with the study by Bakirci and colleagues attributed 60% and 10% to over-hydration and heart failure respectively(51). The study by Rashid-Farokhi and colleague found that heart failure was responsible to 20% of cases, with volume overload 6% of cases(53). Patients with renal failure are also at increased risk of pneumonia and subsequent parapneumonic effusion, due to a depressed humoral and cellular immunity, with parapneumonic effusion felt to be responsible for between 10 and 24% of effusions of patients on longer-term haemodialysis (51-53). Uraemia can contribute to pleural effusion formation by causing necrotizing fibrinous pleural inflammation and resultant typically blood-stained lymphocytic exudate formation, although the pathogenesis is poorly understood(56). This uraemic pleuritis is attributed to between 4 and 24% of cases in the aforementioned studies (51-53)

Patients on peritoneal dialysis (PD) can also develop pleural effusion, usually secondary to passage of dialysis fluid from the peritoneal cavity(57).

Effusions secondary to overload can be treated by optimising fluid balance, either with altering dialysis regimes or diuretics administering. However, this can be limited by symptomatic hypotension and electrolyte disturbances. Uraemic pleurisy is managed with haemodialysis, although it may be refractory to this. PD related effusions are typically managed with short-term switch to haemodialysis.

1.1.4.   Prognosis

A significant body of literature has been published on the outcomes of refractory malignant pleural effusions (MPEs) with several mortality prognosis models available which can be used to predict prognosis in the individual patient. The LENT score is a prospectively validated scoring system using patient characteristics, including pleural LDH, ECOG performance status, neutrophil to lymphocyte ratio and tumour site, to predict survival (58). More recently, the PROMISE score was introduced, an 8 variable prospectively validated model that can accurately predicts 3-month mortality in MPEs(59). However, the overall impact of refractory NMPE, as well as long-term outcomes are less studied.

The presence of pleural effusion in patients with heart failure may not, by itself to be a poor prognostic marker. A study looked at the effect of small incidental pleural effusion, identified on transthoracic echocardiogram (TTE), including 141 patients with heart failure(60), found good overall 5-year survival of 70%. However, there was no comparator group of patients without pleural effusions and the patients were typically young (mean age 60 years of age) and with preserved ejection fractions. A prospective case controlled study of 100 patients with heart

failure, 47 with pleural effusion and 53 without, concluded that an accompanying pleural effusion did not predict mortality(61). This patient cohort appeared to have well controlled pleural disease, with only 3 patients requiring thoracentesis. A recent large retrospective Spanish study of 3245 consecutive inpatients with a primary diagnosis of acute decompensated heart failure (ADHF) appears to support these findings. Whilst pleural effusions were common, present in 46% of these patients, it was not independently predictive of 1-year mortality(29).

Refractory transudative effusions, defined in this context as transudative effusions requiring an invasive therapeutic pleural procedure, do however, appear to have much poorer outcomes. A prospective cohort study examined survival in 308 patients undergoing thoracentesis, 226 of which had a non-malignant aetiology(62). It found that found that patients with effusions secondary to heart failure had a 1-year survival of 53% compared to 77% in malignant effusion (62), and also demonstrated that all patients undergoing thoracentesis for pleural effusion have high short- and long-term mortality.

1.1.5.   Management of the refractory transudative effusion

As described above, 10% of pleural effusions secondary to CHF and 25% of effusions secondary to liver failure are thought to be refractory to medical management. In this PhD we define refractory transudative effusions as transudative effusions which require an invasive pleural procedure to alleviate symptoms.

The high diuretic dosage used in the pursuit of reducing the size of pleural effusion and improving symptoms can lead to significant side-effects, including acute kidney injury, other electrolytes disturbances and postural hypotension. When medical management fails, patients will often require a therapeutic aspiration Repeated pleural aspirations, can often only provide transient relief and can cause complications such as an associated risk of pain bleeding, infection and other complications(63). Thoracentesis is additionally complicated by the fact that many of these patients are on a form of oral antiplatelets or anticoagulation, which increases procedural risks. The cumulative risk of repeated thoracentesis has been shown to be particularly high in patients with hepatic hydrothorax. A comparative case-control study of 82 patients with hepatic hydrothoraces demonstrated increased cumulative risk of complications with sequential thoracenteses. A complication occurring in the preceding intervention was the strongest predictor for subsequent adverse event (OR=17.1, p=0.0013) (64).

An alternative strategy is the insertion of a chest drain and instillation of talc pleurodesis. It has approximately a 70% success rate in controlling effusions in malignant disease(65), however it has not been prospectively studied in patients with non-malignant disease(66-68). One retrospective study of patients with effusions secondary to CHF demonstrated a 75% pleurodesis success rate with talc slurry(67). These patients were managed with a combination of large bore (n 9) and small bore (n 7) drains. However, it was limited by small sample size of 16, and variable follow-up, ranging from 2 months to 3 years. In patient with liver failure, talc pleurodesis is usually reserved in patients without ascites and in whom no other options exist(41), as it thought that the volume of flow of ascitic fluid is typically too great to allow time for pleural apposition. The combined success rates in case series of patients with hepatic hydrothorax, is approximately 50%, which compares unfavourably to the use of talc in MPE(41).

Indwelling pleural catheters have been shown to be an effective method of controlling pleural effusions in malignant disease(2, 69, 70). The evidence base in non-malignant disease is less clear, with no randomised studies examining the efficacy of IPCs for these patients. Herlihy et al published the first case series on the use of Pleurx® IPC in 5 patients with refractory pleural effusion secondary to CHF, demonstrating that the catheter effectively controlled the effusions and symptoms(71). However, 2 patients developed pleural infection, one of whom died of resultant sepsis. This was a very small case series (n 5) of a very heterogenous group (oldest patient was a 92 year old women, youngest a 20 year old man) of highly selected patients and limited conclusions can be made from the results.

Srour et al published a prospective study in patients with cardiogenic pleural effusions, inserting 43 IPCs in 38 patients (72). This study demonstrated an improvement in breathlessness and a proportion of these patients (29%) achieved spontaneous pleurodesis. The study protocol was mindful of minimising catheter infections, with drainages performed by trained home-care personal with rigorous outpatient monitoring, which may partially explain why there were no incidences of empyema. The patients had to see a quaternary centre cardiologist to determine failure of maximal medical therapy prior to enrolment.
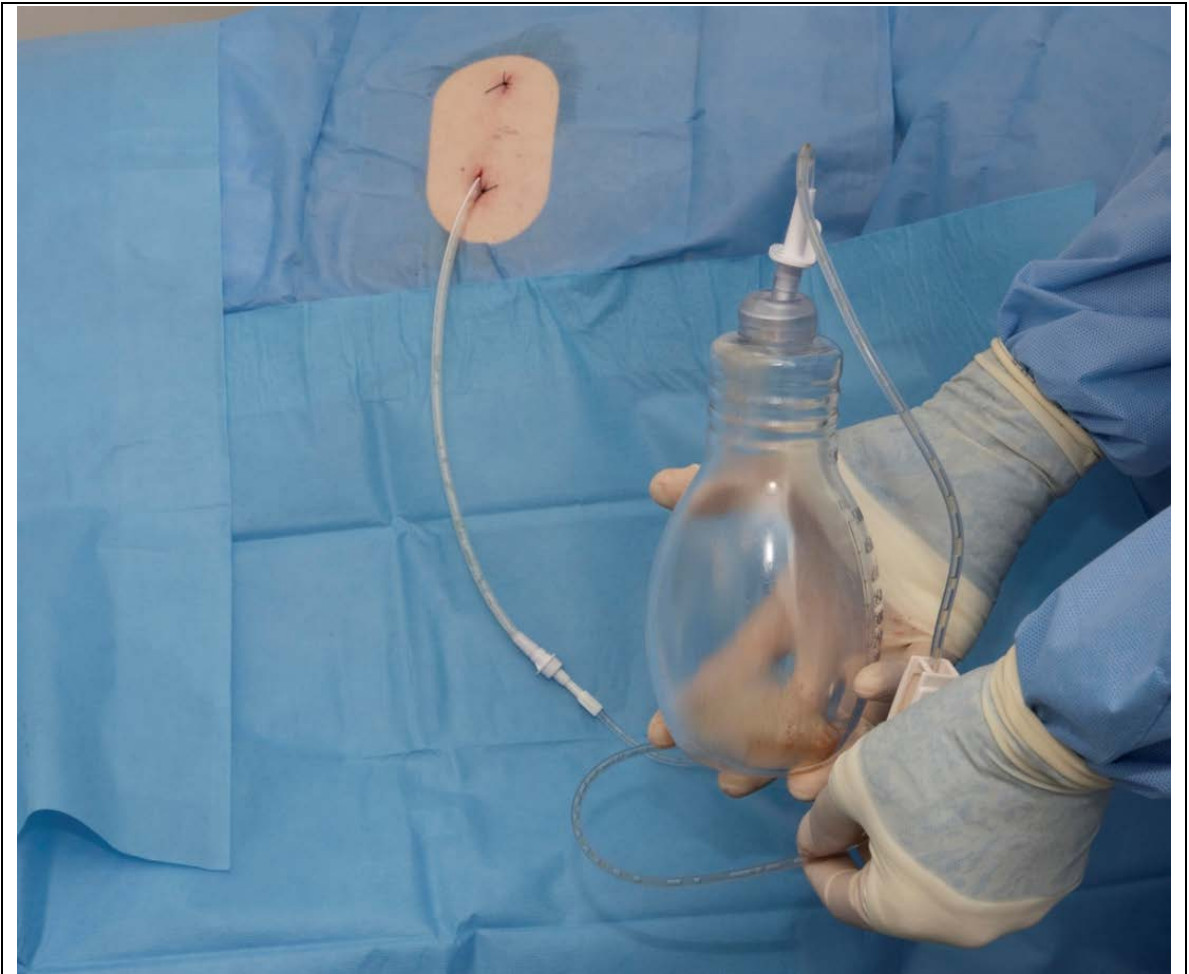
Figure 1.   ***Indwelling pleural catheter with suction bottle attached***

Freeman et al preformed a retrospective cohort analysis on 80 patients with recurrent cardiogenic effusions, in which 40 patients receiving talc poudrage and 40 patients IPCs (66). They defined adequacy of palliation based on reintervention rates, with similarly low reintervention rates in the poudrage (5%) and the IPC (2.5%) cohorts. It must be noted that the talc poudrage arm was performed under thoracoscopy, with contralateral single lung ventilation under general anaesthetic via a single port. This is not a standard method of performing talc instillation, particularly with medical patients, and could explain the low rate of reintervention in the talc arm. The stated hospital length of stay was significantly shorter and the readmission and complication rate lower in the IPC cohort. However, the overall length of follow-up was short in both talc poudrage arm (7 ± 3 months) and IPC (6 ± 3 months). This study was also limited by its retrospective study design.

Majid et al examined in a retrospective cohort study 36 patients (43 IPCs placements) with cardiogenic effusions. Thirteen patients underwent medical thoracoscopy with talc poudrage,

followed by IPC insertion (Group 1). This procedure was performed under 'moderate sedation' with continuous monitoring by an anaesthetist. The patients had between 4 to 8 g (mean 5g) of talc instilled, which is greater than the typical amount used in the UK. At the end of the procedure both the IPC and the 24Fr chest tube introduced though the thoracoscopy cannula were left on -20cm H_2O suction until their combined drainage was less than 24 hours. This was not, therefor a day-case procedure.   The other 23 patients had standard IPC placement (Group 2)(73). Pleurodesis rates were higher in Group 1, with 80% achieving pleurodesis at a median time 11.5 days, compared to a 25% pleurodesis rate at a median time of 66 day in Group 2. There were 3 cases (7%) of cellulitis, two in Group 1 and one in Group 2, and 2 cases of pleural infection, both in Group 2, which were managed successfully with antibiotics and fluid drainage via catheter. The 6-month readmission rates were higher in the group 2 (31) than group 1 (15). There was also higher number of subsequent therapeutic thoracentesis needed in group 1 (63) than group 2 (33). This study was limited by its retrospective and non-randomised study design, with unequal number of patients in each cohort (n 13 in group 1 and n 23 in group 2). This invariable lends itself to selection biases. Ten patients in group 2 had systolic heart failure compared to 3 in group 2. Patients with higher NHYA dyspnoea scores were assigned to the IPC-only group. Additionally, the median serum NT-proBNP was markedly different, at 2,780pg/ml in group 1 and 4,764pg/ml in group 2. This selection bias makes a true comparison between the two groups difficult. As mentioned above, the pleural fluid drainage regime in group 1 was more intensive than is generally performed in similar studies. This could all explained the higher pleurodesis rates in group 1.

For hepatic hydrothoraces, there has been one prospective study(74) and several recent retrospective case series(50, 75). A prospective study by Chen et al examined 25 IPC placements in 24 patients, and demonstrated a spontaneous pleurodesis rate of 33%, with a mean duration of 131.8 days. Pleural infection occurred in 4 in 24 patients, requiring drain removal in 3 patients, although there was no associated mortality from sepsis. This was a non-randomised feasibility study, and as such is limited by confounders and selection bias. It is unclear how many patients were lost to follow-up, although at least one is mentioned in the narrative. No average duration of follow-up was provided, and it is unclear how long the subjects were followed up beyond the stated clinical follow-up of 2 and 6 weeks.

Kniese et al conducted a retrospective review of 62 patients with IPCs, with 5 of 62 patients achieving pleurodesis at a mean of 118 days. There was a high rate of infection, with 10 of 62 patients developing empyema, and 3 patients dying from sepsis. There were several methodological limitations in the study. There was no standardised drainage regime, reasonably

high rates of losses to follow-up (8%) and no documented mean follow-up period. Additionally, the only follow-up data was from visits to their own institution and death was recorded as a composite end-point of actual date of death or discharge to hospice.

Shojaee et al conducted a retrospective multicentre study on 79 patients, in which 22 patients achieving pleurodesis at a median time of 55 days(75). Again, pleural infection rates were high, with 8/79 (8%) of patients developing pleural space infection, 2 of whom died from sepsis. The majority of the IPCs (73%) were inserted with palliative intent, as opposed to a bridge-to-transplant, and likely represented a very unwell patient cohort. The study was limited by its retrospective design and was at high risk of selection bias. All participating institutions were at least tertiary care level and may not be generalisable to the overall cohort of patients with HH or the level of expertise generally available. Mean follow-up durations were also not provided.

As a general point, the reported pleurodesis rates in patients with HH managed with IPCs may be overestimated. Most catheters are removed after liver transplant and may be related to resolution of portal hypertension, as opposed to pleural space symphysis.

Indwelling pleural catheters have not been studied extensively in renal failure. One series examined the use of IPCs in 8 patients with end-stage renal disease, 7 on whom were on dialysis (6 haemodialysis; 1 peritoneal dialysis) (76). The effusions were secondary to a wide range of aetiologies (diastolic heart failure/overload, uraemia, peritoneal dialysis and undetermined) Breathlessness improved in these patients with a spontaneous pleurodesis rate of 37.5% after a median duration of 77 days. This study was limited by its small number of cases, case series design, and comprised of a retrospective review of a mostly prospective collected data set.

A systematic review identified 13 studies, composed of case series and retrospective reviews, concluding that the IPC is effective and a viable option in the management of patients with refractory benign pleural effusion(77). Overall, the average rate of spontaneous pleurodesis was 51.3% (95% CI, 37.1%-65.6%) which is comparable to the pleurodesis rates for IPCs in MPE(78). The average rate of all complications was 17.2% (95% CI, 9.8%-24.5%) with empyema developing in 2.3% (95% CI, 0.0%-4.7%) of cases. The review concluded that the quality of evidence to support the IPC use for BPE was low, and recommended future high-quality RCTs. The paper was limited by several methodological limitations. Its only included papers, for unexplained reasons, from January 2011, although there were relevant studies published before this. No date was given when the initial literature search was made, and a full search criterion was not detailed. No details were provided if more than one author was included in the screening and selection of papers. The study protocol was not published prior to publication on the PROSPERO database, which is

desirable in systematic review. The analysis was limited by the inclusion of entirely non-randomised studies, with significant heterogeneity between studies.

In summary, with the management of MPE there have been efforts to individualise the patient pathway, with options determined by patient choice, disease characteristics including the rate of recurrence, presence of trapped lung, and predicted prognosis (79). Presently for NMPE, there is insufficient research data to predict prognosis, or to determine which treatment choice is optimum.

1.2.   The Pneumothorax

"I could keep this knight from dying and I feel sure I could save him if I had a reed" Von Eschenbach 1210

Pneumothorax, the abnormal collection of air in the pleural space can occur as a result of external injury (traumatic) or in its absence (spontaneous). Traumatic pneumothoraces can be sub-classified as iatrogenic when the trauma is a result of a medical intervention. Spontaneous pneumothorax is typically subdivided into patients with no apparent underlying lung disease (primary spontaneous) or in the presence of lung disease (secondary spontaneous).

The pneumothorax has been described since antiquity. A clinical sign of pneumothorax 'Hippocratic succussion' where on shaking a patient a splashing sound was heard, due to a hydropneumothorax, was documented as early as the 5th century BC by Greek Physicians. Traumatic pneumothoraces account for most of these early descriptions, as a consequence of chest wall trauma from violence, and is described from wounds since Graeco-roman antiquity(80). Unfortunately, open chest wounds were generally considered at the time to be fatal, and no intervention apart from wound packing was typically attempted(81).   There are suggestions in historical literature that individual surgeons attempted to aspirate the pneumothorax. A 15th century illustrated surgical textbook in the Turkish–Islamic (Imperial Surgery) appears to demonstrate a procedure known as "mihceme" (aspiration by negative pressure), where a flame was placed in a glass to burn the oxygen, creating a vacuum, forming a simple form of pneumothorax aspiration(82). A possible description of tube thoracostomy was made by Wolfram von Eschenbach's Parzival, written between 1210 and 1220, where he describes the use of a reed inserted into a chest wound inflicted on a wounded knight named Uriens during a joust *'I could*

keep this knight from dying and I feel sure I could save him if I had a reed… He grasped a branch of the linden tree, slipped the bark off like a tube – he was no fool in the matter of wounds – and inserted it into the body through the wound… The hero's strength revived so that he could speak and talk again."(83)

Spontaneous pneumothorax (SP) was not identified as a medical complaint until more recently, as its presentation was typically less obvious. Jean Marc Gaspard Itard (1774-1838) first used the term pneumothorax in his thesis 'Dissertation sur le pneumo-thorax ou les congestions gaeuses qui deforment dans las la poitrine', published in 1803(84). At that time, it was almost ubiquitous to pulmonary TB, with a report 1880 accounting 78% of 916 patients with SP to tuberculosis. This demographic changed with time and in 1932, a Swedish physician described what we would typically consider a primary spontaneous pneumothorax (PSP), characterised by a male predominance, association with cigarette smoking, and an asthenic, leptosomic, or ectomorphic body habitus, and emphasized the importance subpleural bleb disease(85).

During this time, medically induced pneumothoraces became common after a chance observation of symptomatic improvement of tuberculous after spontaneous pneumothorax. This led to the practice of inducing an artificial pneumothorax by pumping filtered compressed air or nitrogen into the pleural space. The perceived benefits were thought to be either due to resting the lung, mechanical pressure permitted the drainage and closure of tuberculosis cavities or preventing spread of the bacteria to other parts of the lung(86, 87). Carlo Forlanini induced the first artificial pneumothorax in 1888, and went on to publish 25 cases(88). This practice continued until the 1950s, when anti-tuberculous medical treatment became available(88). Inadvertently, this procedure demonstrated that patients could comfortably tolerate a unilateral pneumothorax. Indeed throughout the early 20th century, the treatment of PSP was predominantly conservative, with bed rest for most patients, with invasive treatment reserved for severely symptomatic episodes(89). Observational studies on PSP patients demonstrated that the majority of patients recovered without the need of invasive intervention (90). Moreover, it was suggested that patients managed with a conservative approach had a lower risk of recurrence, due to enhanced healing of the pleural defect when the lung was in a collapsed state. However, despite these encouraging results with an expectant approach, chest tube drainage become the first-line approach, perhaps due to increasing ease of insertion. In the 1980s various authors advocated performing needle aspiration, using a using a narrow lumen catheter, to avoid chest tube insertion and lengthy hospital stays (91-94). Comparative studies between chest drainage and needle aspiration dominated pneumothorax research during the 1990s and 2000s(95-100). A different approach was suggest in the 1960s, with Dr Henry Heimlich describing the attachment of a one-

way flutter valve to the chest drain to facilitate ambulatory management of the pneumothorax(101). This appear to be a safe and effective way of managing the pneumothorax, however there was little subsequent research to fully support its use.

This thesis will explore several aspects of the natural history and management of the pneumothorax, including the role of conservative management in traumatic pneumothorax, the rate of recurrence in PSP, and the role of ambulatory management in secondary spontaneous pneumothorax.

1.2.1. Spontaneous pneumothorax

Pneumothorax is defined as air in the pleural space(102) and is traditionally categorised into spontaneous or traumatic. The spontaneous pneumothorax occurs without preceding trauma and is further sub-categorised into primary or secondary, depending on the absence or presence of underlying lung disease respectively. Traumatic pneumothoraces arise as a result of direct or indirect trauma to the chest. When these occur from a medical procedure, the term iatrogenic is used.

Spontaneous Pneumothorax are categorised into primary or secondary, depending on the absence or presence of underlying lung disease respectively. Primary Spontaneous Pneumothorax (PSP) has an annual incidence of 7.4 per 100,000 population in males and 1.2 per 100,000 in females(103). The annual incidence of Secondary Spontaneous Pneumothorax (SSP) is 6.3 per 100,000 population in males and 2.0 per 100,000 in females(103). There is a bimodal distribution, with a peak incidence in young people aged 15-34 and another in those aged over 55(104). These peaks are often associated with PSP and SSP respectively. Smoking is the most important risk factor in PSP. The relative risk of a first primary spontaneous pneumothorax is increased 22-fold in men who smoke compared to non-smokers and nine-fold in women, with a lifetime risk of developing pneumothorax of 12% in smoking males compared to 0.1% in non-smoking males(105). There is a strong dose-response relationship between the risk of pneumothorax and number of cigarettes smoked per day (105).

Historically, PSP and SSP have been divided into two separate pathophysiology. Secondary Spontaneous Pneumothorax, a pneumothorax which occurs in patient with known lung disease, occurs in a spectrum of diseases and the pathogenesis is multifactorial. Airways disease (COPD, asthma, cystic fibrosis) are the most common underlying disease, though infectious lung disease

(Pneumocystis Jiroveci, tuberculosis, necrotising pneumonia), interstitial lung disease, connective tissue disease and cancer can be underlying causes (106).

1.2.2.   Primary Spontaneous Pneumothorax (PSP)

Primary Spontaneous Pneumothorax is categorised by the absence of apparent lung disease. It has, however, become clearer that the majority of patients with PSP have evidence of lung abnormalities, such as emphysema-like changes (ELC), subpleural blebs and bullae. These ELC were identified in a case control series on CT in 81% of non-smokers with PSP, compared with 0% in a case control of healthy volunteers(107).

These lung abnormalities, identified on CT and thoracoscopy, are thought by many to be responsible for pneumothorax and are often the target for surgical management. It has been hypothesised that there is progression from normal pleural to blebs to the larger bullae which can then rupture(108). This view, however, is not universal, with many patients not having detectable blebs(109). Furthermore studies comparing appearance of blebs and bullae between first episode of PSP with those in recurrent PSP using medical thoracoscopy did not find any significant difference in size, number or locations in the blebs and bullae, suggesting they might not be major risk factors (110). The concept of pleural porosity is another mechanism which has been proposed in the formation of a pneumothorax, in additional to macroscopic changes. This hypothesis was investigated by Noppen et al.(111) using Fluorescein during thoracoscopy to visualise parenchymal abnormalities of the visceral pleural to determine whether this was localised to blebs. Extensive subpleural fluorescein accumulation and fluorescein leakage were exclusively present in PSP and were not necessarily associated with blebs or bullae or other abnormalities visible with white light inspection. They describe this as pleural porosity, postulating that loss of surface mesothelial cells, thinning and rupture of the basement membrane, and/or down-regulation of junctional proteins may play a role. The concept of diffuse pleural porosity may explain the reported significantly higher recurrence rates if pleurodesis of some form is omitted during Video-Assisted Thoracoscopic Surgery (VATS)(112).
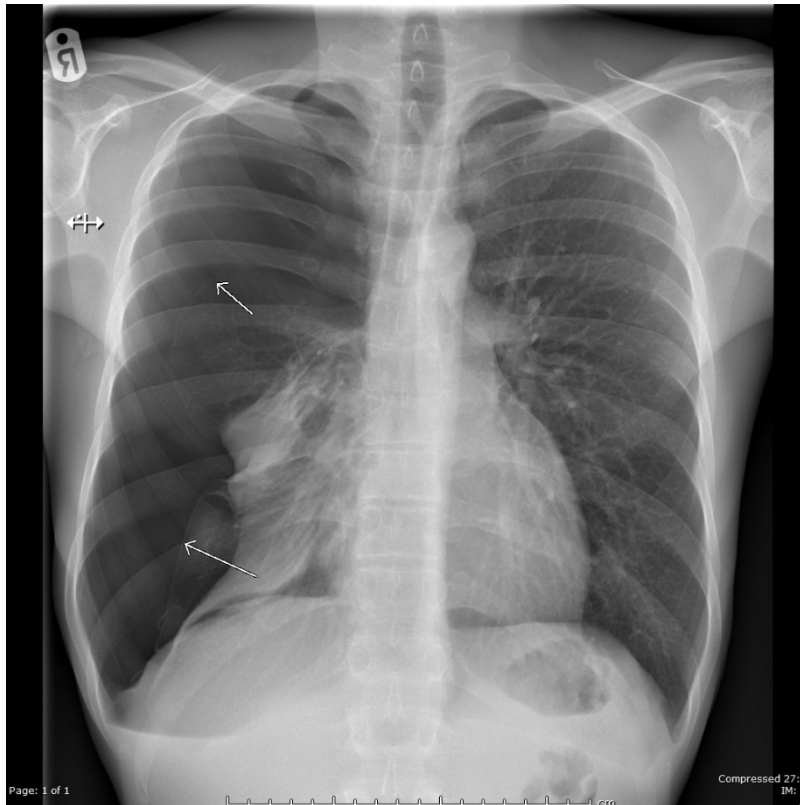
Figure 2. ***Right sided pneumothorax (lung edge marked with arrows)***

Pneumothorax is a heterogeneous condition, influenced by individual modifiable and non-modifiable risk factors and pathophysiology, and accordingly should be managed in a personalised way.

The immediate management of the spontaneous pneumothorax is determined by several factors. If the patient is haemodynamically unstable or has bilateral pneumothoraces, then a chest drain should be inserted as first line(113). If tension pneumothorax is suspected this this should be managed with needle decompression and chest drain.

For all other pneumothoraces, the management pathway is outline by the ATS Delphi consensus 2001 (114) and the BTS guidelines 2010 (113) as determined by:

a) Whether the pneumothorax is deemed as primary or secondary.
b) Presence of symptoms
c) Size of the pneumothorax on chest film

If a patient has a PSP, is asymptomatic and has a small pneumothorax, then a conservative management plan of monitoring is advocated by the BTS(113). The rate of resolution of an untreated PSP has been calculated on CT volumetry at 2.2% per day(115). The use of high flow

oxygen in pneumothorax has been showed to speed up the resolution of PSP fourfold when patients are admitted for observation(116).

If the patient is symptomatic, or has a large pneumothorax, an intervention to remove the air from the pleural space is advised. The ATS and BTS differ on the definition of a large pneumothorax. The ATS suggests >3cm from the apex of the hemidiaphragm to the cupula(114). The BTS defines a large pneumothorax as >2cm from lung margin to chest at the level of the hilum(113).

The BTS suggests that if the pneumothorax is large, or the patient symptomatic then simple aspiration should be attempted. If this is not successful then the clinician should proceed to chest tube insertion, with a recommendation that a small bore (<14 French) Seldinger chest drain should be used(113). The ATS advocate proceeding directly to chest tube insertion(114). The rationale behind the BTS guidance are studies(95, 99) and meta-analyses (117-119)that suggest that simple aspiration is as successful in treating pneumothorax, and led to fewer bed days. It is recommended that if greater than 2.5L of air is removed via simple aspiration that the physician should proceed to chest tube, as it is likely that there is a persistent air-leak (113).

1.2.3.   Secondary spontaneous pneumothorax (SSP)

Secondary spontaneous pneumothorax (SSP) refers to a pneumothorax in the presence of known underlying lung disease. Many diffuse lung diseases can cause an SSP, with COPD being the commonest cause, accounting for around 70% of cases(120). The risk of pneumothorax appears to increase with worsening COPD; around 30% of all patients with SSP have an FEV1 below 1L(121). There also appears to be an association between SSP and increased quantity of CT emphysema in patients with COPD(122). The peak incidence of SSP occurs later in life than PSP, between 60 and 65, paralleling the peak incidence of chronic lung disease in the general population(123).

Rupture of an emphysematous bullae is the usual cause of SSP, typically at the apex of the lung(124). However, unlike PSP, this ruptured bulla can occur anywhere along the lung surface. In 26% of cases of right sided SSP associated with emphysema, the ruptured bullae responsible for pneumothorax is found in the azygoesophageal recess (AER). COPD can cause expansion and deformation of the thorax, causing protrusion of the AER into the right thorax, promoting bullae

formation. This phenomenon may explain why right sided pneumothoraces are more common in patients with SSP (125, 126).

The requirement for emergency transportation to hospital, hospital length of stay, and in-hospital mortality in patients with SSP is greater compared to patients with PSP (125). The mean length of stay in a large French epidemiological study for males with SSP was 12.1 days (SD 14.5) compared to the PSP length of stay of 5.9 days (SD 6.7)(127). Patients with SSP are more likely to experience a recurrent pneumothorax than those with PSP, with a reported rates of 39-47%(121). This is presumable as a result of more severe underlying lung pathology and incomplete wound healing.

The guidance for SSP is similarly based on the size of pneumothorax and symptoms as the management of PSP is. Symptomatic patients or those with large pneumothoraces should have chest tube inserted. The BTS suggest if a patient is asymptomatic and the pneumothorax is between 1-2cm simple aspiration can be attempted. If the pneumothorax is smaller than 1cm then admission with observation is recommended. It suggests all patients are admitted to hospital (113).

The frequency of surgical interventions in the SSP patients is generally much lower than patients with PSP(125). An annual report of surgery in Japan showed only 2350 patients with pneumothorax secondary to COPD had surgery compared to over 11 000 patients with PSP who underwent surgical treatment in 2017 (128). This may be due to perceived risk of operating on patients with SSP, due to their poorer lung function, older age and comorbidities. Retrospective studies have shown morbidity rates ranging 15–27.7% and mortality rates ranging 0–5.5% in patients with SSP associated with COPD undergoing surgical therapy(124). Passlick and colleagues described that postoperative complications occurred in 25% of patients with SSP compared with only 1.7% of patients with PSP(129). Patients with interstitial lung disease (ILD) appear to be at particularly high risk of post-operative complications, with one study demonstrating a significantly higher postoperative mortality rate in the ILD group (21.4%) than in the COPD group (1.4%; p = 0.001)(130). This may be because the lung parenchyma in these patients are fragile and collapse easily due to high negative intrathoracic pressure, and the reported increase rates of exacerbation of ILD post-operatively.

1.2.4.   Tension pneumothorax

Tension pneumothorax is an uncommon, life-threatening emergency. It can be defined (131):

a)   Clinically, in terms of haemodynamic compromise improved by decompression,

b) In terms of pleural pressures, with ipsilateral pleural pressures exceeding atmospheric pressure.

c) Radiographically, with signs of mediastinal shift (although this can present in non-tension pneumothorax).

A tension pneumothorax occurs from a pleural defect forming a one-way valve in the pleural membrane, with air entering the pleural cavity on inspiration but unable to exit on expiration.

A tension pneumothorax can arise in a wide range clinical situation, including ventilated patients, trauma, CPR, patients with acute exacerbation of lung disease, blocked chest drains and patients receiving non-invasive ventilation. It rarely occurs in primary spontaneous pneumothoraces(113).

The patient is often very symptomatic, in haemodynamic compromise, with decreased air entry the most common sign (50-75%). Trachea deviation always from affected lung, hyper-resonance, hypomobility and hyperexpansion occur less frequently(113). It is important to recognise the potential differences in the clinical presentation in the ventilated and non-ventilated patients (113). Diagnosis of tension pneumothorax in ventilated patients requires a high index of suspicion. Its presentation, however, is more consistent than in awake patients, usually presenting with a sudden fall in Sp02 followed by hypotension over a few minutes (131), with tachycardia, decreasing cardiac output, increased inflation pressures and ultimately cardiac arrest(113).

Awake patients show a greater variability of presentation. They manifest compensatory mechanisms and generally have progressive respiratory deterioration with final respiratory arrest. The time lag from initial symptoms or thoracic insult to diagnosis ranged from a few minutes to over 16 hours(131). The chest radiograph is not usually useful and can be misleading, with the size of pneumothorax and mediastinal displacement not correlating with the degree of tension(113).

The management is high flow oxygen and prompt emergency needle decompression in the Mid-Clavicular line (MCL), 2nd Intercostal Space (ICS), recommended prior the chest radiograph. A large study found the mean chest wall thickness of 2,574 healthy volunteers, as determined by MRI, was 5.7 cm on the right and 5.5 cm on the left side in the MCL, 2nd ICS(132), suggesting that a 7cm needle may be required(132).   A review article on tension pneumothorax recognised the standard 14 gauge (4.5 cm) cannula may not be long enough to penetrate parietal pleura in up to one third of trauma patients, leading to treatment failure and diagnostic confusion(131). The use of the trocar instead (7 cm) may negate this problem and prevent kinking. The BTS recommend that if

needle decompression is not possible in the 2nd ICS, then the chest wall may be less deep in the fourth and fifth interspace and may be provide an alternative.(113)

This should be followed-up by a chest tube, with the cannula left in place until bubbling is confirmed with an underwater seal system(113).

1.2.4.1.   Traumatic Pneumothorax

After rib fractures, traumatic pneumothoraces are the most common chest injuries in patients with blunt trauma(133). Approximately one in four blunt traumatic fatalities in North America are a direct consequence of chest injuries(134). Blunt trauma to the abdomen may also precipitate a traumatic pneumothorax(135).

Traumatic injury to the pleura can lead to air accumulation in the pleural space. Additionally, a fifth of traumatic pneumothorax patients have an accompanying haemothorax(136). Whilst an uncomplicated traumatic pneumothoraces may be well tolerated, the risk of tension and resultant cardiorespiratory compromise makes identification important, particularly as a simple procedure, tube thoracostomy insertion, can potentially avert significant morbidity and mortality(134). Because of this, the current guidance by the American College of Surgeons Advanced Trauma Life Support (ATLS) advises chest tube placement for any traumatic pneumothorax(137). It does state asymptomatic pneumothoraces can be managed with observation and aspiration at the treating physician's discretion and it has been previously proposed that small traumatic pneumothoraces can be managed conservatively.

An early retrospective study of 54 patients demonstrated no clinical deterioration in patients with small or moderate sized traumatic pneumothoraces, in the absence of other significant injuries or the need for intermittent positive pressure ventilation (IPPV) (138). Another larger study studied patients not on IPPV with small unilateral traumatic pneumothorax (<1.5cm on CXR) who were managed conservatively. Of the 803 patients, 329 (41%) were treated conservatively and 29 (9%) required chest tube placement due to pneumothorax enlargement(139). IPPV, which increases gas flow through the pleural defect, is thought to increase the risk of tension pneumothorax (131). Because of this, the ATLS recommend that all patients with a traumatic pneumothorax on IPPV are treated with chest tube drainage (137)..

This concept has been challenged, principally due to the increased use of computerised tomography (CT) scans in trauma which identify small, sub-centimetre sized pneumothoraces. This has raised the question whether these small 'occult' pneumothoraces, which can make up to 76% of all traumatic pneumothoraces(140), can be left untreated, particularly when invasive positive pressure (IPPV) is required. Despite early studies indicating a high rate of tension in conservatively managed patients on IPPV (141), more recent studies (133, 134, 140, 142, 143) suggest that occult pneumothoraces can be managed expectantly, including patients undergoing IPPV.

Whether these results can translate to all traumatic pneumothoraces is unclear and needs clarification. With increasing availability, the CT is now almost ubiquitous in multiple trauma patients, and the distinction between occult and overt pneumothoraces may become antiquated. Recent case studies have also suggested it may possible to treat larger pneumothoraces with observation (144, 145).

1.2.5. Managing persistent air leak and failure to re-expand

1.2.5.1. Suction

Routine use of early suction in not recommended by the BTS guidelines (113). A small randomised control trial found no significant difference in the rate of lung re-expansion or duration of hospital stay with suction compared to no suction(146)

There may be a role for the use of high volume, low pressure suction in the persistent air-leak (arbitrarily defined as continued bubbling greater than 48 hours after chest drain insertion) or incomplete re-expansion of the lung, the theory being that the air may be removed from the pleural cavity at a greater rate than it enters via the visceral membrane. The use of suction too early can precipitate re-expansion pulmonary oedema, particularly if the pneumothorax has been present for more than a few days. High pressure high volume suction may lead to perpetuation and/or worsening of the air leak(113). The typical pressure used are between -10cm and -20cm H20.

1.2.5.2. Surgery

The BTS recommends that a thoracic surgical opinion should be sought in cases of persistent air leak or failure of the lung to re-expand after 3-5 days.

The timing of surgical intervention is debated. A study by Chee at al showed that 100% of PSP, and 79% with SSP, with persistent air leak of more than 7 days treated with intercostal drain (ICD) resolved by day 15 and 14 respectively, with no associated mortality(147). However, surgery carries a low morbidity risk, and has good success rates.

There are two main types of surgery, thoracotomy and VATS, with both performed under general anaesthetic (GA). There are several approaches to thoracotomy, either the standard posterolateral thoracotomy or methods using smaller incisions, such as axillary thoracotomy, anterior thoracotomy or various mini-thoracotomies (106). The procedure consists of excision of blebs and bullae, usually via stapling and treatment of smaller bullae with electrocoagulant or laser(106). Usually the surgeon will perform a pleurodesis, either by a parietal pleurectomy, or a mechanical abrasion of the parietal pleura with gauze. Some surgeons perform a chemical pleurodesis. VATS is performed under GA with single lung ventilation. Generally, three ports, a thoracoscope and two lung graspers, are inserted, with the patient in the lateral decubitus position. The same intrathoracic procedure can be performed by VATs as via open thoracotomy (106).

Analysis of RCTs demonstrated equivalent success rate between VATS and thoracotomy, with reduction in analgesia use and shorter hospital stay in the VATS cohort (148). A recent RCT comparing mini-thoracotomy with VATS showed equivalent recurrence rates (2.7% and 3%, respectively) and postoperative pain, but VATS was associated with higher patient satisfaction. (149). A large prospective cohort study of 1415 patients undergoing VATS with talc poudrage found a recurrence rate of 1.9% and a complication rate of 2%. Interestingly the recurrence rate was much higher in smokers (4.2%) compared to non-smokers (0.2%)(150).

Accepted indications for surgical advice are shown in Table 1.

Table 1. *Indications for surgical opinion in management of pneumothorax (113)*
Second ipsilateral pneumothorax
First contralateral pneumothorax
Synchronous bilateral spontaneous pneumothorax
Persisting air leak (despite 5-7 days of chest tube drainage) or failure of lung-re-expansion
Spontaneous haemothorax

Professions at risk (aircraft personal, divers)
Pregnancy

1.2.6.   Pleurodesis

Pleurodesis either by chemical irritant, mechanical abrasion, or parietal pleurectomy, aims to achieve adherence of the pleural membranes by promoting inflammation. Chemical pleurodesis by a sclerosing agent can be delivered by chest tube, medical thoracoscopy, or VATS.

Chemical pleurodesis with intrapleural administration via a chest tube has been investigated with several agents, including antibiotics (minocycline, tetracycline, and doxycycline) and talc preparations. It is a suitable option for patients ineligible or unwilling to have surgery, after assessment by a respiratory specialist. It has been suggested that chemical pleurodesis is an easy, safe, and cost-effective approach for the treatment of spontaneous pneumothorax and could be considered as an initial treatment of PSP[151]. It has the advantage of being administered by the bedside, however potential drawbacks of uneven distribution of talc and the potential for only localised symphysis at the site of administration [152]. A randomised trial investigating the use of minocycline pleurodesis via chest drain versus chest drain with no pleurodesis in patients with PSP showed lower recurrence rates 29.2% vs 49.1% in the minocycline pleurodesis arm[153]. It has been commented that this trial however had a higher recurrence rate in the control group compared to other studies, and compared unfavourably with surgical options[154].

Talc delivered by medical thoracoscopy under direct vision has good long-term success rates. In a randomised control trial in patients with PSP, talc poudrage via medical thoracoscopy had a lower recurrence rates when compared to chest tube alone (5% vs 27% respectively) and was more cost-effective[155].

1.2.7.   Prevention of recurrence and risk stratification

As mentioned in the previous section, surgery and talc poudrage have both been shown to dramatically reduce recurrence. The decision to perform a definitive invasive procedure is based on the risk of recurrence, and the potential consequences if this occurs. Currently most centres wait until the second presentation of PSP before considering definitive management, though it is often considered earlier in patients with SSP, due the potentially life-threatening risk of a recurrence. However, the decision is made difficult due to a wide range in the quoted recurrence

rates, from 13.5–54% (153, 156, 157) and limited data on how individual risk factors affects this. The studies examining recurrence have differing methodologies and include epidemiological and prospective randomised studies with varied inclusion criteria, timescales and definitions of recurrence.

There are two main sources of determining pneumothorax recurrence. Clinical studies, either randomised or non-randomised, often cite recurrence as a study outcome. Population or epidemiological studies obtain from hospital statistics can provide long-term follow up outcome data. Both have their prospective advantages and disadvantages. The generalisability of clinical studies will be influenced by their inclusion criteria and findings are generally only applicable to the populations studied. Their findings will be determined by the study design and their internal validity. Specifically, the length of follow-up will have significant influence on the recurrence rate. However, clinical studies do have strengths. The follow-up data should be robust, and the patient's characteristics and the interventions received should be clearly recorded. Epidemiological studies have the capacity to examine much larger population, and usually for longer durations. However, the data is strongly influence by the quality of clinical coding and data collection. Clinical coding does not distinguish between PSP and SSP and researchers must rely on co-morbidities also being coded. Additionally, these data sources only provide information on patients admitted to the hospital, and do not include patients managed in the community.

In a recent prospective cohort study of 234 consecutive patients with their first episode of PSP admitted and treated conservatively with a chest tube, recurrence was observed in 54% of patients, with 30% of these patients experiencing a pneumothorax in the contralateral lung(158). Conversely, a recent epidemiological study published by Hallifax et al found a five-year recurrence rate of male patients with PSP was 20.6 (20.1-21.1) The study used Hospital In-Patient Enquiry (HIPE) 1968-1985) and Hospital Episode Statistics (HES) 1990-2016, identifying 170 929 hospital admissions in England for spontaneous pneumothorax This risk was higher in the younger cohort of patients (15-34 years old of age) that are typically associated with PSP, at 22.0 (21.3-22.6) in males and 25.1 (23.8-26.5) in females. Another large epidemiological study by Bobbio et al examined 42 595 patients presenting to hospitals in France from 2008 to 2011 with both with PSP and SSP. It found that 28% patients had more than one spontaneous pneumothorax-related hospital stay over the 4-year period, with majority occurring within 1 year of the first recorded episode(127).

Studies looking at SSP have found that 40-50% of patients will have a second pneumothorax if pleurodesis or definitive thoracic surgery is not performed(159). The rate of pneumothorax is also thought to increase with every subsequent recurrence. A study from 1963 found that the risk of

recurrence after first pneumothorax was 57%, 62% for second and 83% for the third(160). However this was only statistically different between the first and third recurrence (161).

One of the aims in the management of pneumothorax should focus on the identification of patients likely to have a recurrence and hence who may benefit from early surgery. Height in men, female sex and low bodyweight are associated with increased rate of recurrence(156, 158). Smoking is associated with a high risk of recurrence, with smoking cessation after an initial PSP associated with a relative risk reduction of over 40% (156). Since the rupture of blebs or bullae are thought to be the main cause of PSP, studies have investigated whether radiology can help in predicting the risk of recurrence, providing conflicting answers. A prospective Study by Martínez-Ramos et al of 55 patients could not demonstrate that the presence, size, or number of bullae on CT scans had any influence on recurrence rate(162). A subsequent study using HRCT on 176 patients with PSP found that the risk of recurrence was significantly related to the presence of blebs or bullae or both (163). Another study looked at the role of the Chest X-ray (CXR) in determining the risk of recurrence. They looked for radiological abnormalities on CXR including pleural thickening; blebs/bullae; pleural irregularities and pleural adhesions. They found that the found that the presence of an abnormality (irrespective of the type) increased the likelihood of recurrence and the risk of recurrence increased with each additional abnormality. They recommended surgical pleurodesis for first episode of PSP when multiple CXR abnormalities are identified at the time of diagnosis(164). It has also been postulated that management of the initial PSP influences recurrence. There are advocates for each management pathway. Various authors suggest that inserting a chest drain creates pleural inflammation and promote prompt pleural apposition, leading to lower rates of recurrence. Conversely, advocates of conservative management suggest that allowing the lung to re-inflate gradually promotes greater wound healing and subsequent lower risk of recurrence(165). There isn't enough evidence at the moment to determine if management affects recurrence, but the recently conducted Australian study comparing patients PSP randomised to either conservative or chest drain might inform on this (166).

1.2.8.   Evidence on best method of recurrence prevention

Surgery is the definitive management to reduce recurrence. The two main types of surgical entry for pneumothorax management are thoracotomy and VATS to perform blebectomy of visible blebs. There is variation of practice on whether pleurodesis, either by pleurectomy or scleroscent, is performed. Analysis of RCTs demonstrated equivalent success rate between VATS and

thoracotomy, with a recent RCT comparing mini-thoracotomy with VATS showed equivalent recurrence rates (2.7% and 3%, respectively) and postoperative pain(149). The VATS is becoming more popular, due to lower lengths of stay and higher patient satisfaction scores. Patients managed with isolated blebectomy appear to have a higher rates of recurrence than blebectomy combined with a pleurodesis procedure, with one study of VATS demonstrating that patients treated with talc poudrage compared with subtotal pleurectomy alone or alongside ligation or stapling of bullae had a recurrence rate of 1.8% compared to 9.2%(167). This supports the concept of pleural porosity, proposed by Marc Noppen, who demonstrated with fluorescein imaging, that the air-leak in PSP is not isolated the blebs themselves, but via the surrounding inflamed pleural(111).

Currently recurrence prevention surgery is recommended for patients who have had more than one recurrence. However, there are advocates for performing surgery as a first-line treatment at the patient's initial pneumothorax. The study by Olesen et al examined performing surgery on patients with their first PSP, finding the risk of recurrence was 34% (32/93) in patients managed with chest drain compared to 13% (11/88) patients after VATS(168). This represented a number need to treat (NNT) of 4.8 patients to have surgery to prevent one recurrence(169). There were low reported adverse events with surgery, however they were no reported quality of life data included in this paper.

Other non-operative methods of recurrence prevention include instillation of a pleurodesis agent via on the ward. A randomised controlled trial demonstrated that minocycline instillation reduced the risk of recurrence from 33.3% in the cohort managed with simple aspiration compared to 12.9% in patients managed to instillation off 300mg of minocycline via a catheter(170). Talc can also be delivered by medical thoracoscopy under direct vision and has demonstrated good long-term success rates. In a randomised control trial in patients with PSP, talc poudrage via medical thoracoscopy had a lower recurrence rates when compared to chest tube alone (5% vs 27% respectively)(155).

Smoking cessation advice should be given all patients. This decreases the risk of recurrence in both the medically, and surgically managed patients(171, 172).

1.2.9.   Recurrence prediction

Presently there is no risk model calculator to determine a personalised recurrence risk for patients. There have been a lot of interest in using low-dose CT to determine recurrence risk, with

4 studies to date examining whether blebs increase the rate of recurrence in medically managed patients. (163, 173-175). These studies have produced conflicting results with two studies finding an association between radiographic evidence of blebs and recurrence risk and two studies not. A proposed dystrophic severity score (DSS), which assessed both blebs and bullae, appeared to be the most useful radiographic scoring system. It demonstrated high negative predictive value of >90% but a low positive predictive value of just 68% suggesting a possible value as a rule-out test(163). More recently Olesen et al's study on first-line surgery suggested the benefits of surgery were best seen when high-resolution computed tomography demonstrated bullae ≥2cm(168). Another possible marker of recurrence is using air-leak data to identify high patients. Digital air-leak data can provide accurate measurement of air-leak and there is evidence suggesting that a high air-leak predicts those patients who will require surgery for persistent air-leak, and there is ongoing work on whether this measurement can predict recurrence(176).

1.2.10. Novel management strategies

1.2.10.1. Conservative management

Conservative management is recommended for patients with a small asymptomatic PSP by the BTS (113). The guidelines suggest that selected asymptomatic patient with large PSP may be managed by observation alone. It has been hypothesised that the collapsed lung is more likely to heal, allowing apposition of the visceral leak sites(90). This is currently under investigation by a multicentre trial in Australasia, designed to compare ambulatory conservative management with standard management in asymptomatic patients with a large pneumothorax(89).

Whilst the guidelines advise that the majority of traumatic pneumothoraces need chest tube drainage, particularly if IPPV is required, there is a growing literature base that suggests that small traumatic pneumothoraces can be managed conservatively including patients receiving IPPV (133, 134, 140, 142, 143).

1.2.10.2. Use of Heimlich valve and pleural vents

Approximately 6000 patients are admitted with spontaneous pneumothorax each year in England, with person-based admission rate of 11.6 per 100,000 population (95% CI, 11.3-11.9). The majority of these admissions are for patients with chronic lung disease, with 59.4% of males and 64.5% of females having secondary spontaneous pneumothorax (177). Patients with SSP typically have a longer length of stay than patients with PSP, with one large epidemiological study demonstrating a more than double length of hospitalisation than the PSP (14.5 vs 5.9)(127). It is

anticipated that shortening the length of stay would reduce healthcare resource cost and increase patient mobility. This would be particularly important for patients with SSP, who will be a higher risk of complication from prolonged bed-rest.

The attachment of a one-way flutter (Heimlich) valve to the end of a chest drain, instead of the standard underwater seal bottle, has been used since the 1970s(178). Various permutations of these devices are available, from the classic Heimlich Valve (HV), to devices which enable collection of fluid secretions from the chest drain, such as the Atrium Pneumostat chest drain valve. More recently, self-contained valves, such as Tru-Close Thoracic Vent and Rocket Pleural Vent, have become commercially available, which have a catheter attached directly to the valve, and therefore do not require prior chest drain insertion.

Despite being used for over 40 years, there have been limited published randomised controlled trials investigating the efficacy of a flutter valve in patients with a pneumothorax and none which have looked exclusively at patients with SSP. Two small RCTs have been performed examining the use of HVs on patients with pneumothoraces, the first by Roggla et al 1996 which examined 30 patients with both spontaneous and iatrogenic pneumothoraces. It used a thoracic vent, a polyurethane catheter connected to a plastic chamber containing a one-way valve. It found similar rates of lung re-expansion and complications compared to standard chest drain attached to an under-water seal attachment, with 70% of patients with thoracic vent successfully managed as outpatients(179). Ho and colleagues randomised patients with PSP to needle aspiration (NA) or minichest tube (MCT) insertion with Heimlich valve attachment in the Emergency Department(97). The MCT consisted of a 12Fr drain with a Heimlich valve attached to the end. It defined two outcomes as its primary outcome, failure rate and admission rate. Failure rate was defined as recurrence of pneumothorax; need for a second procedure or need for surgical procedure, although they reported these outcomes separately. They estimated they wound need 100 patients to detect a 25% difference in failure rate. They recruited 48 patients in total and was therefore underpowered to detect the differences they sought to find. The groups were not similar, with 65% of the NA group having a pneumothorax >5cm from apex, compared to 36% in the MCT group. They found no significant difference in number of patients requiring another procedure (35% in NA group, 20% in MCT) and number of admissions from ED (52% in NA group, 28% in NA). There was a significant difference between patients who had full resolution at their first outpatient review (at three days), with 6(24%) of MCT having full re-expansion, compared to 1(4%) of those who had NA. When admissions from ED and outpatient clinic were combined, both groups had high admission rates, at 61% in NA group 44% in MCT group. Overall, the study was significantly underpowered to detect the differences they were interested in. There were,

additionally, multiple methodological flaws, with poorly defined and reported composite primary outcomes.

A systematic review of ambulatory management in spontaneous pneumothorax examined 18 studies, comprising of 2 RCTS and 16 non-randomised studies, and included 1235 patients, only 10% of which were SSP (180). Overall success with a   HV was 86%, success in the outpatient setting was 78%. If this figure is replicated in larger studies, the paper suggests the adoption of this treatment could save nearly 12 000 bed days per year in England. Additionally, the systematic review concluded that complications were rarely reported in the literature.

There have been no prospective studies which have specifically assessed the effect of HVs in patients with SSP. HVs have been shown to reduce levels of pain during activities for patients with pneumothorax compared with standard treatment(181) and they may offer significant advantages over standard treatment in enabling improved levels of mobility while patients are in hospital, with consequent advantages such as the reduction of rates of pneumonia and venous thromboembolic disease as well as enabling earlier discharge. Establishing the efficacy of HVs in patients with SSP may provide evidence for their use within an outpatient treatment pathway for SSP.

A recent study evaluated the use of HV in patients with iatrogenic pneumothorax post lung biopsy(182). In patients with a large/symptomatic pneumothorax at 30 min post biopsy; enlarging pneumothorax at 60 min; or persisting or symptomatic pneumothorax, a 8 Fr drain was inserted and connected to a Heimlich valve chest drain (HVCD). There were no major complications, and the 8 of the 52 patients who HVCD-related pleuritic pain were successfully managed with 10 mL of intrapleural 0.5% bupivacaine. All patients had their HVCD removed within 48 hours. These results are encouraging, though may not translate to spontaneous pneumothoraces.

Figure 3.   Flutter valves: a) Heimlich flouter valve b) Atrium Pneumostat c) Rocket Pleural Vent
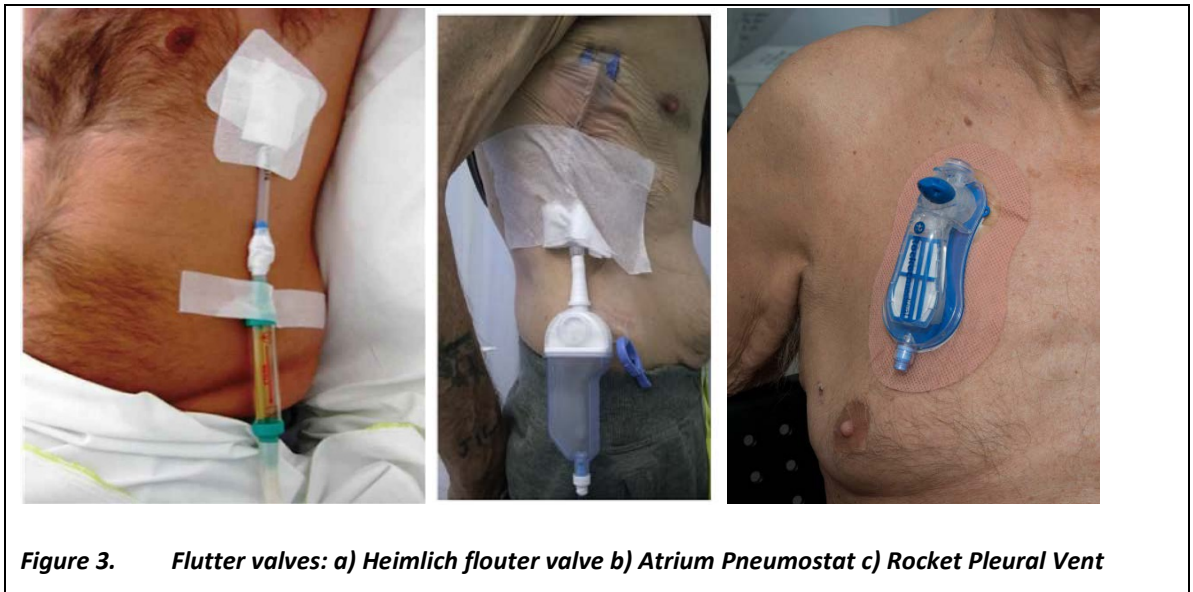
1.2.10.3.   Endobronchial valves

Endobronchial valves (EBV), more commonly used as an alternative to lung reduction surgery in emphysema, have been used in patients with pneumothorax and a persistent air leak who are deemed not fit for surgical management. These one-way valves inserted via bronchoscopy, aim promoting atelectasis of the distal lung, whilst still allowing drainage of secretions. The largest study into this was a retrospective, non-randomized study in 40 patient with pneumothoraces (iatrogenic, PSP and SSP) and demonstrated that 19 patients (47.5%) had complete resolution of acute air leak, 18 patients (45.0%) had reduction, and 2 patients (5.0%) had no change in air leak status.(183) This study was limited by with retrospective, nonrandomised design, which included a heterogenous population.

1.2.10.4.   Air leak monitoring system

Digital drainage systems have been used to allow real-time, continuous quantification of air leak. These devices have been studied in patients with post lobectomy chest drain, with several studies showing a reduction in chest drain duration in patient managed with digital monitoring of air leak compared to a traditional protocol of using visual and subjective assessment of air leak (bubbles) (184-186) This was contradicted by a more recent study which showed no change in chest drain duration(187). However, there are no published studies to date looking at the digital assessment

of air leak in medical patients with PSP or SSP, and caution most be used in applying post-surgical data, in which the outcome was chest drain duration. It is a reasonable suggestion that this is a more accurate way of quantifying the air leak than visual inspection of air bubbles in the chest drain bottle. It may allow earlier identification of patients whose leak is not settling and would benefit from early thoracic surgery. (152)

Figure 4. *Digital air leak monitoring system (Thopaz Digital Chest Drainage System; Medela Inc.*

Healthcare, McHenry, IL, USA).

## 1.3.	Summary

This thesis will explore the clinical course and progression of non-malignant pleural disease. It will focus on the two poorly understood disease processes, the refractory transudative pleural effusion and pneumothorax.

There have been several studies examining the prognostic factors in MPEs, with limited comparable datasets on NMPE. The first study outlined in this thesis, survival in refractory transudative effusions will provide robust prospectively collected data in patients with pleural effusions secondary to organ failures to identify variables which offer prognostic information in this patient cohort. This is a first, important step in developing a prognostic model.

The second study will use a prospectively collected dataset with patients with cardiogenic pleural effusions to determine the proportion of patients who required further therapeutic pleural procedures.

The results of these two study, demonstrating poor median survival in patients with refractory transudative pleural effusions and high rates of refractory cardiogenic effusions, informed the design of the third study outlined in this study, a randomised control trial in this patient cohort, allocating participants to indwelling pleural catheters (IPCs) or standard management. The primary outcome, breathlessness, was chosen to reflect that symptom control is an important outcome in what is for many patients, a palliative condition. A randomised controlled trial design was chosen as the optimal way of comparing these two treatment arms.

As outlined above, there are three main research questions regarding the management of pneumothoraces. Firstly, it is unclear what true rate of recurrence in patients who have experienced a pneumothorax, and a broad range is cited in the literature. The fourth part of this PhD is a systematic review of papers detailing the incidence of recurrence of PSP, the sub-type of pneumothorax with the greatest literature base. The choice was made to examine studies on PSP, as opposed to studies with SSP, which is the focus of a later study in this dissertation, as there were not sufficient number of studies examining recurrence in SSP to form a valid systematic review. Patients with SSP are very unrepresented in clinical studies.

There is increasing interest in managing pneumothoraces conservatively. To investigate this, the fifth study contained in this thesis is an observational study on patients with a traumatic pneumothorax (TP) to determine the safety of a conservative approach. This was a prospective collected study of patients presenting with TP to major trauma centre, examining clinical outcomes in patients managed with an intervention and conservatively.

Lastly, whilst a review of the literature suggests that use of an ambulatory devices is safe in the management of pneumothorax, there is no randomised data investigating efficacy in patients with SSP. The final study in this PhD is an RCT in the use of ambulatory devices in patients with SSP, examining length of stay as a primary outcome.

Aetiology	Transudative pleural effusions	Pneumothorax
Natural History	Survival in refractory transudative effusions	Incidence of recurrence of primary spontaneous pneumothorax
	Natural history of cardiogenic pleural effusions	Conservative management of traumatic pneumothorax
Ambulatory Management	REDUCE trial	HI-SPEC trial
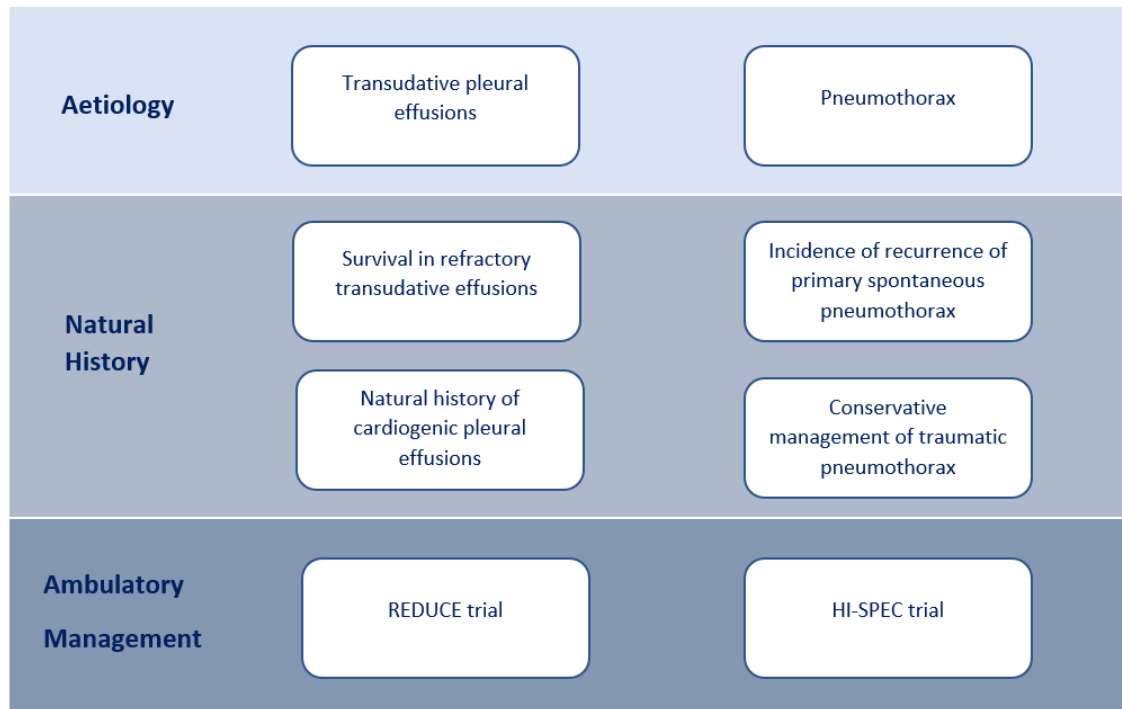
Figure 5.   *Understanding the clinical course and progression of non-malignant pleural disease: thesis structure*

CHAPTER 2.   METHODS

In this chapter I will outline the study design of 4 non-randomised studies and 2 randomised controlled trial undertaken in this thesis. The studies design outlined are:

- Survival in refractory transudative effusions

- Natural history of cardiogenic pleural effusions

- Randomised controlled trial evaluating the efficacy of indwelling pleural catheters in persistent non-malignant pleural effusions - the REDUCE trial

- Results: Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

- Conservative Management in Traumatic Pneumothoraces: An Observational Study.

- Heimlich Valves in Secondary Spontaneous Pneumothorax: Enhancing Care – the HI-SPEC trial

2.1.   Study design: Survival in refractory transudative effusions.

As describe earlier in the thesis, there is a wealth of studies investigating prognosis in exudative pleural effusions, with little comparable data in patients with transudative effusions. The use of prediction models are intended to help doctors make decisions by providing more objective estimates of probability as a supplement to other relevant clinical information (188). To further investigate the prognosis of patients with pleural effusions secondary to organ dysfunction, I conducted a prospectively observational study on 782 consecutive patients at North Bristol NHS Trust. This is the first stage, the development stage, of the consecutive stages to produce a usable multivariable prognostic model. It will be conducted to identify important predictors of prognosis in this patient cohort.

I identified 782 consecutive patients in an observational cohort study, presenting with a new undiagnosed pleural effusion, to a single UK centre, between 03/2008 and 03/2015. The data was collected prospectively and retrospectively analysed. Patients were recruited as both inpatients and outpatients.

Pleural fluid and serum biochemistry, pleural cytology, thoracic ultrasound (TUS) and a chest radiograph were performed on all patients. Echocardiogram, computerised tomography (CT) scans, radiological-guided biopsy and medical thoracoscopy were undertaken as clinically indicated. Patients were followed-up for a minimum duration of 12 months or until death, with the final diagnosis decided following independent review by two respiratory consultants. Where more than one aetiology was felt to be responsible, the principal contributing factor was listed first. There was a high level of inter-observer agreement, as calculated by kappa statistics, with a $\kappa = 0.942$ (95% CI, 0.917 to 0.967). The formula for CI for kappa: $k - 1.96 \times SEk$ to $k + 1.96 \times SEk$, was used. SEk is the standard error of the kappa value and calculated as 0.013. Patients were classified into diagnostic categories for analysis: malignant; CHF; liver failure; renal failure; pleural infection (empyema, complicated parapneumonic effusion, simple parapneumonic effusion, TB pleuritis); benign asbestos pleural effusion & diffuse pleural thickening (DPT); coronary artery bypass graft (CABG), pulmonary embolism, and other (including chylothorax, rheumatic, trauma and drug-induced). This was based on the following criteria:

Malignant pleural effusion

1. Malignant pleural fluid cytology or biopsy or
2. Histologically confirmed pleural malignancy or extra-thoracic/pulmonary malignancy with radiographic evidence of metastasis to ipsilateral pleura on CT or
3. Radiological changes meeting Leung's criteria which have progressed in keeping with malignancy on interval CT scan in the correct clinical context or
4. Autopsy confirming pleural malignancy

Complicated Parapneumonic Effusion

Clinical presentation suggestive of sepsis and

1. Pleural fluid pH ≤7.2 or pleural fluid loculation on ultrasound and follow up for at least 6months inconsistent with pleural malignancy or
2. Pleural fluid gram stain or culture positive or
3. Frank pus or
4. Pleural infection confirmed by pleural biopsy histology and/or microbiological culture or
5. CT scan consistent with pleural infection with radiological resolution following treatment with antibiotics.

Simple Parapneumonic effusion

Clinical presentation suggestive of sepsis with appropriate chest radiology and pleural fluid which is gram stain and culture negative with a pH >7.2 and an absence of loculation on thoracic ultrasound and resolution of effusion on CXR after antibiotics

Connective tissue disease (including RA)

1. Systemic features or known diagnosis of connective tissue disease and
2. chest radiology (including CT imaging) showing benign features (e.g. doesn't meet any of Leung's criteria) with at least 6 months follow-up and /or pleural biopsy negative for malignancy.

Pulmonary embolism

1. Evidence of PE on CT pulmonary angiogram (CTPA) and
2. No alternative explanation for pleural effusion on cross sectional imaging or pleural fluid analysis. (NB the CT shows no evidence of pleural thickening – which would suggest another cause)

BAPE or diffuse pleural thickening due to asbestos

History of asbestos exposure or evidence of pleural plaques on CT and

1. Stable or improving CT appearances with follow-up for at least 12 months (the development of enfolded lung is allowed) or
2. Negative thoracoscopy (benign pleural biopsy).

Congestive heart failure

1. History and examination features of CHF or
2. Evidence of at least moderate LV systolic or diastolic failure or severe valvular disease on echo or
3. Improvement of effusion and symptoms with diuretic therapy.

CABG

1. CABG in 3 months prior to development of pleural effusion in the absence of an alternative cause

Hepatic hydrothorax

1. Known history or clinical presentation consistent with liver disease and
2. Recurrent transudative pleural effusion and
3. Negative cytology

Renal failure or hypoalbuminaemia

Biochemical confirmation of renal failure or hypoalbuminaemia in the absence of clinical, radiological or pleural fluid analysis suspicious of an alternative cause.

TB pleuritis

1. Culture or AAFB positive sputum, pleural fluid or pleural tissue and
2. Resolution of pleural effusion with anti TB therapy at 6-month follow-up.

Inflammatory pleuritis (Non-specific pleuritis)

1. Demonstration of non-specific inflammatory pleuritis on pleural biopsy and
2. Follow-up for 12 months without progression that would suggest a malignant cause.

Undiagnosed

1. Exhaustive investigations including 12 months follow-up with interval CT scans has not demonstrated a diagnosis or
2. Patient unfit for further investigation and follow up or
3. Patient died without definitive diagnosis and no postmortem examination conducted

Effusions were defined as malignant if either the primary or secondary diagnosis included a malignant cause.

Effusions were classified either as transudative or exudative by Lights criteria(11) and either bilateral or unilateral based on PA chest radiograph appearance. The effusions were categorised by cytology as either blood, macrophage, neutrophilic or lymphocytic predominant (>50%), mixed if no clear predominance in cytology and eosinophilic if >10% eosinophils. Eastern Cooperative Oncology Group Performance score (ECOG-PS)(189) was recorded for 77.6% of patients.

Survival data was calculated from date of study entry to date of death. Surviving patients were censored on 07/2016.

The study protocol was approved by local ethical approval, South-West Bristol Research Ethics Committee (Ref 08/H0102/11), in accordance with the Declaration of Helsinki. Study participants gave written informed consent.

2.1.1.　Statistics Analysis

Descriptive statistics were used to summarise patient characteristics and clinical data. Means (±SD) were calculated for age and percentage values for subgroups. Univariable analysis was used, examining the association with each exposure of interest, to provide an initial idea of the variable that were strongly associated with survival. Univariables chosen were fluid biochemistry (exudate versus transudates), chest radiograph appearance (bilateral versus unilateral) and cell differential (blood, macrophage, neutrophilic or lymphocytic predominant, mixed, cytology and eosinophilic. These variables were chosen as they are clinically available and objective parameters that have been shown to influence prognosis in previous studies(62). Univariables that achieved statistical significance ($p < 0.05$) were selected for multivariate analysis. The analysis was not controlled for age or other comorbidities.

Multivariate proportional hazard ratios were calculated using Cox regression analysis for 6 and 12-month mortality for presence of bilateral pleural effusion (compared to unilateral), transudative effusions (compared to exudative), and the following aetiologies (compared to malignant pleural effusion cohort): CHF, liver failure, pleural infection, renal failure, BAPE/DPT, CABG, PE, and other. Kaplan-Meier plots for survival probabilities were created for overall mortality and stratified for aetiologies, bilateral vs unilateral effusions and transudative for exudative effusions. All statistical analyses were performed using IBM SPSS statistics version 23.0 (SPSS Inc. Chicago, IL)

2.2. Natural history of cardiogenic pleural effusions

The natural history of cardiogenic pleural effusions is unclear. The cited figure of 10% refractory to medical management is based on a small study of 60 patients with a short median follow-up of 16 days(20). In order to get a better idea of the rate of refractory cardiogenic pleural effusions I examined patients with cardiogenic pleural effusions in an observational study, documenting the rate of pleural re-accumulation in the patient with heart failure.

The study used the same database are described in the previous study on survival of transudative effusions. It was conducted at a later date, including patients from 03/2008 to 03/2017. It was a retrospective analysis of consecutive prospectively enrolled patients presenting to the pleural service with an undiagnosed pleural effusion were prospectively recruited. Pleural biochemistry, cytology, thoracic USS and chest radiograph were performed at baseline. Patients with unilateral and bilateral effusions on CXR were included. Patients without a contemporary echocardiogram were excluded.

As with the previous study, patients were followed-up for a minimum duration of 12 months or until death, with the final diagnosis decided following independent review by two respiratory consultants. Where more than one aetiology was felt to be responsible, the principal contributing factor was listed first. Patients were classified into diagnostic categories for analysis: malignant; CHF; liver failure; renal failure; pleural infection (empyema, complicated parapneumonic effusion, simple parapneumonic effusion, TB pleuritis); benign asbestos pleural effusion & diffuse pleural thickening (DPT); coronary artery bypass graft (CABG), pulmonary embolism, and other (including chylothorax, rheumatic, trauma and drug-induced).

Pleural effusions were considered as secondary to CHF if history and examination features indicated CHF or there was evidence of at least moderate LV systolic or diastolic failure or severe valvular disease on echo or there was improvement of effusion and symptoms with diuretic therapy. Patients were malignancy was a possible secondary contributor to the effusion were excluded.

Effusions were classified either as transudative or exudative by Lights criteria(11) and either bilateral or unilateral based on PA chest radiograph appearance. The transthoracic echocardiography (TTE) results were based on reports provided by the sonographer. These reports provided variable amounts of descriptive and objective measurements. There was no standardised approach. When ejection fraction was provided, >50% was deemed as perseved (normal) systolic function. Descriptive categorisation, provided by the sonographer typically

classified the LV function onto normal, mild, moderate or severe. Pulmonary hypertension was classified when described as such by sonographer, or a raised pulmonary arterial systolic pressure (PASP) >55 mmHg. The presence or absence of atrial fibrillation (AF) was determined by ECG. The size of the pleural effusion was graded as per Light's chest x-ray grading from 0 to 5 (0 for no fluid to 5 for complete opacification of hemithorax) for the largest effusion side. NT-proBNP was performed as a serum sample. Prior to 2010 a bedside NT-ProBNP assessment was used, which had a maximum cut-off value of >3000pg/ml. After this, NT-ProBNP were processed in the laboratory, with no upper cut-off.

The outcome of the study was proportion of refractory cardiogenic effusion. Refractory cardiogenic effusion was defined as requiring an additional therapeutic pleural procedure (therapeutic aspiration, chest drain drainage or IPC insertion) after initial index aspiration (either diagnostic aspiration or therapeutic) in a patient receiving diuretics.

The study protocol was approved by local ethical approval, South-West Bristol Research Ethics Committee (Ref 08/H0102/11), in accordance with the Declaration of Helsinki. Study participants gave written informed consent.

2.2.1.   Statistics Analysis

Descriptive statistics were used to summarise patient characteristics and clinical data. Means (±SD) were calculated for age and percentage values for subgroups. Univariable analysis was used, examining the association with each exposure of interest, to provide an initial idea of the variable that were strongly associated with survival. Univariables chosen were fluid biochemistry (exudate versus transudates), chest radiograph appearance (bilateral versus unilateral), Albumin (≥20 g/liter or < 20 g/liter), gender (male or female), NT-proNBP (>3000pg/l), degree of LV dysfunction (severe vs non-severe), pulmonary hypertension (severe vs non-severe) and presence of cardiac rhythm (AF versus sinus rhythm).

Categorical data was analysed using Chi-squared test. Odd ratios were calculated for the variables. All statistical analyses were performed using IBM SPSS statistics version 23.0 (SPSS Inc. Chicago, IL)

2.3. Study design: A randomised controlled trial evaluating the efficacy of indwelling pleural catheters in persistent non-malignant symptomatic pleural effusions (REDUCE trial)

As part of this thesis, I conducted a multicentre randomised controlled trial designed to evaluate whether the insertion of an IPC is associated with a reduction in breathlessness, as assessed by use of a visual analogue scale (VAS) score, compared with repeated thorancentesis in patients with a pleural effusion due to heart failure or liver failure.

The study design was conceived by Prof Maskell and the initial protocol was written by Dr Bintcliffe, who conducted the initial site set-ups. I took over trial management after 5 patients had been recruited and increased the number of sites from 8 to 14. I completed various minor and major amendments. At the time of writing the thesis, 65 patients had been recruited

An RCT design was decided, as it is considered the gold standard for evaluating efficacy in clinical research(190). IPC was chosen as the intervention due to promising retrospective data on reducing length of hospital stay and low rate of major complications(77). Studies on IPC in patients with MPE have indicated that IPCS are equally as efficacious as talc slurry pleurodesis in controlling symptoms of breathlessness and reducing number of pleural procedures needed(191). There is no prospective RCT on IPCs in this patient cohort, and limited patient related outcomes data. Talc pleurodesis would be an alternate method of managing refractory NMPE. However, the only comparative data, in form a propensity-matched cohort study, comparing talc poudrage under general anaesthetic and IPC in patients with heart failure demonstrated that IPCs had a significantly shorter hospital stay (2±2 days) and a lower rate of operative morbidity and readmissions than patients undergoing thoracoscopic pleurodesis. Patients undergoing thoracoscopic pleurodesis had 6±4 day hospital length of stay, 23% readmission rate and 5% operative mortality. Respiratory insufficiency, pulmonary embolism and atrial fibrillation were among the reported complications with overall morbidity of 20% compared to 2.5% morbidity in the IPC group(66). In terms in comparator, as-needed thoracentesis as a control group was chosen as this represents the most common practice in patient with refractory NMPE.

Patients were identified from respiratory, hepatology and cardiology services and the trial is being conducted from centres with established pleural services and experience of pleural trials. Eligible

patients had symptomatic non-malignant pleural effusions due to CHF or liver cirrhosis, on maximal medical management. Eligible patients had previous sampling of pleural fluid and treatment optimised and will have an effusion that persists despite this. Potentially eligible patients are screened against the inclusion and exclusion criteria. Suitable patients were given a patient information sheet (PIS). A hospital visit is arranged, prior to which the patient will have had sufficient time (as defined by the patient) to consider trial participation and read the PIS.

2.3.1. Inclusion criteria

1) Clinically confident diagnosis of non-malignant pleural effusion secondary to either advanced stage CHF or liver failure requiring, and amenable to, pleural intervention for relief of breathlessness

2) Assessment by a cardiologist or hepatologist determining the presence of established heart failure or liver failure and a pleural effusion that persists despite optimised medical therapy

3) At least one previous aspiration of pleural fluid with results consistent with the cause of the effusion being due to CHF or liver failure

    Either:

    a) a) A transudate by Light's criteria in cases of effusions due to liver failure

    OR

    b) b) Either a transudate in effusions due to CHF or an exudate in cases where diuretics have been used and CHF can confidently be stated to be the cause

4) No evidence of malignancy on pleural fluid cytology

5) Expected survival >12 weeks

6) Written informed consent to trial participation.

These criteria were chosen as they are the key features for the target population I am seeking the examined. The population of interest is patients with CHF and liver failure requiring, and amenable to, pleural intervention for relief of breathlessness who have been medical optimised. This is consistent with the definition of refractory transudative effusions that has been used throughout the thesis, and therefor the results of the previous two studies outlined should be applicable to this study. Whilst the second inclusion criteria creates a potential recruitment

barrier, by involving additional speciality opinion, is was felt necessary for the trial to be translatable to clinical practice. Allowing both transudates and exudates, secondary to CHF, maintained external validity, as this is the case in clinical practice.

2.3.2. Exclusion criteria

1) Age < 18 years

2) Known pleural malignancy

3) Pleural fluid pH < 7.2

4) Previously sited indwelling pleural catheter on the side requiring intervention or current indwelling

5) Pleural catheter on the contralateral side

6) Pregnancy, lactation or intention to become pregnant

7) Inability to give informed consent

8) Absolute contraindication to IPC insertion or therapeutic aspiration of pleural fluid

9) Patient has no access to a telephone

The exclusion criteria excluded comorbidities that could bias the results of the study, in this case pleural malignancy and pleural infection. Previous exposure to the intervention arm was also felt an unnecessary bias, and so these patients were excluded. I also excluded patients with features that would increase risk of missed follow-up appointments or pose of safety risk in the community, like exclusion criteria 9.

2.3.3. Randomisation

Patients were randomly assigned to either an IPC (intervention) or a therapeutic aspiration (control) for their pleural effusion. Randomisation is minimised with 1:1 allocation. Minimisation factors are underlying aetiology of pleural effusion (CHF or liver failure) and the size of the effusion as assessed on the pre-randomisation chest radiograph (≥½ hemithorax, <½ hemithorax).

2.3.4. Post-randomisation

The therapeutic aspiration, or IPC insertion were performed according to an established standard operating procedure (SOP). Patients in the intervention arm had the catheter placed in a suitable procedure room or theatre and are discharged for drainage in the community. Patients in the control arm had a pleural therapeutic aspiration of up to 1.5L in a suitable procedure room prior to discharged. In both cases, a written SOP for the interventions is provided to all participating centres to ensure standardised practice and either procedure should be performed within 24 hours of randomisation. Patients in the IPC arm were drained at least three times a week for the first two weeks, and subsequently at a frequency considered appropriate by clinicians and patients. This was undertaken by community district nurses or alternatively by relatives, carers or the patient themselves. Records were kept for the dates and volume of drainage. Those in the control arm were offered pleural aspirations and further day-case attendances as necessary, coordinated through the trial team to control symptoms, reflecting standard practice. The dates and volumes of drainage were recorded.

2.3.5. Follow-up assessments

All patients were followed up at the recruiting unit as out-patients at four, eight and twelve weeks. These assessments included completion of the EQ-5D-5L questionnaire and assessment of the IPC site in the intervention arm. A chest radiograph was performed at the discretion of the primary physician during the follow-up period and performed at the 12-week assessment in all patients to establish if pleurodesis has occurred.

2.3.6. Human albumin solution

In the REDUCE trial we recommend that use of HAS infusions is considered in patients with hepatic hydrothorax undergoing IPC drainage or repeated therapeutic aspirations. The precise administration is not protocolised, and it is advised that clinicians follow local practices and policies which may already be in place for this patient group. We advise that HAS is given in relation to the volume of fluid drained off. As guidance, a suggested regime of 100ml of 20% HAS per 3L of pleural fluid drained may therefore be appropriate. Albumin levels will be recorded at baseline and at the 4, 8 and 12 week clinic appointments.

2.3.7.   Primary outcome

The primary outcome is the difference in daily breathless score as assessed by VAS over 12 weeks, which has proven to be a robust and clinically important outcome measure in previous studies by this collaboration(2). The intention behind pleural aspiration or drainage of cardiac, renal and hepatic failure related effusion is relief of disabling breathlessness, and the primary outcome measure of this study reflects this outcome which clinically relevant to both patients and clinicians. As demonstrated in the subsequent chapters, the median survival of patients with refractory transudative effusions is poor, and hence patient centred, symptom-based outcomes are important. VAS has been shown to be useful in demonstrating real-life symptomatic benefit in patients post therapeutic pleural intervention(192). A prospective study demonstrated the majority of patients (86%) experienced symptomatic benefit from pleural fluid drainage (mean VAS improvement 42.6 mm, SD 24.7, 95% CI 37.9 to 47.3), with a correlation between symptomatic benefit and volume of fluid removed (192). Additionally, VAS has been shown to be robust in previous randomised studies of IPC in malignant pleural effusion (2). In summary, VAS is clinically relevant, sensitive to the effects of the intervention and interpretable.

Visual analogue scales of breathlessness have been studied in varied aetiologies, with recent RCTS in pleural medicine using visual analogue scale for dyspnoea (VASD) to assess mean daily breathlessness and determine the efficacy of the study intervention. The VASD is a patient reported outcome, consisting of a 100mm horizontal line, labelled from 0mm with "'Not breathless at all' to 100mm with 'Worst possible breathlessness'. The score is the measurement from 0mm to the mark made by the study participant. Work has been performed to calculate the smallest difference in VASD that patients find worthwhile and that would lead to change in management(193). This minimal important difference (MID) has been calculated for dyspnoea in a range of other conditions, including asthma and COPD (194, 195). In malignant pleural effusions, the population that most closely resembles the population of interest in this study, Mishra et al attempted to calculate the MID (193). This figure was achieved by analysing data collected by the authors during their clinical practice, asking 123 patients' pre-pleural procedure to record their baseline VASD and estimated the greatest post-procedural VASD that the patient would consider 'worthwhile'. After 24 hours post-procedure the patients completed a post-procedural VAD and a 7-point Likert scale. The MID was calculated as 19mm (95% CI 14-24mm), corresponding with 'a small but just worthwhile improvement' on the Likert scale. This is a larger MID than demonstrated in earlier studies on COPD (MID of 10mm) (196, 197), although similar to the MID demonstrated to be meaningful in patients with interstitial lung disease (198). The population in the REDUCE study is different from the MPE population, with differing underlying

pathophysiology. It is feasible that pleural drainage will have less effect on dyspnoea with patients, who with cardiac dysfunction have a pre-existing cause of breathlessness, independent of pleural effusion volume. Therefor it is possible these calculated MIDs may not be applicable to our patient cohort.

There are limitations to using a subjective endpoint, such as VAS outcomes as the primary outcome. Subjective endpoints are more susceptible to individual interpretations, and this effect may be compounded by the unblinded nature of the trial. Efforts have been taken to minimise the effect, by having two independent blinded measurements of the VAS score.

The VAS scores were recorded daily (at the same time each day, ideally in the morning) by participants over 12 weeks post-randomisation, with encouragement by the trial team to the participants in order to ensure compliance at follow-up visits. VAS score measurements was conducted using a standard operating procedure (SOP) with two assessors measuring each VAS score independently, with the first person's measurement taken, where there is a difference of ≤2mm between the two measurements and in the event of a difference of >2mm a written policy will be followed with respect to re-measurement.

The daily VAS scores will be analysed to provide an average measure of breathlessness for each individual.

2.3.8. The secondary outcomes

- The proportion of patients achieving pleurodesis at 12 weeks.

- Health related QoL: EQ-5D-5L.

- Hospital visits and bed days.

- Number of pleural interventions

- Volume of fluid drained

- Cost-effectiveness analysis

- Albumin levels in patients with liver failure

- Failure of initially randomised treatment

- Adverse events attributed to trial intervention.

2.3.9. Clarification of secondary endpoints

2.3.9.1. The proportion of patients achieving pleurodesis at 12 weeks.

The proportion of patients achieving pleurodesis was chosen as a secondary outcome as it has important clinical implications for patients. It is recognised that by repeated drainages, and apposition of the visceral and parietal pleura, and subsequent adhesion formation, a proportion of patients with an IPC will achieve spontaneous pleurodesis. After this pleural symphysis, there should be minimal subsequent pleural fluid production, and the IPC can be removed. In patients with MPE the average rate of spontaneous pleurodesis was cited at 45%, based on evidence from non-randomised controlled trials(78). Subsequent RCTs have provided a more conservative estimate of between 17 and 29% (4, 5, 191, 199). In patients with non-malignant pleural effusions, an average from non-randomised studies give an average pleurodesis rate of 51.3% (95% CI, 37.1%-65.6%)(77). In patients with cardiac pleural effusions, with rate was 42.1% (95% CI, 20.1%-64.1%)(77). If the experience from MPE studies is repeated, the actual value may be lower.

The rate of spontaneous pleurodesis, and the subsequent removal of the IPC, is felt to be of importance to patients. In this study, we defined pleurodesis as:

- The most recent CXR showing an effusion less than 1/3 of the total hemithorax on the side of the effusion initially randomised. This measure must be agreed by two clinicians, at least one of whom must be blind to the treatment allocation.

AND one of:

- Less than 50ml aspirated from the IPC on three occasions over no less than 1 week with a patent IPC

- IPC removed and no further pleural intervention required

- In the control group: no further pleural fluid intervention since the initial aspiration

- In those who had talc pleurodesis outside study protocol: No pleural fluid intervention required since pleurodesis attempt

2.3.9.2. Health related QoL: EQ-5D-5L.

Although the primary outcome measure in this study is assessment of patient related breathlessness (a clinically important and reliable outcome measure), IPCs may have important effects on other aspects of health related QoL. The proposed sample size will detect a clinically significant difference in health related QoL.

2.3.9.3. Hospital visits and bed days.

The number of hospital attendances, excluding trial visits and the number of hospital bed days was collected to assess the difference between control and intervention groups. The average length of hospital stay for an intervention is felt to be of interest to our patient population.

2.3.9.4. Number of pleural interventions

The number and type of pleural interventions required during the 12 week trial period was collected to include therapeutic aspiration and chest drain insertion during the course of the trial.

2.3.9.5. Volume of fluid drained

Data regarding the total volume of pleural fluid drained was collected to include the volumes removed via therapeutic aspirations, IPC drainage and chest drain insertion.

2.3.9.6. Cost-effectiveness analysis

Cost per QALY gained was evaluated from utility scores calculated using the UK general population tariffs for the EQ-5D-5L.

2.3.9.7. Albumin levels in patients with liver failure

Albumin levels was recorded at baseline and at the 4, 8 and 12 week clinic appointments. This is an important outcome, as the effect of recurrent drainages of hepatic hydrothoraces is unclear.

2.3.9.8. Failure of initially randomised treatment

Failure of allocated treatment was recorded at the final 12 week appointment. Patients was considered to have failed initial treatment if they require a pleural intervention other than that which they were randomised to. For example, patients randomised to therapeutic aspirations who subsequently undergo talc pleurodesis or have an IPC inserted during the trial period were considered to have 'failed' standard care. Patients randomised to an IPC were considered to have 'failed' intervention treatment if they require IPC removal for a reason other than pleurodesis and go on to require further pleural intervention or if the IPC ceases to function such that other pleural interventions are required.

2.3.9.9. Adverse events attributed to trial intervention.

Any relevant adverse events related to trial interventions (indwelling pleural catheter insertion and drainage or therapeutic aspiration) was recorded to evaluate rates of associated

complications including pleural infection, chest pain, bleeding or renal impairment attributed to pleural fluid drainage.

2.3.10.   Sample Size Calculations

2.3.11.   Pilot Data

To assess the effect on indwelling pleural catheters on short term breathless control using a daily VAS scores we compared breathlessness over 28 days in ten patients with an IPC with ten patients receiving standard care (chest drain insertion and talc pleurodesis) in a cohort of patients with malignant pleural disease. VAS quantified breathlessness scores were recorded daily and corrected for breathlessness not due to pleural effusion. A clinically significant improvement in breathlessness was seen in the ambulatory pleural catheter group (ambulatory catheter mean daily VAS 14mm (SD +/-11 mm), standard care 21mm (SD +/-10 mm), difference 7mm (95% CI for -3 to 17mm).

2.3.12.   Power Calculation

From this pilot data we can determine this trial will require 78 patients (randomised 1:1) to show a benefit with IPCs (alpha 0.05, power 80%). We anticipate a loss to follow-up of 8%. Thus, we intend to study 86 patients.

2.4.   Study design: Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

Primary spontaneous pneumothorax (PSP) is a disease of young people, with an annual incidence of 7.4 per 100,000 in males and 1.2 per 100,000 in females(103). Current BTS guidelines advise that pneumothorax recurrence is an indication for surgery (whether second ipsilateral or first contralateral) (113), however the true incidence of recurrence is unknown. PSP recurrence rates are typically cited as between 16 and 52%, which makes counselling about future risk challenging and creates uncertainty regarding the optimal management(161).   If recurrence rates are genuinely as high as 50%, an argument could be made for definitive surgical repair at an earlier stage. If the true rate is closer to the lower estimate, however, waiting for a recurrent episode before considering surgery might be appropriate. The wide range in cited recurrence values is likely a result of highly varied study design. The studies providing these estimates are mixture of non-randomised and randomised studies. The study population vary from population-based studies to studies which examine a small number in a specific populations, such as women of reproductive age(200). They examine a range of interventions, from observational, medical pleural drainage and surgery, all of which have the potential to influence recurrence rates. The follow-up periods vary, from 3 months to over a decade.

There are no factors that precisely predict recurrence and consequently no method for risk-stratifying patients. Female gender, low body weight, smoking and height in males have all been postulated as risk factors for recurrence, however studies have provided conflicting results on each of these factors (120, 156, 158, 201). Certain radiographic features have also been suggested to confer additional risk, including bullae on CT and pleural thickening on chest radiograph, however studies arrive at differing conclusions of the significance of bullae (163, 164, 173). Importantly, there is no consensus on which treatment offers the greatest reduction in risk of recurrence, with proponents advocating for either conservative and pleural drainage as the optimal method of reducing future recurrence (99, 126, 174, 202). Equally important, there is no current method of quantifying how each of these individual factors influence a patient's risk of recurrence and therefor, no way of creating a risk model to calculate an individualised risk score.

There is little literature detailing the recurrence rates in patients with SSP. The earlier studies did not differentiate between PSP and SSP, and even in more recent studies, there often do no differentiate to the extent which you can determine a separate recurrence risk. Light et al conducted an RCT on tetracycline in patients with spontaneous pneumothorax, 171 of whom had SSP. The recurrence rate in the control group with SSP was 43% during the 5-year follow-up

period(203). In an observational study conducted between 1975 and 1987, Lippert el al found that 7 out of their 20 (35%) of patients with SSP had recurrence at 10 years(159). A more recent retrospective analysis of 61 patients with SSP at a Japanese hospital found recurrences in 25 patients (40.9%), over an average observation period was 37.5 ± 30.3 months(204). Another recent Japanese study had recurrence in 39/224 (17.4%) of SSP patients who were managed non-operatively. Follow up was only described as 'for a few weeks', explaining the relative low rates (125). The limited number of studies examining recurrence rates in SSP precluded formal meta-analysis, and a decision was made to focus on patients with PSP in this analysis.

This thesis undertook a study aimed to systematically review, appraise and synthesise the existing literature to determine an accurate estimate of PSP recurrence rates and to describe risk factors associated with recurrence. The primary research question was "what is the rate of recurrence of PSP in adults who have undergone medical management and what factors are associated with increased risk of recurrence?". The secondary research question was "what patient factors increase recurrence risk?".

2.4.1. Search Strategy and selection criteria

A systematic review was conducted to identify English-language studies, including randomised trials, non-randomised trials, and observational studies of more than 10 participants. Review articles, editorials, conference abstracts, animal or in vitro studies and studies with no abstract available were excluded. The population of interest was adults (≥18 year of age) with PSP, although studies including adolescents of 11 years and older were included if they comprised less than 25% of the study population or if recurrence data for adults could be extracted separately. Studies that examined patients with first occurrence or subsequent occurrence were included. It is recognised that subsequent recurrences increase the risk further recurrence (121). Limiting the inclusion to only first recurrence would significantly reduce the number of eligible studies, and loss useful information regarding patients who had had previous events. Secondary spontaneous pneumothorax, iatrogenic and traumatic pneumothoraces were excluded and mixed studies where PSP recurrence outcomes could not be differentiated from other types of pneumothorax (secondary spontaneous, iatrogenic, traumatic) were also excluded. Non-PSPs were excluded due to differing underlying pathophysiologies. Interventions and comparators included in the review were conservative management, needle aspiration (NA), intercostal drainage (ICD) and ambulatory management. Studies which only examined surgical, thoracoscopic or pleurodesis interventions were excluded, as were mixed studies where surgical and pleurodesis outcomes

could not differentiated from non-surgical/pleurodesis outcomes. Surgical and pleurodesis procedures dramatically decrease the risk of recurrence, typically less than 5%(150). The outcome of interest was recurrence (either ipsilateral or contralateral) at any time point. Studies that only documented contralateral recurrence rates were not eligible. These studies tended to be surgical studies, interested in pneumothorax recurrence post-surgery in the non-operative lung.

The initial electronic search was performed on 18/1/18 within Medline (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Janaury 2018) and EMBASE (1950 to January 2018). The full search strategy is shown in Appendix A and included MeSH headings and keyword searches of "pneumothorax", "recurrence" and "epidemiology". Two authors (SW and PH) independently screened abstracts for eligibility and excluded studies that did not meet the inclusion criteria. Discrepancies were resolved with discussion with third author (NAM). Eligible studies were obtained in full-text format and reviewed independently by two reviewers (SH and PH). The search was repeated on 22/2/18 to capture recently published studies.

2.4.2.   Data-analysis

Data were extracted independently by two authors (SW and PH), using the data collection sheet shown in Appendix A. Name of study, type of study, sex, age, number of PSP cases, interventions, whether PSP cases were first or recurrent episode, 1-year; 2-year; and overall recurrence rates, and follow-up period were extracted from each study.

The principal summary measure was overall recurrence rate for all included studies, described using basic descriptors (mean, 95% confidence intervals (CI)). 1-year and 2-year recurrence rates pooled for all studies that reported these outcomes. Odd ratios for recurrence were calculated, where possible, for different interventions. Odds ratios were calculated for smokers vs non-smokers, males vs females, and body mass index (BMI) (greater/less than 20 kg/m2). Hazard ratios were extracted for males versus females where available. In studies with mixed population (e.g. PSP and SSP, or adolescents and adults) only data pertaining to adults with PSP were extracted. If a study stated in its methodology that data relevant to the PICO criteria was collected but did not report it, the authors were contacted and asked to provide raw data.

Separate meta-analyses were conducted to examine overall recurrence rates, and 1-year and 2-year recurrence rates. All studies that reported the outcome of interest were included in the meta-analyses. Due to high anticipated heterogeneity between study populations and interventions, a random-effects model was used. Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. Heterogeneity was calculated using estimates of I^2.

The I² statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance(205). As I² was anticipated to be high in our study, due to wide variation between the trials, a random-effects model was chosen, as it allows the study outcomes to vary in a normal distribution between studies. A fixed-effect model would be more appropriate if all of the studies examined were considered to have been conducted under similar conditions with similar subjects. Pooled recurrence rates were calculated separately for clinical cohorts and epidemiological studies reporting data from the general population. Separate meta-analyses were performed for studies that reported recurrence stratified by gender, intervention, weight and smoking status to provide estimates of recurrence based on patient characteristics. Random effects models were used for all these analyses due to high anticipated heterogeneity. Univariable meta-regression was used to assess whether study-level characteristics were associated with increased reported recurrence rates. Characteristics examined were type of study (RCT vs non-RCT), year of publication (before 2000, after 2000), PSP type (first or recurrent), sample size and follow-up period (greater or less than two years). All analyses were conducted in Stata MP Version 13.1 by SW.

Randomised studies that met the inclusion criteria were assessed using the Cochrane risk of bias tool. Bias was assessed over the following pre-specified domains: random sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other potential sources of bias. Non-randomised studies that met the inclusion criteria were assessed using the Newcastle-Ottawa assessment tool over the following pre-specified domains: selection, comparability and outcome (15). Risk of bias was assessed independently by two reviewers (SW and AB). Differences of opinion were resolved by discussion or by involvement of a third party (NAM).

The review was registered prospectively on the PROSPERO database, registration number CRD42018089409. Full methodological details are available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018089409).

2.5.   Study design: Conservative Management in Traumatic Pneumothoraces: An Observational Study

As part of this thesis we were interested in the outcomes of patients with a traumatic pneumothorax who were managed without a pleural intervention. I used a large trauma patient cohort to create a profile of consecutive patients presenting with traumatic pneumothoraces to

examine the outcomes of conservatively managed patients and determine whether there are factors that can help predict whether a chest tube is required

Patients were identified, from April 2012 to November 2016, as part of the Trauma Audit and Research Network (TARN) on patients presenting to emergency department at Southmead Hospital, a regional UK Adult Major Trauma Centre (MTC). It covers a population of 2.3 million, is supported by 6 other trauma unit hospitals and admits over 1000 major trauma patients/year. The TARN registry is a prospective, observational registry of hospitalised major trauma patients in England and Wales. It holds Health Research Authority CAG section 251 approval for research on anonymised data submitted by member hospitals. The TARN database includes all trauma patients irrespective of age who have a direct admission or transferred in whose length of stay is 3 days or more or admitted to a High Dependency Area regardless of length of stay. It also includes deaths of trauma patients occurring in the hospital including the Emergency Department and those transferred to other hospital for specialist care or for an ICU/HDU bed. Certain specific injuries were excluded), including isolated neck of femur or inter/greater trochanteric fractures over 65 years.

ICD-10 codes included were S270 (Traumatic pneumothorax), S270 (Traumatic pneumothorax closed), S2701 (Traumatic pneumothorax open), S271 (Traumatic haemothorax), S2710 (Traumatic haemothorax closed), S2711 (Traumatic haemothorax open), S272 (Traumatic hemopneumothorax), S2720 (Traumatic haemopneumothorax closed), S2721 (Traumatic hemopneumothorax open).

Information was collected on demographics, injury (mechanism of injury, description of injuries, Injury Severity Score (ISS)), management (type, size of drain, length of drain placement) and pneumothorax characteristics (laterality, size and accompanying haemothorax). Airway support was characterised as either requiring positive pressure ventilation pre-hospital or in the Emergency Department (initial PPV) or requiring PPV subsequently due to GA administration or clinical deterioration (subsequent PPV). Size of pneumothorax was taken for chest radiographs at hilum and apex, as per the BTS guidelines of pneumothorax(113). On CT, the largest collection was measured along a line perpendicular from chest wall to lung or mediastinum, this parameter is used in other clinical studies on traumatic pneumothoraces, due to the unreliability of chest radiographs(206). Clinical parameters were taken from initial observations on attendance to the Emergency Department. Respiratory distress was determined if either respiratory rate was ≥30 or <8; if supplementary 02 or mechanical or manual ventilation was used; a Sp02 ≤90% or if the patient was in respiratory arrest. Hemodynamic instability was determined if SBP <90mmHg or heart rate ≥ 100bpm. Conscious level impairment was determined if either GCS <15 or the patient

was ventilated at arrival. Treatment failure was defined as requiring an invasive pleural intervention.

2.5.1. Statistical analysis

Descriptive statistics were used to summarise patient characteristics and clinical data. Means (±SD) were calculated for parametric data and medians (IQR) were calculated non-parametric data. Several checks for normality, including Kolmogorov-Smirnov, Shapiro-Wilk, kurtosis and skewness calculations were performed. Continuous parametric variables were analysed using independent t-test and continuous non-parametric variables were analysed using Mann-Whitney test. Categorical data was analysed using Chi-squared test. A P-value of <0.05 was considered statistically significant.

Univariate proportional hazard ratios were calculated using Cox regression analysis for factors associated with failure of conservative treatment (size of pneumothorax, mechanism of injury, ISS, presence of ribs fractures, clinical features (respiratory, hemodynamic, GCS), presence of haemothorax, bilateral versus unilateral pneumothorax, use of PPV and surgical procedures). Further multivariable cox regression analysis was performed to determine which factors (size of pneumothorax, ISS, presence of ribs fractures, clinical conditions (respiratory, hemodynamic, GCS), presence of haemothorax, bilateral versus unilateral pneumothorax, use of PPV and surgical procedures) were independently predictive of failure of conservative management. These factors were decided on in a priori statistical analysis plan. All statistical analysis was performed using IBM SPSS statistics version 23.0 (SPSS Inc. Chicago, IL)

2.6. Study design: Heimlich Valves in Secondary Spontaneous Pneumothorax: Enhancing Care (HI-SPEC trial)

As part of this thesis, I undertook a multicentre randomised controlled trial to evaluate the effect of Heimlich valves on length of stay in patients admitted to hospital with secondary spontaneous pneumothorax.

The study design was conceived by Prof Maskell and the initial protocol was written by Dr Bintcliffe. I submitted the protocol to ethics and the HRA. I designed the CRFs, constructed the on-line database and initiated site setup. I completed various minor and major amendments (see Appendix G). I was the RCT's trial manager, involved in recruitment and managing safety issues. At the time of writing the thesis, 35 patients had been recruited.

2.6.1. Primary outcome measure description

The primary outcome is the total number of hospital bed days due to a secondary spontaneous pneumothorax, during the first 30 days from randomisation. This will include readmissions.

Patients remaining in hospital overnight will be classed as 1 day; those discharged on the same day will have a zero length of stay. Otherwise figures will be rounded up to the nearest complete day.

This outcome was chosen as the primary outcome as it was felt to the most clinically relevant in a trial of ambulatory management of pneumothorax, and an outcome of most interest to patients.

It is recognised that it would not be feasible in adequate blind the study participants to the intervention, so a trial outcome was chosen that was easily measurable, objective and can be measured in an unbiased manner.

2.6.2. Secondary outcome measures

1. Daily VAS Score for Breathlessness over the first 28 days after randomisation
2. Daily VAS Score for Chest pain over the first 28 days after randomisation
3. Quality of Life measured by EQ-5D-5L questionnaire daily over first 14 days after randomisation

4. Quality of Life measured by EQ-5D-5L questionnaire at 4 and 12 weeks after randomisation

5. Length of hospital admission until classified medically fit for discharge

6. Length of initial hospital admission from randomisation to initial discharge

7. Length of initial hospital admission from date of admission with pneumothorax until discharge

8. Failure of initially randomised treatment in 1st week

9. Time till pneumothorax resolution

10. Time till drain removal (Days from randomisation)

11. Time till further intervention (Days from randomisation)

12. Surgical intervention for pneumothorax elective (Days from randomisation until thoracic surgical intervention)

13. Adverse events (See Adverse event section for detail)

14. Recurrent pneumothorax (Occurrence of ipsilateral recurrent pneumothorax at end of follow up)

2.6.3. Clarification of secondary endpoints

Secondary outcomes where chosen that were measurable and clinically meaningful.

2.6.3.1. Daily VAS Score for Breathlessness

A secondary outcome is the difference in daily breathless score as assessed by VAS over 28 days. Outcomes will be reported over the first 7 and 28 days. This outcome was chosen as it is patient centred and felt to be of clinical significance. Breathlessness is a common and disabling symptom in pneumothorax.

This secondary outcome measure is difference in breathlessness measured using VAS scores, which has proven to be a robust and clinically important outcome measure in previous studies by this collaboration. The VAS scores will be recorded daily (at the same time each day, ideally in the morning) by participants over 28 days post-randomisation, with encouragement by the trial team to the participants and ensuring compliance at follow-up visits. VAS score measurements will be conducted using a standard operating procedure (SOP) with two assessors measuring each VAS score independently, with the first person's measurement taken, where there is a difference of ≤2mm between the two measurements and in the event of a difference of >2mm a written policy will be followed with respect to re-measurement.

The daily VAS scores will be analysed to provide an average measure of breathlessness for each individual.

2.6.3.2. Daily VAS Score for chest pain over the first 28 days after randomisation

A secondary outcome is the difference in daily pain score as assessed by VAS over 28 days. Outcomes will be reported over the first 7 and 28 days. This outcome was chosen as it is patient centred and felt to be of clinical significance. Chest pain is a common and disabling symptom in pneumothorax.

This secondary outcome measure is difference in pain measured using VAS scores. The VAS scores will be recorded daily (at the same time each day, ideally in the morning) by participants over 28 days weeks post-randomisation, with encouragement by the trial team to the participants and ensuring compliance at follow-up visits. VAS score measurements will be conducted using a standard operating procedure (SOP) with two assessors measuring each VAS score independently, with the first person's measurement taken, where there is a difference of ≤2mm between the two measurements and in the event of a difference of >2mm a written policy will be followed with respect to re-measurement.

The daily VAS scores will be analysed to provide an average measure of pain for each individual.

2.6.3.3. Quality of Life measured by EQ-5D-5L questionnaire daily over first 14 days after randomisation

In addition to the outcome measure in this study of patient related breathlessness and pain, HVs may have important effects on other aspects of health related QoL

2.6.3.4. Quality of Life measured by EQ-5D-5L questionnaire at 4 and 12 weeks after randomisation

In addition to the outcome measure in this study of patient related breathlessness and pain, HVs may have important effects on other aspects of health related QoL

2.6.3.5. Length of hospital admission until classified medically fit for discharge

In addition to the primary outcome measure duration of hospital admission, the number of inpatient days until the patient was deemed medically fit will be collected. This will be for the

index admission only. This was chosen as an outcome, as it is recognised that there will other, non-pneumothorax related factors that will influence hospital length of stay.

Patients remaining in hospital overnight will be classed as 1 day; those discharged on the same day will have a zero length of stay. Otherwise figures will be rounded up to the nearest complete day.

2.6.3.6. Length of initial hospital admission – date of randomisation until date of discharge

In addition to the primary outcome measure duration of hospital admission, the total number of inpatient days from randomisation until the patient was discharged will be collected for the index admission only.

Patients remaining in hospital overnight will be classed as 1 day; those discharged on the same day will have a zero length of stay. Otherwise figures will be rounded up to the nearest complete day.

2.6.3.7. Length of initial hospital admission - date of admission with pneumothorax until discharge

In addition to the primary outcome measure duration of hospital admission, the total number of inpatient days from the date of admission with pneumothorax until the patient was initially discharged or deemed medically fit for discharge, will also be collected for the index admission only. Patients remaining in hospital overnight will be classed as 1 day; those discharged on the same day will have a zero length of stay. Otherwise figures will be rounded up to the nearest complete day.

2.6.3.8. Failure of initially randomised treatment in 1st week

Failure of allocated treatment will be recorded for the first week appointment. Patients will be considered to have failed initial treatment if they require a pleural intervention other than that which they were randomised to. This is a measurable and clinically meaningful outcome.

2.6.3.9. Time till pneumothorax resolution

The time (in days) until full resolution of initial pneumothorax will be recorded. Whether ambulatory management expedites or slows time until full pneumothorax resolution is clinically meaningful.

2.6.3.10. Time till drain removal

The time (in days) from the index drain insertion until the drain is removed will be recorded. Whether ambulatory management increases or decreases time until drain is removed is clinically meaningful.

2.6.3.11. Time till further intervention (Days from randomisation)

The date of any further interventions will be captured. Interventions of interest are pleural aspirations, pleural vent insertion or chest drain insertion during the 6 month trial period.

2.6.3.12. Surgical intervention for pneumothorax (Days from randomisation until thoracic surgical intervention)

The date of any thoracic surgical intervention for the index pneumothorax will be documented. This will be documented as either urgent (surgery for cessation of ongoing airleak) or elective (to prevent recurrence).

Time and date of medical talc pleurodesis will also be recorded.

2.6.3.13. Adverse events (See Adverse event section for detail)

Any relevant adverse events related to trial interventions (Heimlich valve or chest drain with underwater-seal) will be recorded to evaluate rates of associated complications (including subcutaneous emphysema, pleural infection, chest pain and bleeding)

2.6.3.14. Recurrent pneumothorax (Occurrence of ipsilateral recurrent pneumothorax at end of follow up)

The date of any ipsilateral pneumothorax recurrence within the first 6 months will be documented. Recurrence is defined as an ipsilateral pneumothorax identified on chest x-ray, after a chest x-ray has confirmed complete resolution for at least 24 hours following the removal

of all catheters/drains. Any re-accumulation prior to this will be attributed to the initial pneumothorax (i.e., ongoing leak) rather than a recurrence.

2.6.4. Recruitment

Hi-SPEC is a multi-centre trial recruiting from centres with interest and experience of recruiting to trials in pleural disease. Patients admitted to a recruiting centre with SSP are identified within emergency departments, acute medical or respiratory wards. Patients are screened using the inclusion and exclusion criteria. Consecutive eligible patients are invited to participate. Patients are provided with the patient information sheet and the trial will be explained. Written informed consent is obtained prior to enrolment.

Recruiting centres kept records of all patients screened and this information will be provided to the coordinating centre for review and monitoring purposes.

2.6.5. Assessment and Treatment of Patients

2.6.5.1. Pre-randomisation

Potential patients are screened against the eligibility criteria. Consent for trial entry is obtained prior to enrolment and randomisation. Eligible patients have a newly identified SSP. There is no maximum specified time after a diagnosis for enrolment and randomisation to take place however eligible patients need a chest drain for management of the current episode. Clinical management must not result in a clinically important delay as a result of trial participation.

2.6.6. Inclusion Criteria

New diagnosis of a secondary spontaneous pneumothorax as confirmed by a chest radiograph or CT scan

AND

Secondary spontaneous pneumothorax defined by known underlying lung disease or a patient > 50 years old with a significant smoking history (>20 Pack years)

AND

Chest drain insertion indicated for treatment of pneumothorax according to current BTS guidelines

AND

Chest drain insertion possible at both 2nd intercostal space in the midclavicular line and in the mid axillary line (safe triangle)

2.6.7. Exclusion Criteria

1. Current iatrogenic or traumatic Pneumothorax

2. Drain already in place for Pneumothorax

3. Previous history of tension pneumothorax.

4. Features of tension pneumothorax associated with current presentation

5. Evidence of significant hydropneumothorax or haemopneumothorax

6. Age <18 years

7. Patients bed-bound prior to pneumothorax

8. Contraindication to either chest drain insertion or Rocket Pleural Vent insertion

9. Females who are pregnant or lactating

10. Patients with no access to a telephone

11. Inability to comply with trial requirements or provide informed consent

2.6.7.1. Randomisation

Eligible patients who provide informed consent are randomised (1:1) to treatment with a Seldinger chest drain and underwater seal (standard care) or to treatment with a Rocket Pleural Vent (intervention). Treatment allocation is performed through a randomisation server. A member of the trial team randomises the patients as soon as eligibility has been confirmed and consent obtained. Every effort was made to minimise delays between randomisation and the procedure being performed.

2.6.7.2. Trial Procedure

The procedure, to which patients have been randomised to, is performed by an appropriately trained member of staff. Procedures followed a standard operating procedure which will ensure

standardisation of practice. A trial specific procedure manual was provided to each site to encourage a standardised approach and trouble shoot questions.

2.6.7.3.   Post-randomisation

Following insertion of a Rocket Pleural Vent or a standard chest drain, patients' care proceeds according to standard care guided by the treating clinician. Clinical observations are performed following drain insertion and at regular intervals subsequently. Abnormal observations or a failure to symptomatically improve following intervention prompt clinical review by an appropriately qualified member of staff and consideration of necessary radiological investigation for further evaluation. Patients are provided with instructions on the care of the Rocket Pleural Vent or chest drain respectively.

2.6.7.4.   Removal of Drains

Decisions regarding removal of the chest drains or Pleural Vent are made by the treating clinician in reference to BTS guidance and standard local practice. Chest drains or Pleural Vents should be removed at the earliest opportunity following clarifying the absence of an ongoing air leak. An ongoing air leak can be excluded through the absence of bubbling through the underwater seal or air leak through the Heimlich valve device and full lung re-expansion on CXR.

2.6.7.5.   Hospital discharge

Patients should be discharged when clinically appropriate to do so, and patients with a Heimlich valve device can be discharged with the device in place provided discharge is safe and there are local arrangements for outpatient follow-up. As is standard practice, patients randomised to standard care are not be discharged with a chest drain and underwater seal. The discharge criteria should have been met prior to discharging a patient with a Heimlich valve in place. Patients are provided written information in relation to care of the Heimlich valve and with contact details in the event of any deterioration or problem with the device.

2.6.7.6.   Clinical Follow up

Patients are followed up as frequently as necessary. Specifically, patients discharged with a Heimlich valve device in place should be reviewed closely to enable safe and efficient care, the

prompt identification of any complications that may arise and to ensure Heimlich valves are removed at the earliest clinically appropriate opportunity.

2.6.7.7. Trial Follow up

Data is collected from patients from follow up at 4 weeks (+/- 3 days) and at 12 weeks (+/- 1 week). Data relating to the trial outcomes was collected at the 4 week and 12-week trial visit. Patients have a CXR at 4 weeks and 12 weeks. Spirometry was performed at 12 weeks when not contraindicated. Patients have telephone follow up at 26 weeks (+/- 1 week) to gather data on episodes of recurrent pneumothorax.

Data is collected from the day of randomisation (Day 0), which may not be the same day as chest drain insertion.

2.6.8. Statistics and Data Analysis

2.6.8.1. Sample Size Calculation

The primary outcome measure in this study is length of hospital stay (days). Length of stay is significantly longer in SSP than in PSP (207). Audit data demonstrated a length of stay of 115 days in secondary spontaneous pneumothorax patients. This data is positively skewed, the mean length of stay in these patients is 12.30 (SD = 9.89) and median length of stay is 8 days (interquartile range: 4 – 17.5 days).

Overall length of stay in primary pneumothorax in the UK was 6.3 days in data collected from 2010 to 2012 (110). In a prospective case series studying the use of Heimlich valves in pneumothorax length of stay was reported as 3.3 days +/- 3.5.(208)

Assuming 90% power and 5% significance the sample size is determined by the coefficient of variation and the effect size. The coefficient of variation is 0.8 (standard deviation divided by the usual mean).

In order to detect an effect size of 0.5 (halving in length of stay) with a coefficient of variation of 1 we would require 30 patients per group. The calculated coefficient of variation within our audit data is lower, suggesting a smaller sample size is necessary; however, a study size of 60 patients allows some margin for error in relation to the effect size. Including a 10% loss to follow up rate would suggest a total required sample size of 66.

2.6.8.2. <u>Recruitment Target</u>

The recruitment target of the trial is 66 patients. Assuming the trial runs across 9 sites an estimated recruitment rate of 4 patients per site per year would lead us to achieve the recruitment target within the estimated trial duration of 2 years. Progress towards the recruitment target will be reviewed by the TSC. Recruitment targets will be agreed with individual sites based on local experience and expectations.

CHAPTER 3. RESULTS

In this chapter I will outline the full results of 4 non-randomised studies and the interim results of 2 randomised controlled trials:

- Survival in refractory transudative effusions

- Natural history of cardiogenic pleural effusions

- Randomised controlled trial evaluating the efficacy of indwelling pleural catheters in persistent non-malignant pleural effusions - the REDUCE trial *(interim results)*

- Results: Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

- Conservative Management in Traumatic Pneumothoraces: An Observational Study.

- Heimlich Valves in Secondary Spontaneous Pneumothorax: Enhancing Care – the HI-SPEC trial *(interim results)*

3.1. Results: Survival in refractory transudative effusions

In the observational trial on outcomes of patients with non-malignant pleural disease, data was obtained for a total of 782 patients, with 774 included in analysis. Eight participants were excluded for multiple reasons, including no diagnosis reached at 12 months and withdrawal of consent. Further analysis was conducted on the 356 (46%) patients with NMPE (see Figure 6)

Figure 6. **Flow chart of patient numbers**
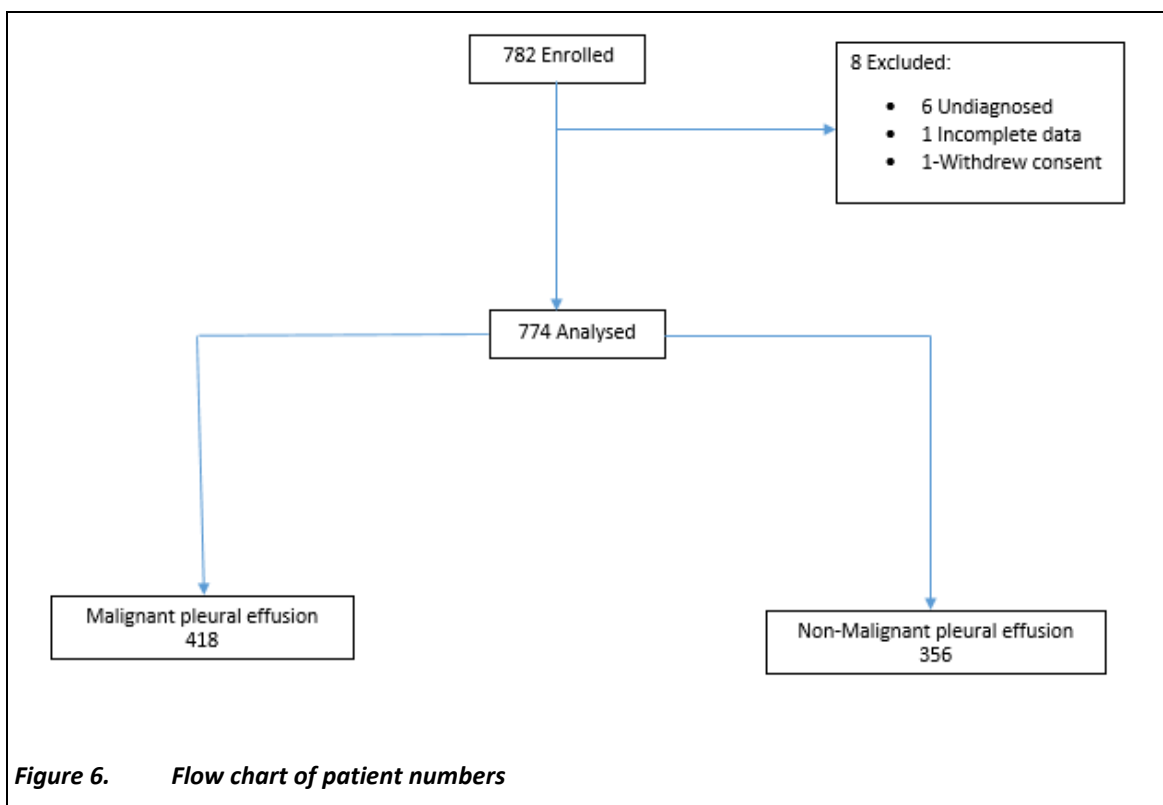
The baseline characteristics for NMPE cohort are presented in table 2, with characteristics by aetiology presented in table 3. The majority of NMPE were exudative (73%), unilateral (88%) with pleural infection being the commonest aetiology (40.6 %). Nearly a quarter (23.6%) of the NMPEs were felt to have more than one identifiable cause.

Table 2.	*Clinical Characteristics of non-malignant pleural effusion cohort.*
Characteristics	
Age, mean (SD), y	68 (17)
Male	245 (69)
Inpatient	171 (48)
ECOG PS	
0	54 (20.6)
1	97 (37)
2	70 (26.7)
3	33 (12.6)
4	8 (3.1)
Bilateral	42 (11.8)
Transudates	90 (27)
Diagnosis	
Heart failure	86 (24.2)
Liver failure	12 (3.4)
Renal failure	13 (3.7)
Inflammatory pleuritis	35 (9.8)
Pleural infection	144 (40.6)
Post Coronary Artery Bypass Graft	6 (1.7)
Diffuse pleural thickening/ BAPE	28 (7.9)
Pulmonary embolism	5 (1.4)
Other	27 (7.6)

*Values expressed as number (percentage) unless otherwise indicated. ECOG PS, Eastern Cooperative Oncology Group Performance score; BAPE, benign asbestos pleural effusion.

Table 3.	*Characteristics by Aetiology*			
	Mean Age	ECOG –PS (0-4)	Transudate (%)	Bilateral (%)
Heart failure	78.7	1.8	65	19.8
Liver failure	61.8	1.2	75	0
Renal failure	78.1	2	66.6	23.1
Inflammatory pleuritis	67.6	0.72	10	8.6
Pleural infection	60.7	1.4	8.9	9
Post CABG	69.8	1.2	0	16.7
BAPE/DPT	71	1	11.1	3.6
Pulmonary embolism	70.4	1	0	20
Other	63	1.1	12	7.4

CABG, Coronary Artery Bypass Graft; BAPE, benign asbestos pleural effusion; DPT, Diffuse pleural thickening.

Mortality rates and multivariate predictors of mortality in NMPE cohort are displayed in table 4, with hazards ratio of bilateral compared to unilateral effusion, transudative compared to exudative effusion and aetiology compared to malignancy. There were high 1-year mortality rates in patients with congestive heart (50%), renal (46%) and liver failure (25%). Thirty-day mortality was low, at 9% for CHF and no deaths in the liver and renal failure cohort. Malignant pleural effusions had the highest mortality at 49% and 70% at 6 and 12 months respectively. In patients with NMPE, bilateral and transudative effusions were associated with a significantly worse prognosis with HR 3.55(2.22-5.68) and 2.78(1.81-4.28) when compared to unilateral and exudative effusions respectively. A serosanguinous effusion was associated with a significantly increased risk of death (HR 2.8, CI 1.1-6.8, p-value 0.027) when compared to eosinophilic effusions.

Table 4.	Mortality rates and multivariate predictors of mortality in non-malignant pleural effusion cohort.					
	6 month mortality			**1 year mortality**		
	Mortality (%)	HR (95% CI)	p-value	Mortality (%)	HR (95% CI)	p-value
Characteristics						
Bilateral[1]	43	3.44(2.00-5.93)	<0.001	57	3.55(2.22-5.68)	<0.001
Transudates[2]	33	2.81(1.71-4.62)	<0.001	43	2.78(1.81-4.28)	<0.001
Aetiology[3]						
Heart failure	40	0.72 (0.50-1.04)	0.077	50	0.61(0.44-0.84)	0.02
Liver failure	8	0.13(0.18-0.90)	0.39	25	0.23(0.07-0.71)	0.011
Renal failure	31	0.53(0.20-1.44)	0.213	46	0.51(0.23-1.14)	0.101
Pleural infection	13	0.22(0.13-0.34)	<0.01	19	0.19(0.13-0.28)	<0.001
Post CABG	17	0.25(0.04-1.81)	0.172	33	0.32(0.80-1.29)	0.108
BAPE/DPT	11	0.17(0.05-0.53)	0.002	11	0.10(0.03-0.31)	<0.001
PE	20	0.34(0.05-2.43)	0.283	20	0.20(0.03-1.45)	0.112
Other	7	0.11(0.03-0.45)	0.002	11	0.10(0.03-0.33)	<0.001

[1] referent to unilateral effusions; [2] referent to exudative effusions; [3] referent to malignant pleural effusions

CABG, Coronary Artery Bypass Graft; BAPE, benign asbestos pleural effusion; DPT, Diffuse pleural thickening; PE, Pulmonary embolism.

Figure 7. ***Kaplan-Meier survival plots for long-term mortality by aetiology***

Figure 8. ***Kaplan-Meier survival plots for long-term mortality for unilateral versus bilateral effusion***

Figure 9. *Kaplan-Meier survival plots for long-term mortality for exudate versus transudate effusion*
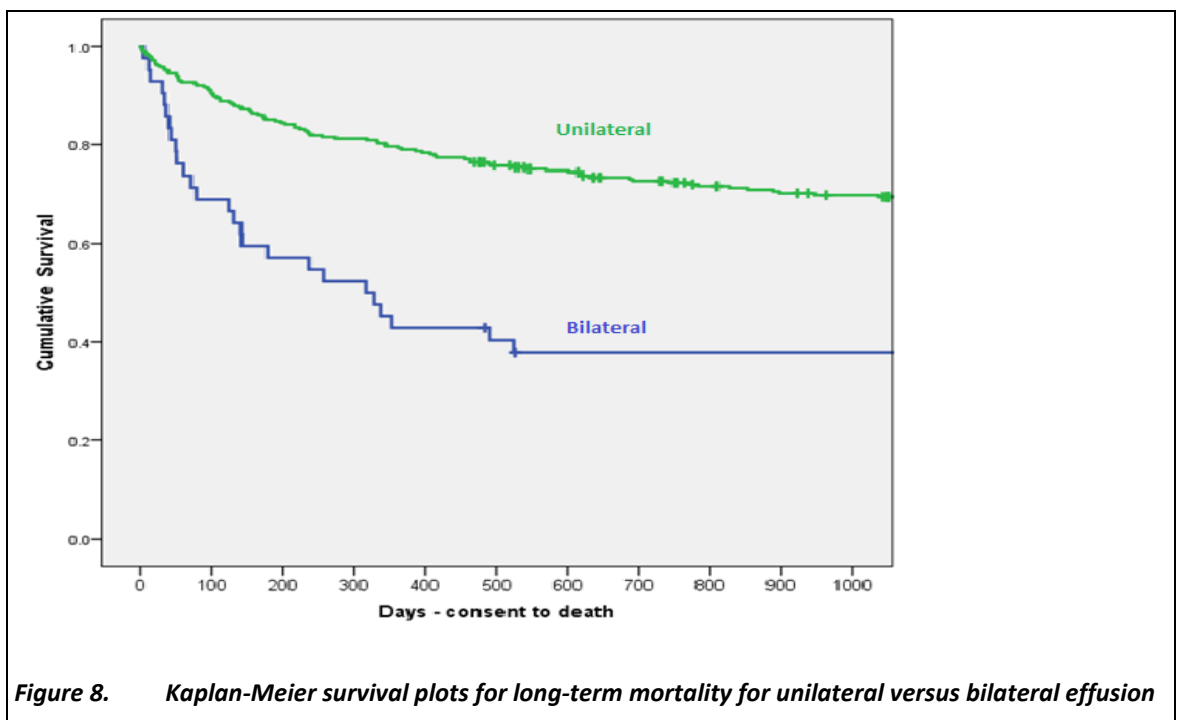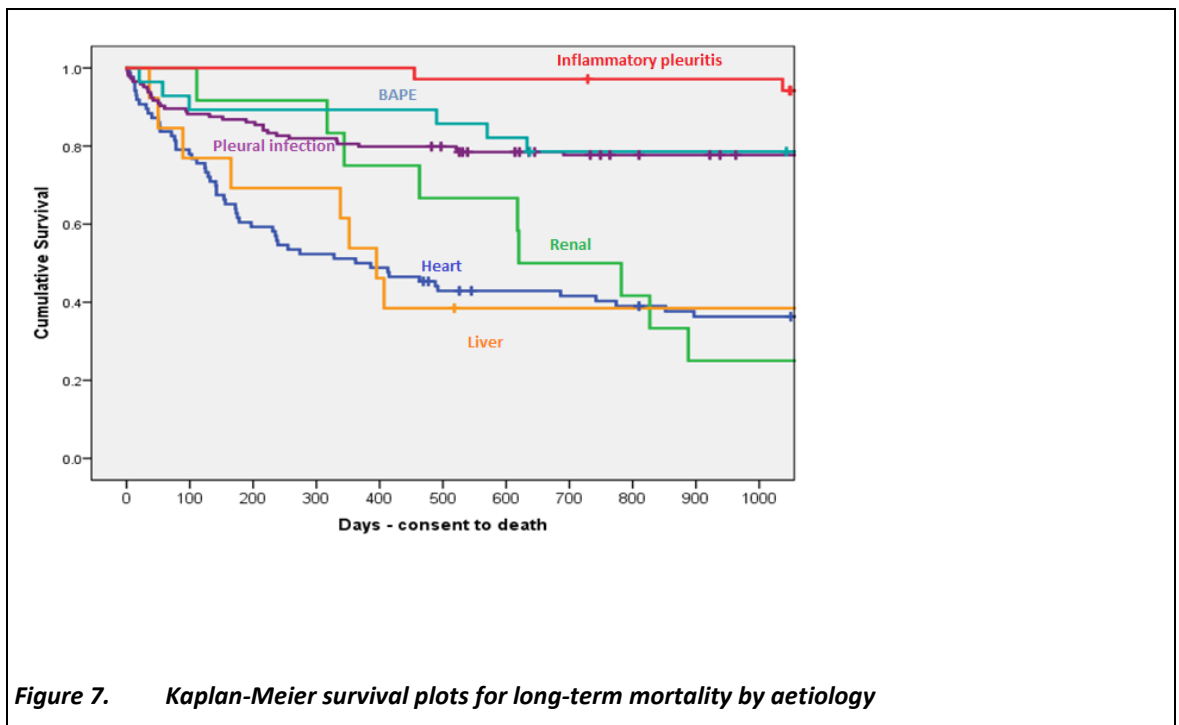
3.2.　Results: Natural history of cardiogenic pleural effusion

In this observational study on natural history of cardiogenic pleural effusion, 110 patients, out of 1142 patients in the pleural patient database had a primary diagnosis of a cardiogenic pleural effusion. Five patients were excluded due to no echocardiogram, leaving 105 patients in final analysis. The patient demographics are listed below. The average age was 78.9 years (SD 9.6), with 64/105 (60%) males. The majority of effusions were unilateral, 62/105 (59%) and transudative, 54/96 (59%). The left ventricular (LV) function was described in 98 patients, with 54/98 (55%) having a least mild LV dysfunction. 72(69%) were recruited as an outpatient.

Table 5.	*Clinical Characteristics of the cardiogenic pleural effusions*
Characteristics	
Age, mean (SD), y	78.9 (9.6)
Male	64 (60)
ECOG PS	
0	3 (3)
1	29 (28)
2	29 (28)
3	20 (19)
4	3 (3)
Unknown	21 (20)
Bilateral	43 (41)
Transudates	54 (51)
NT-ProBNP (SD), pg/l	7796.8 (15383)
Echocardiogram n(%)	
Preserved LV	44 (44.9)
Mild LV impairment	13 (13.3)
Moderate LV impairment	20 (20.4)
Severe LV impairment	19 (19.4)
Severe Pulmonary hypertension	15/97 (15.5)
Size of pleural effusion on CXR, n(%)	
1	4 (3.8)
2	34 (32.8)
3	43 (41)
4	21 (20)
5	1 (1)
missing	2 (1.5)
Diuretic dose (furosemide equivalent) mean (SD) mg	60.7 (50.4)

*Values expressed as number (percentage) unless otherwise indicated. ECOG PS, Eastern Cooperative Oncology Group Performance score; BAPE, benign asbestos pleural effusion.

In 8 patients, it could not be determined if they required further invasive pleural management during their disease course. Of the remaining 97 patients, 23 (23.7%) were defined as refractory and 74 (76.3%) were defined as non-refractory. 67 patients were taking per oral (po) furosemide, 10 were taking po bumetanide, 8 were not receiving diuretic, and in 20 patients the medications were not clear. The diuretic dose of furosemide (using a bumetanide dose equivalent of 1mg:40mg furosemide) was 60.7mg (SD 50.4). Of the non-refractory patients, 47 had a diagnostic aspirate and 23 had a therapeutic aspiration as first-line management. 1 had an I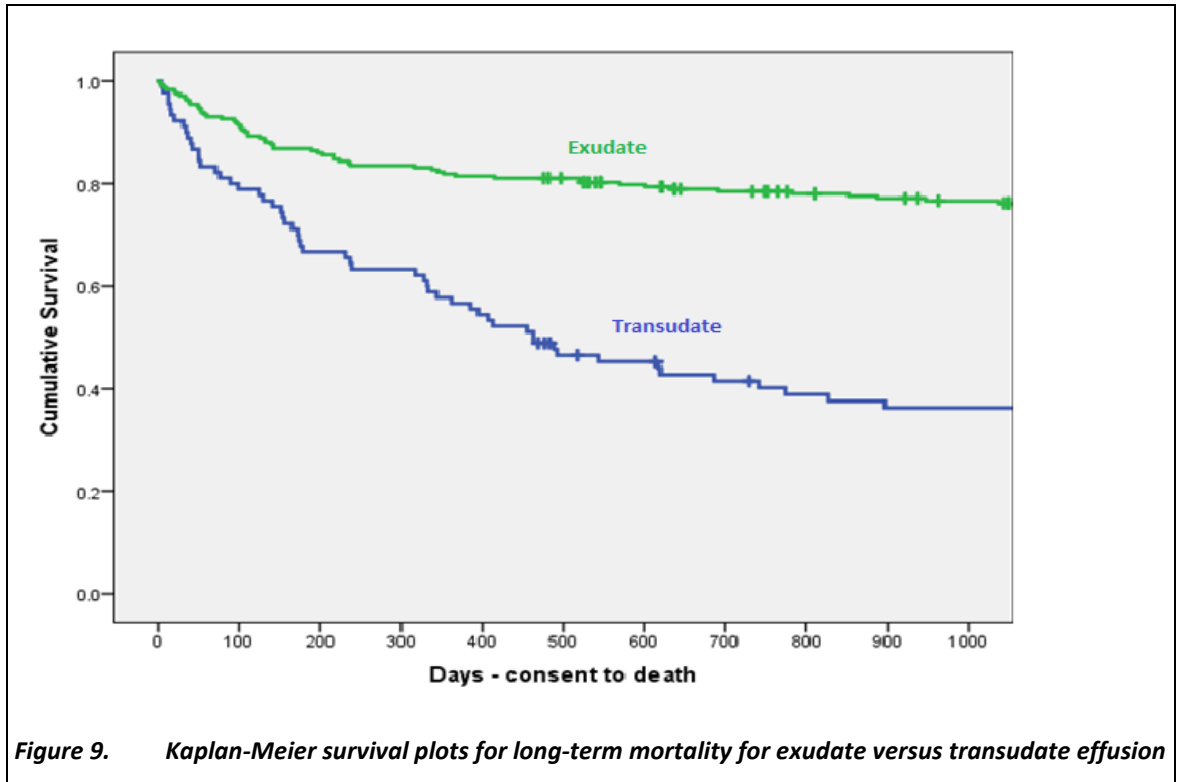CD as first line, two had a LAT, without talc instillation as 1st line. Two patients had IPCs placed, although these weren't classed as refractory cases as the patients were not on diuretics. 2 patients were described as having full resolution after valve replacement. Of the 23 patients who had refractory pleural effusions, they had a mean of 1.9 (SD 1.7) therapeutic aspirations. 5 had IPCs inserted. One of these patients also had contralateral chest drain and talc pleurodesis. One patient had a chest drain inserted, and one had a LAT with talc poudrage.

Table 6.	*Univariant analysis of refractory versus non-refractory cohort in cardiogenic effusion patients*		
Variable	**Refractory cohort (n 23)**	**Non-refractory cohort (n 74)**	**OR (95% CI)**
Albumin			3.3 (0.2, 55.2)
<20	1	1	
≥20	22	73	
NT-ProBNP			1.5 (0.4, 5.7)
≥3000	7	15	
<3000	12	31	
Left Ventricular dysfunction			1.4 (0.5, 4.6)
Severe	5	12	
Non-severe	18	62	
Pulmonary hypertension			1.9 (0.5, 7.1)
Severe	4	8	
Non-severe	16	69	
Gender			1.3 (0.5, 3.4)

	15	44	
Male			
Female	8	30	
Distribution			0.9 (0.4, 2.5)
Bilateral effusion	9	30	
Unilateral Effusion	14	44	
ECG Rhythm			0.7 (0.3, 1.9)
Atrial fibrillation	12	44	
Sinus rhythm	11	30	
Biochemistry			0.4 (0.2, 1.1)
Transudate	8	42	
Exudate	13	28	
Pleural effusion on CXR			1.1 (0.4, 2.9)
Moderate to Large (Grade ≥3)	15	46	
Small (Grade <3)	8	27	
OR: Odd ratio- 1st row versus 2nd row			

No single variable of the 8 analysed were predictive of the refractory cardiogenic pleural effusion (see table 6).

3.3.   Results: Randomised controlled trial evaluating the efficacy of indwelling pleural catheters in persistent non-malignant pleural effusions (REDUCE trial)

The first patient was recruited for the REDUCE trial on the 7th April 2015. The trial is currently recruiting, with an end-recruitment date of 1st August 2019. Currently 65 patients have been recruited (see Appendix C for full recruitment details). The proposed recruitment date is 1st August 2019, with 3-month follow-up, and a study end date of 1st December 2019.   Monthly reminders will be sent for data queries and missing data from 1st May 2019. The data will be cleaned from August 2019 and Stata code will be developed by the trial statistician from the statistical analysis plan in November 2019. We anticipate the final manuscript will be ready for publication by Summer 2020.

3.3.1.   Screening

Centres were asked to be place potential candidates with pleural effusion suspected from being secondary to heart, liver or renal failure, requiring or being considered for a pleural aspiration. The main purpose of this screening data is as an indicator of whether trial participants were likely to be representative of all eligible participants.

A total of 214 patients were screened for the REDUCE trial from the 13 centres. 70 of the patients included in the screening data were deemed ineligible for the trial by the local trial team.

Eighteen out of the 214 (8%) were described as improving with diuretics. A time scale for this improvement was not available from the screening log. 22/214 (10%) patients were described as requiring optimisation, although none of these patients were subsequently randomised. One of these patients died during this optimisation period, 14 days after initial screening.

19 patients declined the trial, with 6 patients explicating stating they did not want an IPC. 4 patients were described as not receiving benefit from the initial aspiration. 9 patients at the time of screening had pleural effusions that were too small and didn't required an aspiration.

From this screening data, only a small proportion (8%) improved were explicitly excluded due to improvement on diuretics. It is possible that the further 10% of patients who were described as requiring optimisation, but not subsequently enrolled also improved, though this is uncertain. This figure is smaller than we'd anticipate would improve with diuretics(20), however the screening patients were very likely a highly selected group of patients themselves to have been identified by the trial team, and had likely failed to respond to initial medical therapy. The screening data in this trial was meant to determine whether trial participants were likely to be representative of all patients seen. It must be noted that there is often substantial between-site variability in how screening data are collected and for whom(209). The accuracy of accuracy of the reported reasons for screen failures may limited, as sites often limit the reason for non-enrolment to the primary reason. Additionally, certain eligibility criteria such as, in this case, whether 'a pleural effusion that persists despite optimised medical therapy' can take longer to ascertain than others. This results in a bias against the reporting of reasons that are more resource intensive to assess.

This screening data for this trial is not suitable for determining, for the above reasons, the natural history of transudative effusions. The screening data does imply the screened patients are a more highly selected patient cohort, than patients who present de-novo with a cardiac and liver related pleural effusion, where we would anticipate a higher proportion of response to medical management.

Figure 10. ***REDUCE Trial Consort diagram***

IPC: indwelling pleural catheter
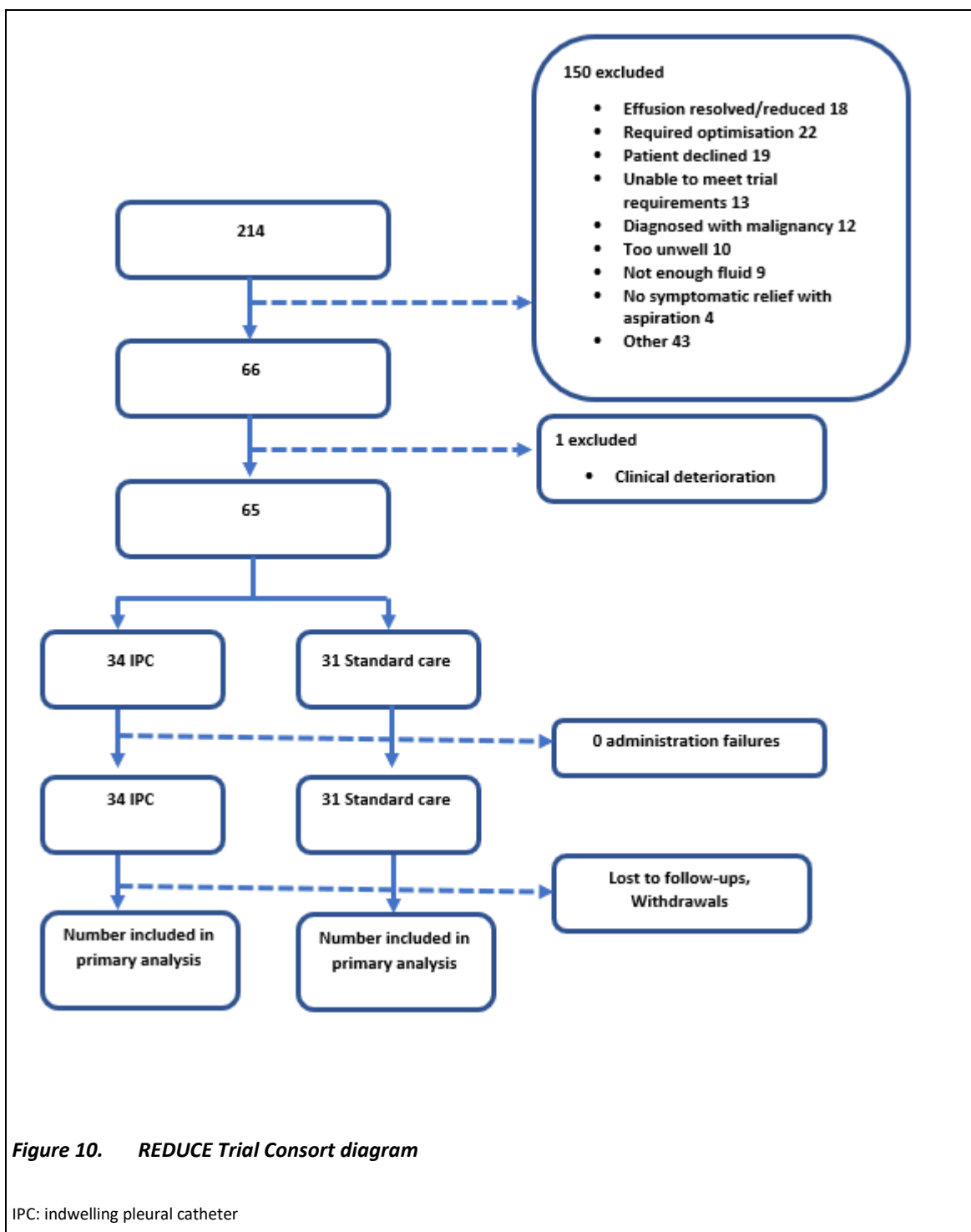
3.3.2.   Baseline characteristic of trial patients

The baseline characteristics of the first 60 randomised patients are displayed in table 7. Baseline data was missing for one patient. The mean age was 73.7 years (SD 12.9) and 47/59 (80%) were male. The majority of effusions 39 (66%) secondary to heart failure, which is consistent with the

available literature(19). There was no significant difference between the IPC and standard care cohort in pre-determined characteristics.

Table 7.	*Baseline Characteristic of 1st 60 patients in the REDUCE trial*		
		IPC (n=30)	Standard care (n=30)
Age – mean (SD)		72.1 (11.7)	75.3 (14.1)
Male – no. (%)		24 (80)	23(76.7)
Primary cause of effusion- no. (%)			
Heart failure		19 (63.3)	20(66.7)
Renal Failure		3 (10)	1 (3.3)
Liver Failure		8 (26.7)	8 (26.7)
Missing		0	1 (3.3)
Smoking status – no. (%)			
Current smoker		1 (3.3)	1 (3.3)
Ex-smoker		14 (46.7)	16 (53.3)
Never-smoker		15 (50)	12 (40)
Missing		0	1 (3.3)
WHO performance status at randomisation – no. (%)			
0		1 (3.3)	0 (0)
1		9 (30)	12 (40.0)
2		11 (36.7)	13(43.3)
3		8 (26.7)	4 (13.3)
4		1 (3.3)	0 (0)
Missing		0	1 (3.3)

The majority of patients in this patient cohort had a poor performance status, with 62% (37/59) of patients having an ECOG-PS (Eastern Cooperative Oncology Group-Performance Status) ≥2.

ECOG-PS of 2 denotes patients that are 'ambulatory and capable of all selfcare but unable to carry out any work activities and up and about more than 50% of waking hours'. ECOG-PS of 3 denotes patients 'capable of only limited selfcare and confined to bed or chair more than 50% of waking hours'. ECOG-PS of 4 denotes patients who are 'completely disabled, cannot carry on any selfcare and totally confined to bed or chair'(189).

3.3.2.1. Sub-Analysis per aetiology

Most study participants had pleural effusions secondary to heart failure, 39(66%), with 16(27%) secondary to liver failure and 4(7%) secondary to renal patients (see figure 11). Patients with heart failure were older with a mean age of 78.00 (9.37) compared to 62.85 (8.17) and 63.84 (12.69) for liver and renal failure respectively. Seventy two percent of heart failure patients had a WHO performance status ≥2, compared to 37.5% and 75% for liver and renal failure respectively.
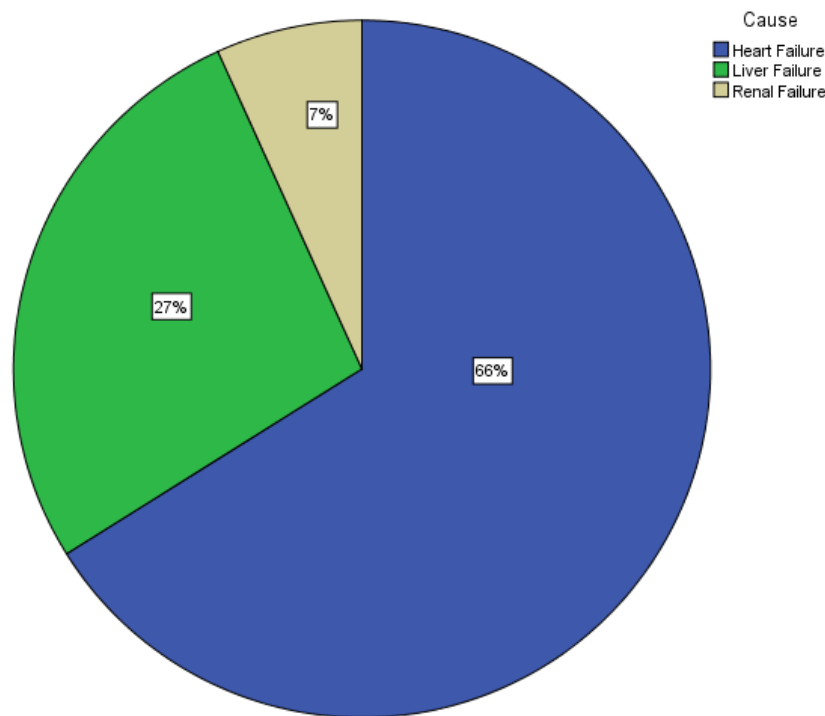
Figure 11. **Distribution of first 60 REDUCE study subject by aetiology**

3.3.2.2. Pleural effusion characteristics

Most pleural effusion's requiring intervention were right-sided, 48/59 (81%). In 35/59 (58.3%) the effusion occupied less than half the hemithorax. This is consistent with the literature

detailing most transudative effusions as small to moderate in size(29). The mean LDH was 162.8 (SD 88.2) and mean protein 29.4 (SD 9.9), which would be consistent with a transudative effusion. The pleural fluid characteristics for each study group are displayed in table 8.

Table 8.	*Characteristic of Pleural effusions of 1st 60 patients in the REDUCE trial*	
	IPC (n=30)	Standard care (n=30)
Side of effusion requiring intervention- no. (%)		
Right	25 (83.3)	23(76.6)
Left	5 (16.7)	6 (20)
Missing	0	1 (3.3)
Size of effusion- no. (%)		
Less than half hemithorax	19 (63.3)	16 (53.3)
Greater than half hemithorax	11 (36.7)	13 (43.3)
Missing	0	1(3.3)
Fluid biochemistry		
Fluid LDH, U/L- mean (SD)	177.1 (97.9)	148.0 (75.9)
Fluid Protein, g/L- mean (SD)	29.3 (9.1)	29.7 (11.0)

3.3.2.3. Management at baseline

Data was collected on the management of patients at enrolment, including ipsilateral drainages during the last 3 months month and diuretic medications. The baseline management for each study group are displayed in table 9. Most patients, 46/60 (76.7%) were on a loop-diuretic, typically furosemide, 35/46 (76.1%), with 11/46 (23.9%) on bumetanide. The mean dose of furosemide was 52.8mg (SD 65.6) and mean dose of bumetanide was 0.65mg (SD 1.6). 14/60

(23.3%) of patients were taking spironolactone, at a mean dose of 32.3 mg (SD 74). 45/60 (75%) of patients had an ipsilateral aspiration in the last 3 months. There is limited comparative data to determine if this is representative of other studies on refractory transudative effusions. The study by Kataoka et al which demonstrated a 75% improvement resolution rate in patients with cardiac pleural effusions, did not state medication doses. In that study 48% of patients were on diuretics, 38% on digoxin and 30% on ACE-inhibitors(20). The study by Srour et al detailing the use of IPCs for cardiogenic pleural effusions also did not state medication dosing, only that patients 'were required to have failed to respond to maximal medical therapy or have complications from medical therapy (e.g. renal failure while receiving diuretics or hypotension during dialysis)'(72). Other similar studies also are limited by their lack of dosing data(66, 71, 75). The mean dose of diuretics appears lower than one would anticipate in a population managed for refractory transudative effusions. This may be that patient were experiencing complications secondary to high-dose diuretics, or perceived unresponsive of the pleural effusions to diuresis.   The mean aspiration volume in the 3 months prior to enrolment was 2228.6ml (SD 2627.8). Again, there is little comparable data detailing aspiration amounts in this patient cohort.

Table 9.	*Baseline management of 1st 60 patients in the REDUCE trial*	
	IPC (n=30)	Standard care (n=30)
Ipsilateral Pleural Drainage in last 3 months- no. (%)	23 (76.7)	22 (73.3)
Ipsilateral drainage amounts in last 3 months, mls- mean (SD)	2549.9 (2889.72)	1907(2343.7)
Loop Diuretic- no. (%)	21 (70)	26 (89.3)
Furosemide dose, mg- mean (SD)	53.7 (69.3)	51.8 (62.0)
Bumetanide dose, mg- mean (SD)	0.6 (1.6)	0.7 (1.6)
Spironolactone- no (%)	4 (13.3)	10 (33.3)

Spironolactone dose, mg-mean (SD)	21.7 (66.2)	45.8 (81.3)

Table 10. *Diuretic dose per aetiology*

Drug	Heart Failure (n 38)	Liver Failure (n 16)	Renal failure (n 4)
Furosemide	25	8	2
20mg	2	1	0
40mg	9	5	0
60mg	1	0	0
80mg	4	1	0
120mg	2	1	0
160mg	6	0	1
250mg	1	0	1
Bumetanide	11	0	0
1mg	1		
2mg	3		
3mg	2		
4mg	1		
5mg	2		
6mg	2		
Spironolactone	6	8	0
25mg	4	0	
50mg	2	0	
75mg	1	0	
100mg	0	2	
200mg	0	4	
300mg	0	2	

Table 10 details the breakdown of diuretic doses in patients with heart, liver and renal failure. The majority on heart failure patients were on loop diuretics (either furosemide or bumetanide), with 36/38 on diuretics. This is compared to lower proportions in patients with liver and renal failure, with 8/16 and 2/4 respectively on loop diuretics. Potassium-sparing diuretics such as spironolactone were used more frequently in liver failure patients with 8/16 receiving them, compared to 6/38 and 0 in heart failure and 0/4 in renal failure.

3.4. Results: Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

We undertook a literature search of adult with PSP, with an outcome of interest was recurrence, as outlined in the method section. The search identified 3,607 publications, of which 29 were eligible for inclusion (Figure 12). Overall pooled recurrence rate was 32.1% (95% CI 27.0% to 37.2%) (Figure 13). 12 studies documented 1-year recurrence, with a pooled recurrence rate of 29.0% (95% CI 20.9% to 37.0%).

Figure 12. ***PRISMA flow diagram of study selection.***

PSP: primary spontaneous pneumothorax.
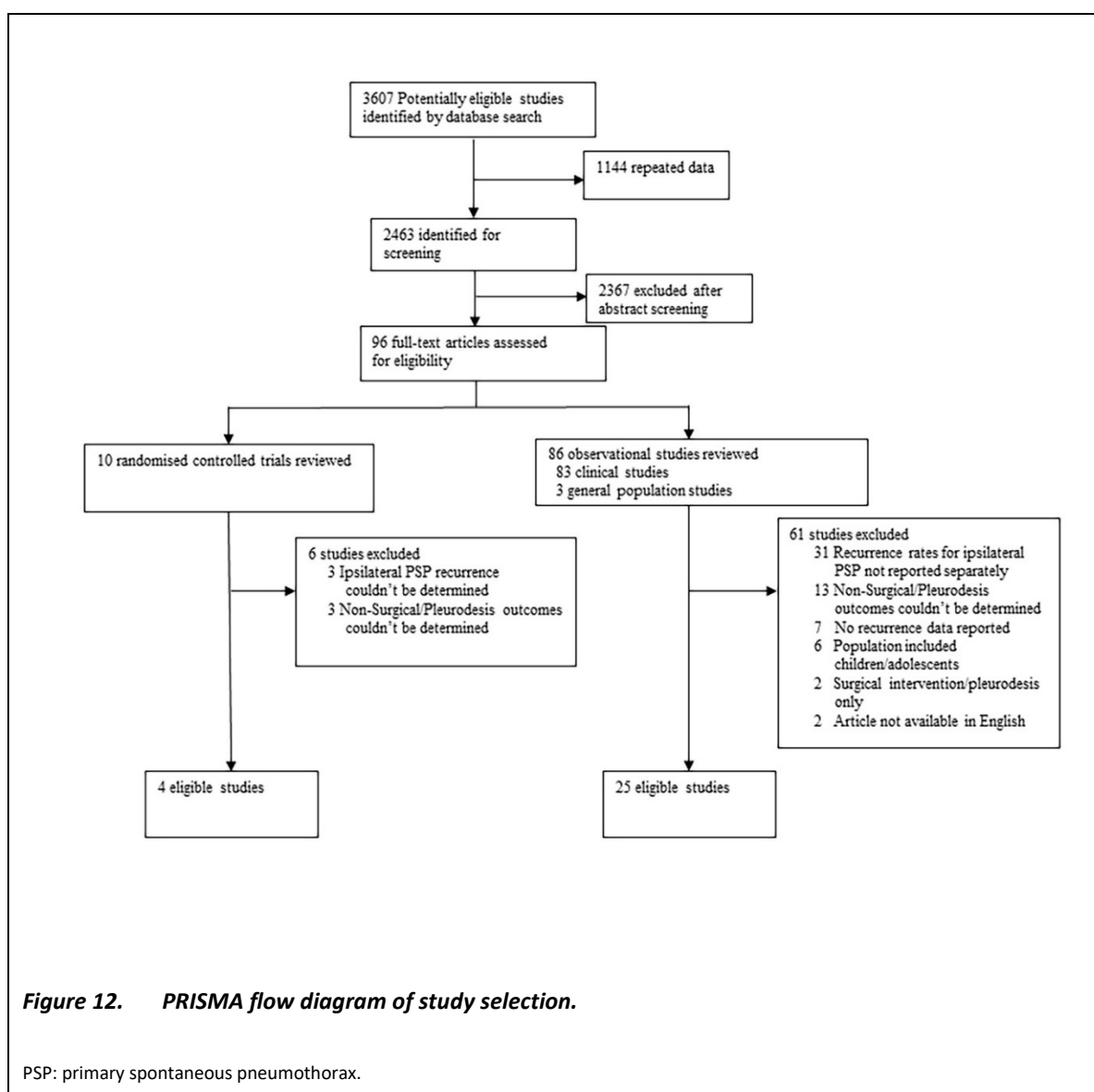
A total of 13,548 patients were included in the studies, with a median sample size of 79(range 18 to 10,956). 85% were male. Study dates ranged from 1965 to 2017. Four randomised control trials

(RCT) were included; one compared NA to ICD insertion, 2 compared pleurodesis with standard care and one compared conservative management to surgery. Twenty-five observational studies were included: 21 retrospective, 3 prospective and one population-based epidemiological study. Average follow-up time varied significantly between studies, with mean duration ranging from 3 to 96 months. A summary of included studies is provided in Table 11.

There was considerable variation in reported recurrence rates, ranging from 8% to 74% (173). I^2 for the random effects meta-analysis was 94% (p<0.0001). This is likely to reflect the wide variety of patient populations, methodologies and interventions studied in the included papers. Assessment of risk of bias showed a high risk of bias in at least one domain for all included studies.

Table 11.		Characteristics of included studies						
Name	**Date**	**Type of study**	**N (PSP)**	**Interventions**	**Excluded patients (n)**	**1st episode**	**Follow-up (months)**	**Overall Recurrence rates**
Al-Alawi (210)	2009	Retrospective	208	Cx, ICD,	Nil	Not stated	42[MN]	0.35
Al-Mourgi (211)	2015	RCT	22	Cx, S	Underwent surgery(19)	1st	32.4[MN]	0.41
Andersen (212)	1965	Retrospective	138	Cx, ICD	SSP (48)	1st	71[MN]	0.16
Casali (163)	2013	Retrospective	176	Cx, ICD,	Nil	1st	58 [MN]	0.46
Chan (202)	2006	Retrospective	89	NA	Nil	1st & recurrent	12	0.16
Chen (213)	2008	Retrospective	18	ICD, S	Underwent surgery (34)	1st	16[MN]	0.28
Chen (214)	2008	Retrospective	33	NA, P	Underwent pleurodesis (31)	1st	13 [MN]	0.33
Chen (215)	2013	RCT	108	ICD, P	Underwent pleurodesis (106)	1st	12	0.49
Ganesalingam (164)	2010	Retrospective	100	Cx, ICD	Nil	1st	57[MN]	0.54
Harvey (95)	1994	RCT	73	NA vs ICD	Nil	1st	12	0.21
Huang (216)	2017	Epidemiological	10956	Cx, ICD, S	Underwent surgery (8606)	1st	60 to 144	0.24
Karasaki (217)	2014	Retrospective	93	HVCD	Underwent surgery (6)	1st	12.5[MD]	0.34
Kim (218)	2014	Retrospective	55	Cx, ICD, S	Underwent surgery (1)	1st & recurrent	Unclear	0.16
Kuan (219)	2009	Retrospective	48	Cx, NA, ICD, S	Underwent surgery (13)	1st	3	0.08

					Recurrent pneumotherax (21)			
Lichter (220)	1974	Retrospective	24	Cx, ICD, S	SSP (54) Underwent surgery (18)	1st	60-144	0.08
Light (203)	1990	RCT	22	ICD, P	SSP (171) Underwent tetracycline pleurodesis (19)	1st & recurrent	29.1[MN]	0.32
Martinez-Ramos(162)	2007	Retrospective	55	Cx, ICD	Nil	1st	30.7[MN]	0.24
Mehta (200)	2016	Retrospective	216	ICD	Nil	Not stated	14 [MD]	0.13
Nishiuma (221)	2012	Retrospective	66	NA	Failed NA (25)	1st & recurrent	12	0.36
Noh (222)	2015	Retrospective	109	Cx, ICD, S	≤19 age (328) + Underwent surgery (76)	Not stated	Unclear	0.48
Noh (223)	2015	Retrospective	79	Cx, ICD	Underwent surgery (183)	Not stated	Unclear	0.37
Olesen (158)	2016	Prospective cohort study	257	Cx, ICD	Nil	1st	43.2[MD]	0.56
Ouanes - Besbes (174)	2006	Prospective	63	Cx, NA, ICD, P, S	Underwent pleurodesis (16) Underwent surgery (1)	1st	34 [MN]	0.23
Primavesi (173)	2016	Retrospective	23	Cx, ICD, S	Underwent surgery (33)	1st	67 [MD]	0.74
Sadikot (156)	1997	Retrospective	153	Cx, NA, ICD	Nil	1st	54 [MN]	0.54
Sayar (224)	2014	Prospective	154	ICD, S	Underwent surgery (27)	Not stated	30.6 [MN]	0.14
Schramel (225)	1996	Retrospective case control	78	Cx, ICD, S	Underwent surgery (97) No follow up (34)	1st & recurrent	96 [MN]	0.39
Tan (201)	2017	Retrospective	97	Cx, NA, ICD, S	Underwent surgery (176)	1st	39 [MD]	0.56
Tulay (226)	2015	Retrospective	68	ICD, S	Underwent surgery (14)	1st	Unclear	0.27

Cx: Conservative; HVCD: Heimlich valve chest drain; ICD: intercostal drain; MN: mean; MD: Median; NA: needle aspiration; NS: not stated; RCT: randomised control trial; P: Pleurodesis; S: Surgery

3.4.1.   Study types

All studies included participants drawn from clinical populations, apart from one epidemiological study that analysed population-level data, from a national health research database in Taiwan(23). This study of over 10,000 people, from a 13 year period, reported a slightly lower recurrence rate of 23.7% (95% CI 22.9 to 24.5), when surgically managed patients were excluded, compared with the pooled estimate for clinical studies (32.6%, 95% CI 26.1 to 39.2). Recurrence rates were similar for randomised and non-randomised studies (35.4%, 95% CI 18.7 to 52.1 vs 31.7%, 95% CI 26.3 to 37.1).
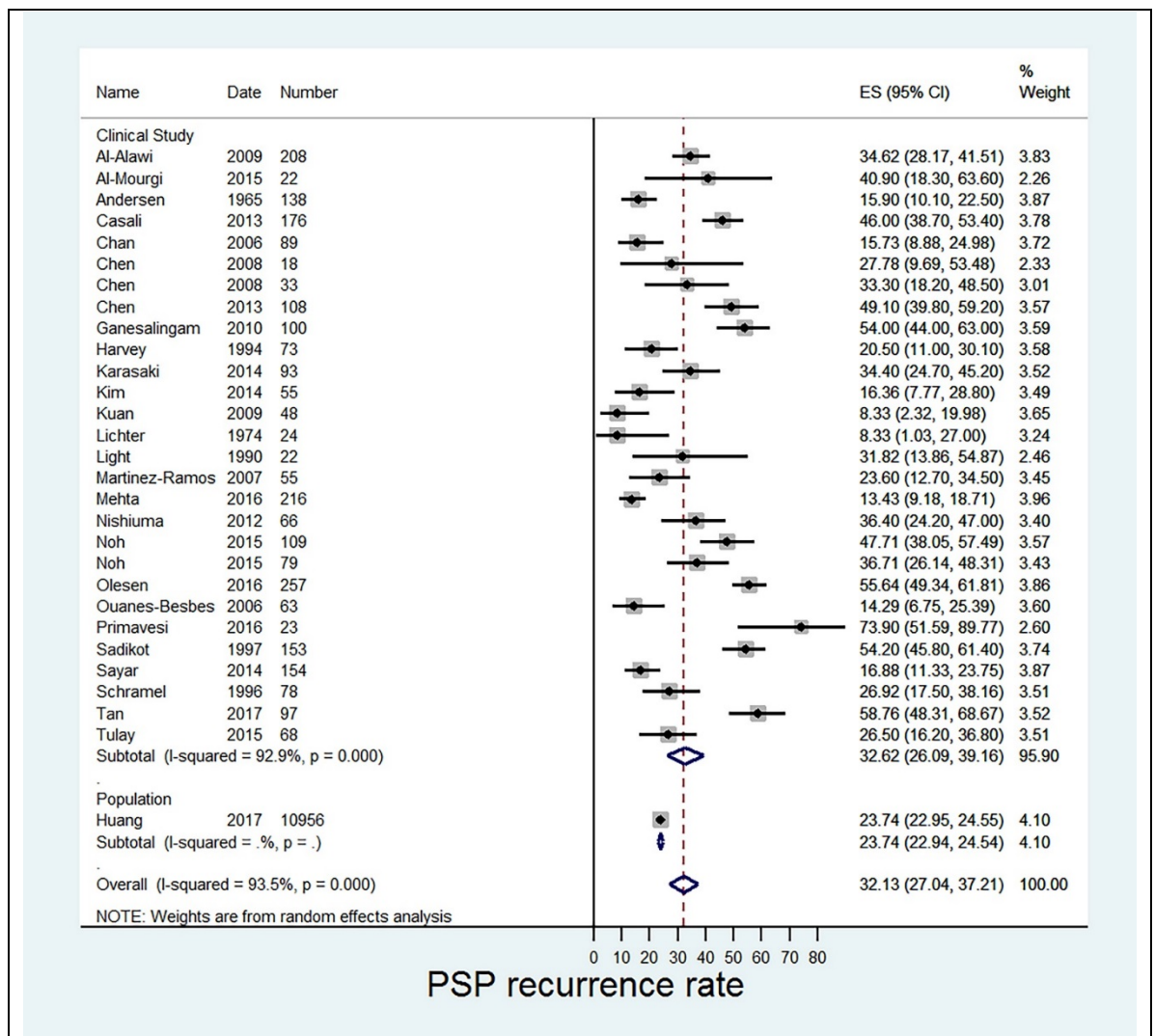
Figure 13.   *Estimate of recurrence of primary spontaneous pneumothorax (PSP) in clinical and populations studies.*

NA: not applicable. #: weights are from random effects analysis.

3.4.2. Factors associated with recurrence

Twelve observational studies examined the association between gender and PSP recurrence(156, 158, 163, 164, 173, 174, 200, 201, 210, 216, 222, 223), with eight demonstrating increased recurrence rates in females (156, 158, 163, 164, 174, 201, 210, 222). Odd ratios could be determined from seven studies,(156, 164, 174, 200, 201, 210, 222) with random-effects meta-analysis demonstrating an OR of 3.0 (95% CI 1.24 to 7.41, p=0.015) for female gender (see Figure 14). 4 studies reported hazard ratios for gender and meta-analysis yielded an estimated HR of 1.2 (95% CI 0.83 to 1.67, p=0.35) associated with being female (158, 163, 164, 173). Two studies, which demonstrated no difference between genders, were not included as either OR/HR could not be calculated(216), or only contralateral recurrences were examined in the gender subgroup analysis(223).
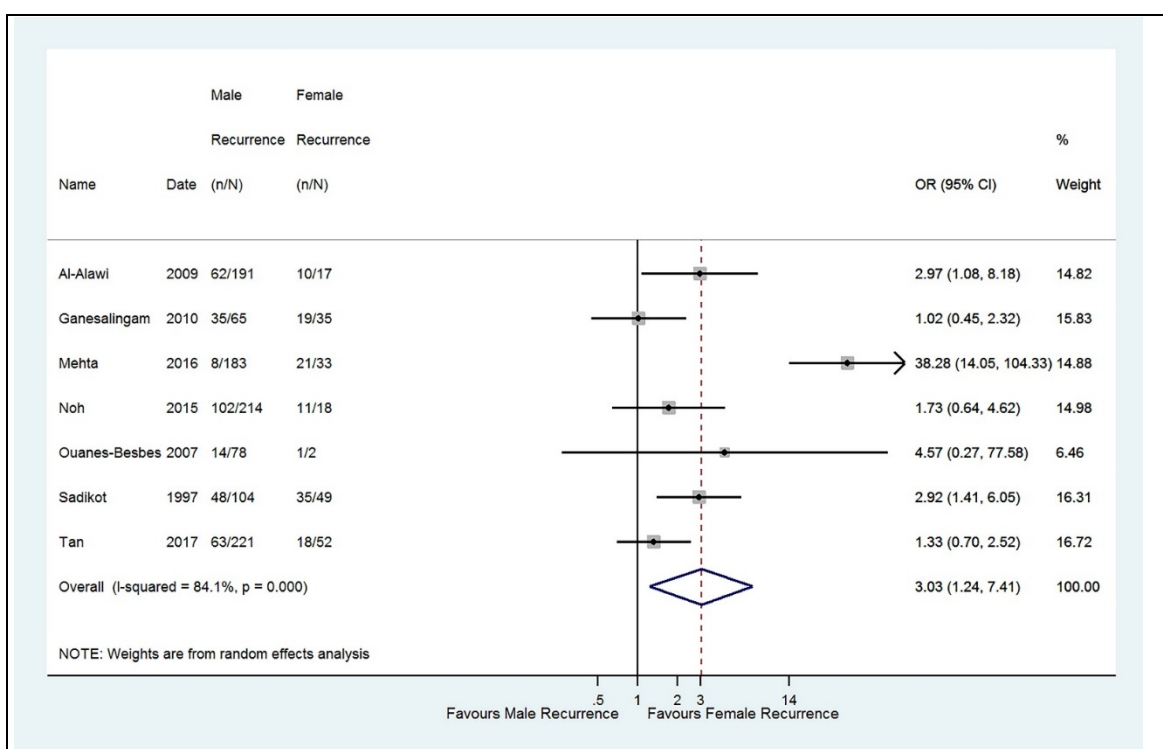
Figure 14. *Meta-analysis of odds ratios for primary spontaneous pneumothorax recurrence in males versus females from seven observational studies.*

#: weights are from random effects analysis.

Several different definitions and cut-offs were used to categorise smoking habits, weight and age, and therefore meta-analysis was not possible. Five observational studies examined the relationship between current smoking and recurrence (156, 158, 164, 201, 210) with only one

demonstrating a convincing association(210). However, smoking cessation was associated with reduced recurrence in 2 studies with OR of 0.22 (95% CI 0.05 to 0.97) and 0.28 (95% CI 0.10 to 0.89) respectively, with a pooled OR 0.26 (95% CI 0.10 to 0.63) (156, 210).

Eight observational studies examined BMI or weight (156, 158, 163, 173, 201, 210, 222, 223) with 2 demonstrating a significant association between low BMI/weight and recurrence(158, 201). Thirteen studies examined whether age correlated with recurrence(156, 158, 163, 164, 173, 174, 201, 202, 210, 216, 218, 222, 223), with ten studies finding no association (156, 158, 163, 164, 174, 201, 210, 218, 223, 227, 228). Three studies demonstrated an increased risk with younger patients (216, 222, 223)

Four studies examined CT radiographic scoring systems, based on number, size and distribution of air-filled lesions (162, 163, 173, 174). The scores were not comparable, and produced conflicting results, which were not suitable for meta-analysis. Two studies found an association between radiographic evidence of blebs and recurrence risk (163, 173) and two studies did not (162, 174). One study concluded that chest radiograph features such pleural thickening, blebs/bullae, pleural irregularities and pleural adhesions were associated with an increased likelihood of recurrence (164).

Only one study compared recurrence in patients treated with needle aspiration versus chest drain (164), therefore precluding meta-analysis. There were no RCTs comparing medical interventions with conservative management. Six non-randomised studies compared conservative management with either NA or ICD, with neither approach demonstrating a reduction in recurrence risk (OR 0.78, 95% CI 0.47 to 1.31, p 0.353 - see Figure 15) (156, 158, 164, 216, 218, 222).
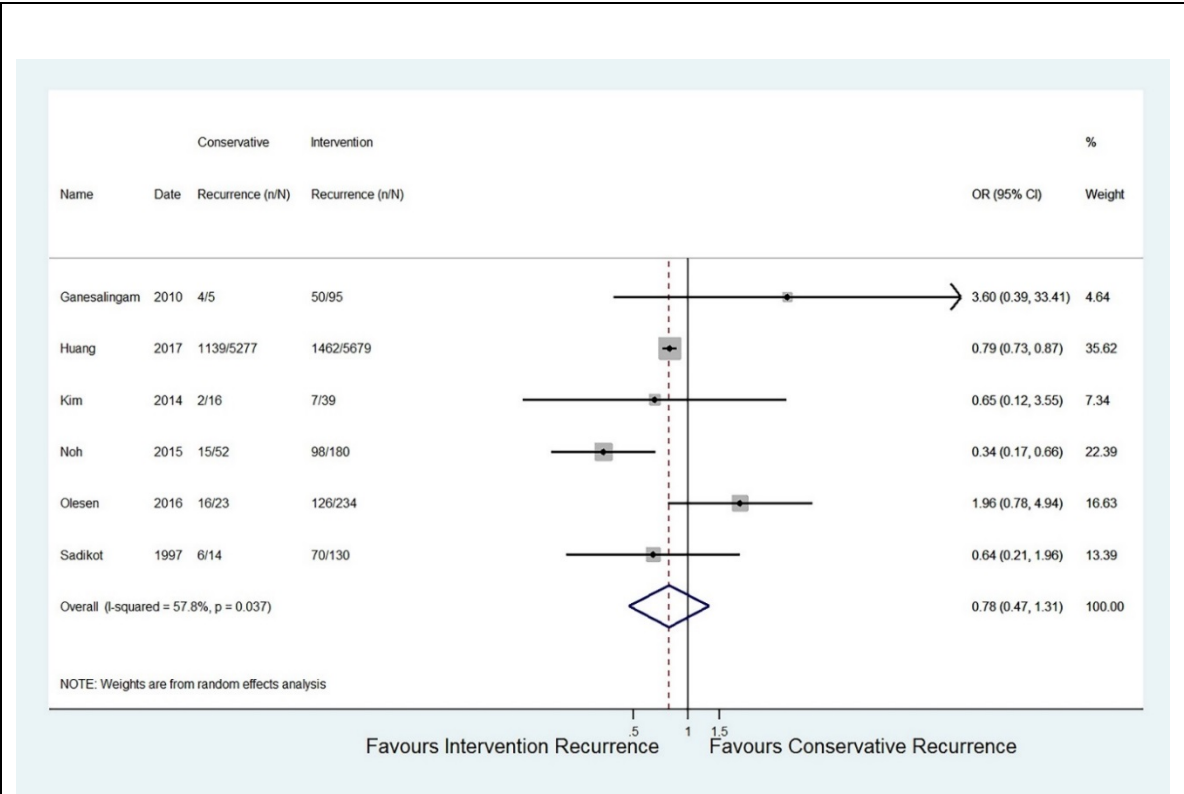
Figure 15. *Odds ratios for recurrent pneumothorax following conservative management or intervention (needle aspiration or intercostal drainage) from six observational studies.*

3.4.3.   Meta-regression

Univariable meta-regression did not demonstrate any significant association between PSP recurrence and study size, publication year, eligibility criteria, type of study, PSP type (first or recurrent) or follow up period (see Table 12).

There was considerable unexplained residual heterogeneity even after adjusting for the different study characteristics.

Table 12. Univariable meta-regression of study characteristics				
	N Studies	Pooled recurrence rate, % (95% CI)	P for difference	Residual I^2
Study sample size				
<100	18	28.8 (21.7, 36.0)	0.234	94.05%
>100	11	37.0 (28.4, 46.6)		
Publication year				
Before 2000	6	26.3 (11.5, 41.1)	0.324	94.05%
After 2000	23	33.6(27.8, 39.4)		
Pneumothorax type				
1st pneumothorax	18	35.7 (27.9, 43.5)	0.273	94.02%
1st & recurrent pneumothorax	6	23.4 (16.7, 30.1)		
Not stated	5	29.4 (17.0, 41.8)		
Follow-up period				
<24 months	10	26.5 (17.7, 35.2)	0.303	93.84%
>24months	15	35.9 (27.9, 43.9)		
Not stated	4	31.9 (18.4, 45.4)		
Type of study				
Non-randomised	25	31.7 (26.3, 37.1)	0.729	93.91%
Randomised	4	35.4 (18.7, 52.1)		

3.5. Results: Conservative management in traumatic pneumothoraces: an observational study

3771 trauma patients presenting to major trauma centre (MTC) at Southmead Hospital, Bristol, were registered on the TARN database from April 2012 to December 2016. 765 patients were identified using the search criteria. 636 patients with pneumothoraces were identified, with 602 patients (see Figure 16) included for analysis. Table 13 summaries patient demographics, mechanism of injuries, ISS, pneumothorax characteristics, management and outcomes for patients managed non-conservatively and conservatively. Table 14 summaries the characteristics and outcomes for successful and failed observed management.
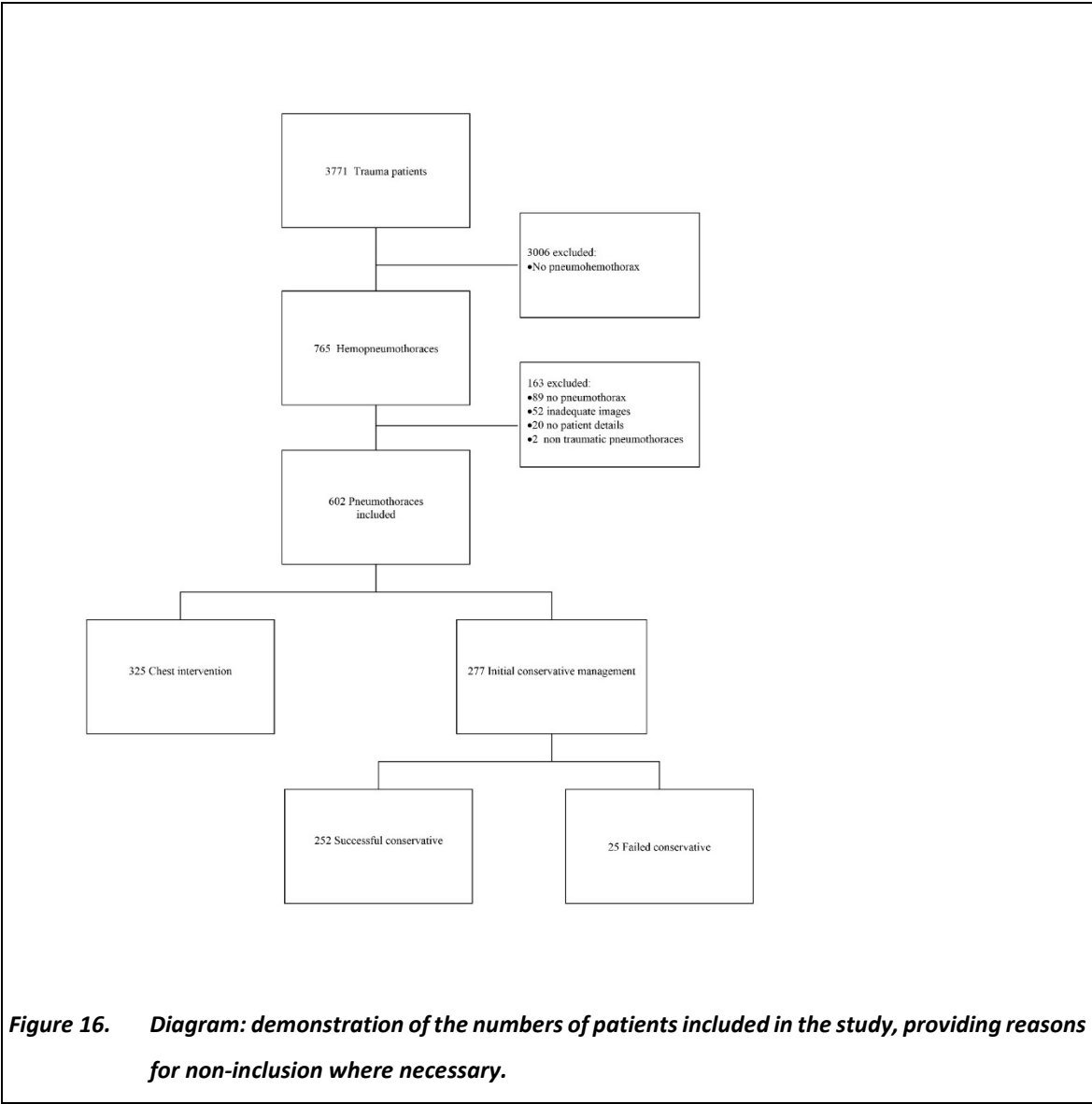
Figure 16. *Diagram: demonstration of the numbers of patients included in the study, providing reasons for non-inclusion where necessary.*

Traumatic pneumothoraces were present in 636/3771 (17%) of trauma patients during the study period. The mean age was 48 (SD 22), 438/602 (73%) were male, and 330/602 (55%) suffered their injury as a result of a road traffic accident. The mean ISS score (26) represented very severe injuries; and 189/602 (31%) required immediate invasive ventilation and 56/602 (9%) died during admission. 325/602 (54%) of patients had an intervention performed pre-hospital or on admission, either with needle decompression, chest tube insertion or chest surgery, with the remaining 277/602 (46%) of the pneumothoraces were initially treated conservatively. The patients managed conservatively, had significantly smaller pneumothoraces compared to patient managed with an immediate intervention (median 5.5mm vs 22mm), with the majority less than 10mm in size (see Figure 17).

Table 13.	*Characteristics and Outcomes of Non-Conservative vs Conservative Patients*		
	Initial Non-Conservative Management (325)	Conservative Management (277)	p value
Age, yr (SD)	48.8 (21.5)	47.1 (21.9)	0.36
Male Gender (%)	252 (77.5)	186 (67.1)	0.04
Mechanism of injury (%)			0.04
• Vehicle collision	175 (53.8)	155 (56)	
• Fall <2 meters	58 (17.8)	55 (19.9)	
• Fall >2 meters	52 (16)	48 (17.3)	
• Stabbings	25 (7.7)	5 (1.8)	
• Crush injuries	7 (2.2)	8 (2.9)	
• Blows	8 (2.5)	6 (2.2)	
Mean ISS (SD)	26.9 (14.7)	25.0 (12.3)	0.08
Median Pneumothorax size, mm (IQR)	22 (35.9)	5.5 (8.8)	<0.001

Significant (>2cm) haemothorax (%)	58 (17.8)	17 (6.1)	<0.001
Initial PPV (%)	127 (39.1)	62 (22.4)	<0.001
Subsequent PPV (%)	159 (48.9)	139 (50.2)	0.12
Presence of Respiratory distress (%)	199 (61.2)	138 (49.8)	0.06
Presence of hemodynamic compromise (%)	132 (40.6)	71 (25.6)	<0.001
Presence of decreased GCS (%)	135 (41.5)	90 (32.5)	0.03
Median Hospital length of stay, days (IQR)	10 (17)	10 (13.5)	0.351
Median ICU length of stay, days (IQR)	2 (9.5)	0 (5)	<0.001
Mortality (%)	11.1%	7.2%	0.1
GCS: Glasgow coma scale, ICU: intensive care unit,			

Figure 17. *Distribution of pneumothorax size in conservatively management patients*
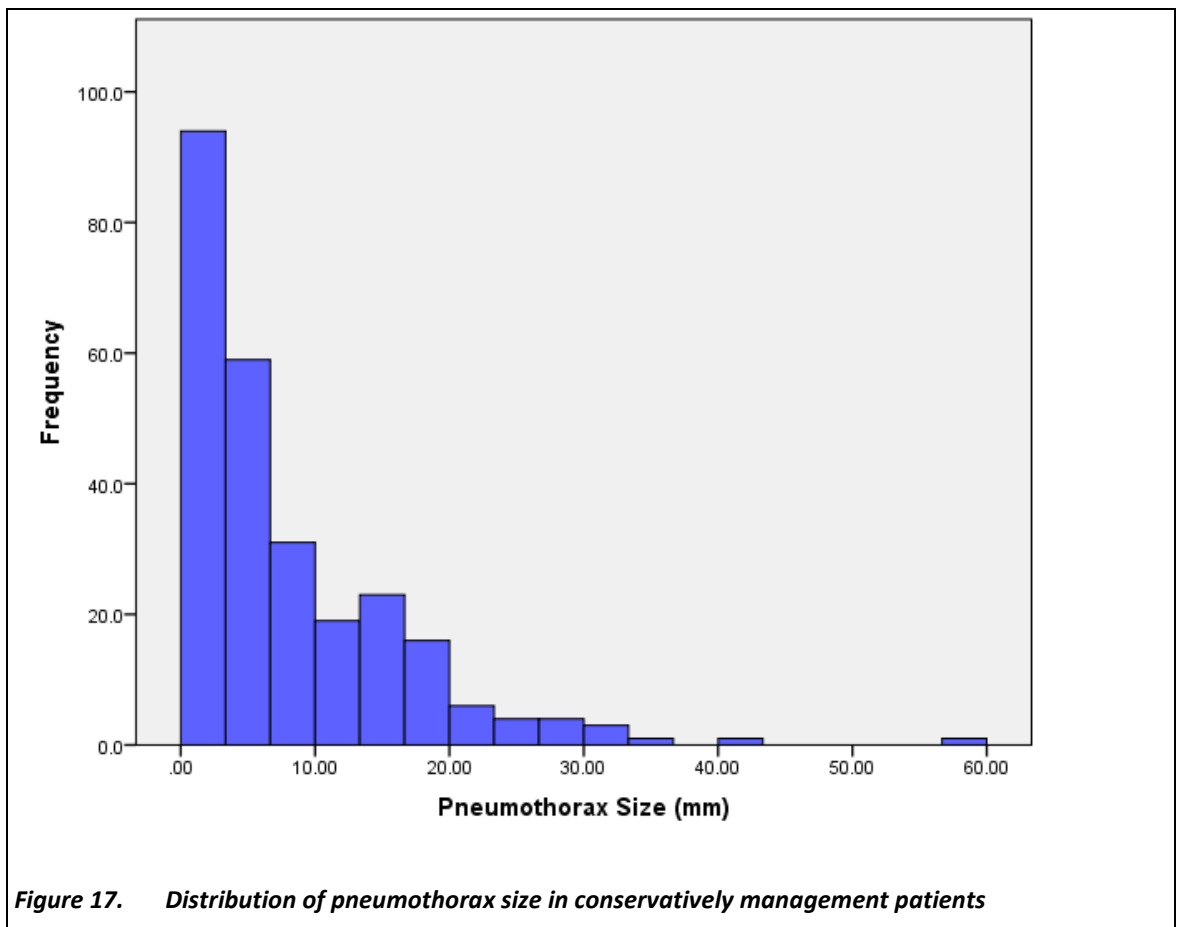
Patients who were managed with an immediate intervention also had a higher incidence of respiratory, hemodynamic and neurological compromise, and a higher proportion of significant haemothorax than those managed conservatively. Both groups, have comparable ages, ISS score, mortality rate and total LOS.

Of the 277/602 (46%) of patients managed conservatively, 252/277 (90%) did not require subsequent thoracic intervention. This included the majority, 56/62 (90%), of patients requiring immediate PPV who were treated conservatively. There was no significant difference in the failure rate between the patients on PPV (6/62, 9.7%) and those not requiring PPV (19/215, 8.8%) in the conservative arm.

Table 14. *Characteristics and Outcomes of Conservatively Managed Patients*			
	Conservative management (Successful) (252)	Conservative management (Failed) (25)	p value
Age, yr (SD)	46.7 (22.4)	51.2 (16.2)	0.33
Male Gender (%)	169 (67.1)	17 (68)	0.92
Mechanism of injury (%)			0.72
• Vehicle collision	142 (56.3)	13 (53)	
• Fall <2 meters	49 (19.4)	6 (24)	
• Fall >2 meters	42 (16.7)	6 (24)	
• Stabbings	5 (2)	0	
• Crush injuries	8 (3.2)	0	
• Blows	6 (2.4)	0	
Mean ISS (SD)	24.9 (12.5)	25.0 (11.0)	0.97

Median Pneumothorax size, mm (IQR)	5.3 (8.6)	8.2 (16.5)	0.13
Significant (>2cm) haemothorax (%)	12 (4.9)	5 (20)	<0.01
Initial PPV (%)	56 (22.2)	6 (24)	0.84
Subsequent PPV (%)	123 (49)	16 (64)	0.15
Presence of Respiratory distress (%)	124 (50.2)	14 (60.9)	0.33
Presence of hemodynamic compromise (%)	67 (27.2)	4 (18.2)	0.36
Presence of decreased GCS (%)	80 (32.3)	10 (40)	0.43
Median Hospital length of stay, days (IQR)	10 (13.8)	11 (14.5)	0.66
Median ICU length of stay, days (IQR)	0 (4)	3 (12.0)	0.15
Mortality (%)	7.1%	8%	0.88
GCS: Glasgow coma scale, ICU: intensive care unit, PPV: Positive Pressure Ventilation			

Using univariate analysis, size of pneumothorax, mechanism of injury, presence of rib fractures, clinical condition, surgery and ISS were not significantly associated with failure of conservative management (Table 15). The median size of pneumothorax (5.3 vs 8.2 mm p 0.13) was comparable between groups and did not increase the likelihood of progression requiring chest tube insertion, with HR of 1.61 (p 0.08) and 2.84 (p 0.07) on univariate and multivariable analysis

Table 15. *Hazard ratios for failed conservative management*			
	Hazard ratio	P value	95% Confidence interval
Male Gender	1.05	0.92	(0.45, 2.2)
Size of pneumothorax (≥2cm vs <2cm)	1.61	0.08	(0.94, 2.76)
Bilateral vs unilateral pneumothorax.	1.34	0.25	(0.83, 2.12)
ISS score (very severe vs severe and moderate severe)	1.17	0.69	(0.54, 2.58)
Presence of rib fractures	1.15	0.57	(0.71, 1.88)
Haemothorax (>2 cm)	4.08	<0.01	(1.53, 10.88)

Received initial Positive Pressure Ventilation	1.1	0.84	(0.44, 2.76)
Received subsequent Positive Pressure Ventilation	2.10	0.08	(0.91, 4.87)
Presence of Respiratory distress	1.23	0.33	(0.810, 1.87)
Presence of hemodynamic compromise	0.78	0.37	(0.45, 1.34)
Presence of decreased GCS	1.17	0.45	(0.78, 1.74)
ISS: Injury severity score, GCS: Glasgow coma score			

Table 16.	*Multivariable Cox Regression Analysis For Failure Of Conservative Management*		
	Hazard Ratio	P Value	95% Confidence interval
Haemothorax >2cm	5.29	<0.01	(1.78, 15.79)

Univariate and multivariable analysis also confirmed that acute PPV does not appear to confer an additional risk of failure of conservative management (HR 1.56 p 0.51 and HR 1.05 p 0.96 respectively). Additionally, requiring subsequent PPV during inpatient stay, either due to clinical deterioration, or for general anaesthesia did not represent an increase risk of failure of conservative management. In contrast, the presence of a haemothorax was associated with increased likelihood of failure of expectant management (hazard ratios of 4.08 (p < 0.01)) and confirmed by multivariable cox regression analysis (Table 17).

Table 17.	*Overt and Occult pneumothoraces characteristics*	
	Occult pneumothoraces (61)	Overt pneumothoraces (65)
Age, yr (SD)	52.04 (23.80)	56.30 (20.45)
Male Gender (%)	48 (78.7)	47 (72.3)
Median size of pneumothorax on CT, mm (IQR)	7.26 (12.39)	25.07 (37.46)
Median ISS (IQR)	20.00 (9.50)	16.00 (11)
CT: computerised tomography		

Of the 25/252 patients who failed observed management, 23 had a large chest drain inserted and 2 went to have thoracic surgery (rib fixation with haemothorax evacuation). The main indication for chest tube insertion was increasing pneumothorax (19/23) and enlarging haemopneumothorax (4/23). The mean duration prior to chest tube insertion was 2.96 days (SD 4.03). Requiring subsequent chest insertion in the conservative arm led to a non-significant increase in length of stay (11 vs 10 days p 0.597). The 2 mortalities in this group had severe ISS of 40 (>25 represents severe/critical injuries) with intracranial haemorrhages and it is unlikely that the pneumothorax contributed to the overall outcome.

Table 17 demonstrates the characteristics of patients with a pneumothorax visible on chest radiograph (overt pneumothorax) and those not visible on chest radiograph (occult pneumothorax). 177 patients had a chest radiograph as their initial chest imaging. 137 of these patients proceeded to a CT chest. Of these 137 patients, 11 had a chest drain in-situ at time of chest radiograph. Of the remaining 126, 61/126 (48%) had no visible pneumothorax. Occult pneumothoraces were generally smaller than the overt pneumothoraces, with respective median size of 7.26mm vs 25.07mm (p<0.001).

There was a 10% complication rate associated with chest tube insertion. 15 (4.4%) patients required their drain to be re-sited, 4 (1.2%) patients had their drains dislodged, 5 (1.5%) had intraparenchymal drains on CT, 2 (0.6%) patients developed an empyema, and 1 (0.3%) patient had a guidewire left in the pleural cavity. 8 (2.4%) patients required a subsequent drain after initial removal due to re-accumulation of air or fluid.

3.6. Results: Heimlich Valves in Secondary Spontaneous Pneumothorax: Enhancing Care (HI-SPEC trial)

The first patient was recruited for the Hi-SPEC trial on the 21st March 2017. The trial is currently recruiting, with an end-recruitment date of 12th June 2019. Currently 35 patients have been recruited (see Appendix F for full breakdown of recruitment).

The end-recruitment date is 12th June 2019, with 6-month follow-up, and the study end date will be 12th December 2019. Monthly reminders will be sent for data queries and missing data from 1st June 2019. The data will be cleaned from August 2019 and Stata code will be developed by the trial statistician from the statistical analysis plan in November 2019. I anticipate the final manuscript will be ready for publication by Summer 2020.

3.6.1. Screening

92 patients were screened for the Hi-SPEC trial, with 35 enrolled at time of PhD submission. The majority of patients were excluded from the trial (33/92) as they had already had a drain inserted prior to screening. This was either due to the drain inserted as an emergency procedure out of hours (n 18) or the potentially eligible patient was missed by the trial team (n 15). The technical reasons were typically concerning difficult drain placement, i.e. tethered lung or apical or small pneumothorax.

92 Excluded:
- Chest drain already inserted 33
  o Out of hours 18
  o Missed 15
- Technical reasons 15
- Not SSP 16
- Too unwell 6
- Patient factors 4
- Not documented 5
- Other 13

127

35

0 run-in failures

35

19 HMV   16 Standard care

0 Administration failures

19 HMV   16 Standard care

Lost to follow-ups, Withdrawals

Number of HMV included in primary analysis

Number of standard care included in primary analysis

Figure 18.   HI-SPEC trial Consort diagram

HMV: Heimlich valves, SSP: Secondary spontaneous pneumothorax

3.6.2.   Patient Baseline characteristics

The baseline patient characteristics for the first 30 patients is included in table 18.

Table 18. *Baseline characteristic of first 30 patients in Hi-SPEC trial*		
	Heimlich Valve (n=15)	Standard care (n=15)
Age – mean (SD)	64.4 (12.3)	66.5 (8.6)
Male – no. (%)	10 (66.7)	12 (80)
Side of pneumothorax - no. (%)		
Right	9 (60)	9 (60)
Left	6 (40)	6 (40)
Size of pneumothorax at presentation (Interpleural distance at hilar point) -cm	3.8 (2.7)	4.7 (2.)
Smoking status – no. (%)		
Current smoker	6 (42.9)	5 (38.5)
Ex-smoker	8 (57.1)	7 (53.8)
Never-smoker	0	1 (7.7)
Pack year history- Mean (SD)	32.8 (15.5)	31.7 (16.4)
Previous pneumothorax – no. (%) -	6 (42.9)	9 (38.5)
Respiratory history – no. (%)		
COPD	10 (71.4)	10 (76.9)
Asthma	1 (7.1)	4 (30.8)
Interstitial Lung Disease	0	0
Non-CF Bronchiectasis	0	0
Lung Cancer	0	0
Pulmonary infection	0	1 (7.7)

From the analysis of the baseline characteristics for the first 30 patients, there was no significant difference between the HV and standard care cohort in pre-determined characteristics. The patients were predominately male (67%), with right sided pneumothorax (60%), predominately secondary to COPD (71%). This COPD and right sided preponderance of SSP is consistent with pre-existing literature(124). The overwhelming majority were smokers or ex-smokers (97%).

3.6.3. Adverse events

The population of patients involved in the Hi-SPEC trial is such that a high number of AEs are to be expected. By virtue of the eligibility criteria all patients will have pre-existing lung disease and at risk of AEs related to pre-existing disease. Additionally, AEs may be expected from trial interventions. Expected AEs are those documented in the reference documents for events associated with trial interventions. Data will be collected on CRFs for expected AEs.

Expected adverse events which relate to chest drain insertion or Rocket Pleural Vent insertion include:

- Minor Bleeding (defined as not causing haemodynamic compromise or requiring blood transfusion)
- Minor Pain (defined as settling spontaneously or controlled with analgesia)
- Subcutaneous emphysema (unless causing airway compromise or requiring surgical intervention)
- Pleural infection (unless requiring surgical intervention)
- Subcutaneous infection at drain insertion site
- Unintentional removal or dislodgement of chest drain or Rocket Pleural Vent
- Requirement for further pleural procedures

Other expected adverse events include:

- Delayed discharge (unless due to a device defect)
- Recurrent pneumothorax
- Readmission to hospital
- Death due to pre-existing disease

Non serious AES

All such events, whether expected or not, should be recorded in patients' clinical records. Information related to specific non-serious AEs will be collected within the trial data collection.

<u>Serious AEs</u>

Any event which meets the criteria for an SAE should be discussed with the local principal investigator. If in their opinion there is a reasonable possibility that the event is related to trial intervention, or if the event is of particular medical interest, it should be recorded on an SAE form. An SAE form should be completed and faxed to North Bristol NHS Trust (the trial sponsor) within 24 hours of the investigator's knowledge of the event. However, events meeting the criteria for an SAE but which are attributed to pre-existing lung disease or comorbidity, and hospitalisations for elective treatment of pre-existing conditions do not need reporting on the SAE form.

3.6.3.1. <u>Serious Adverse Events</u>

As of 15th January 2019, there were 11 SAEs. The breakdown according to cohort was as follows:

- Intervention arm: 7 SAEs

- Standard care arm: 4 SAEs

3.6.3.2. <u>Relevant AEs with Pleural vents</u>

There was particularly interest in AEs for the Pleural vent, which were felt relevant to a safety signal, but did not meet the criteria for SAE.

Overall, when AEs and SAEs were examined for the pleural vents there were 7 events which needed to be examined further by the TSC:

- 2 vents dislodged - one resulted in subcutaneous emphysema, both required chest drain insertion (one developed subcutaneous emphysema after chest drain insertion)

- 5 non-functioning vents - all resulted in subcutaneous emphysema, 4 required chest drain insertion

3.6.4. Details of Adverse Events with Pleural Vent

3.6.4.1. <u>N06</u>

Event: subcutaneous emphysema and vent blocked

When: 2 days after insertion

Description: subcutaneous emphysema 05/05/2017 to 27/06/2017 requiring suction. Vent blocked 12/05/2017. Discharged with vent in place 16/05/2017

Outcome: vent removed due to successful lung re-expansion 26/05/2017.

3.6.4.2. <u>B08</u>

Event: Rocket pleural vent became dislodged

When: 1 day after insertion (01/09/2017)

Description: Rocket pleural vent become dislodged whilst patient was sleeping.

Outcome: Chest drain inserted 02/09/2017. Subcutaneous emphysema 05/09/2017. VATS bullectomy and pleurodesis 11/09/2017. Pleural infection 13/09/2018. chest drain removed 16/09/2017

3.6.4.3. <u>N13</u>

Event: Pneumothorax increased in size + developed subcutaneous emphysema – vent removed

When: 1 day after insertion

Description: Pneumothorax increased in size and developed subcutaneous emphysema despite vent

Outcome: Chest drain inserted 02/05/2018 and 08/05/2018 while having bullectomy and talc pleurodesis. Discharged 17/05/2018

3.6.4.4. <u>S15</u>

Event: subcutaneous emphysema on day 2, vent blocked and removed.

When: 2 days after insertion

Description: 'Vent blocked- not working'

Outcome: Chest drain inserted

3.6.4.5. N18

Event: subcutaneous emphysema on day 2, vent blocked and removed.

When: 2 days after insertion

Description: 'Vent blocked- not working'

Outcome: Chest drain inserted

3.6.4.6. N27

Event: Pneumothorax increased in size + developed subcutaneous emphysema

When: 2 days after insertion

Description: Initial Vent inserted. Initially good re-inflation. Static pneumothorax next day – Discharged. Day 2 review: Pneumothorax increased in size with evidence of subcutaneous emphysema, vent removed

Outcome: Admitted- Chest drain inserted

3.6.4.7. F28

Event: Pneumothorax increased in size + developed subcutaneous emphysema

When: 2 days after insertion

Description: Initial Vent inserted. Initially good re-inflation. Discharged day 2. Re-presented with SOB and subcutaneous emphysema.

Outcome: Admitted and wide-Bore Chest drain inserted

3.6.5. Trial safety: Adverse events in the Hi-SPEC study

Trial participant safety was the most important consideration for the Hi-SPEC trial. Adverse events were recorded in a written log, and this was uploaded to the online database by the local trial

team. These were reviewed episodically by the trial coordinators. Any event which met the criteria for an SAE was faxed to the trial sponsor within 24 hours of the investigator's knowledge of the event. All SAEs were reviewed monthly by the trial team, with no predefined safety stopping boundary. As this trial was unblinded to both investigator and patient, the SAEs could be analysed as the trial progressed.

In January 2019, in the Hi-SPEC trial, it was recognised that there was a numerical imbalance between SAEs in the intervention (7) and the standard care treatment arm (4). On review of the SAEs, there appeared to be related causality to the study intervention (pleural vent) in the majority of cases. Additionally, on review of the AEs log, there were AEs which shared common features as the SAEs, although not reaching the threshold criteria for SAEs. Of particular concern were 5 pleural vents which become non-functional, with 4 of these patients requiring subsequent chest drain insertion. Additionally, 2 pleural vents became dislodged, both requiring chest drain insertion.

These concerns were addressed at an emergency TSC meeting. These SAEs were not felt to be associated with any particular study site or a procedural competency that could be remedied. No patients came to significant harm from the pleural vent and no patients died as a result of the intervention. A discussion was held as to whether to terminate the trial prematurely.

3.6.6. Rationale for early trial cessation

Randomised controlled trials can be stopped early for four major reasons(229). Firstly, the trial can be stopped early due to concerns regarding for unacceptable safety if it shows serious adverse effects. Secondly, the trial can be stopped due to 'futility', where interim differences between the two groups are so unimpressive that any prospect of a positive result with the planned sample size is deemed to be extremely unlikely. Thirdly, new external information may arise during the conduct of the study that either convincingly answers the primary study question or raises serious safety issues. Finally, interim analysis may demonstrate such convincing benefit in the intervention, that the investigators may elect to stop the trial early due to the apparent benefit.

In our trial, a discussion was held to consider whether to stop the trial early due to potential harm to the trial participants in the intervention arm (pleural vent). There are several ethical considerations to be made at this point. Before starting a randomized controlled trial there must be a defined area of uncertainty amongst the medical profession. This is sometimes referred to as 'group' or 'collective equipoise'(230). In our study, there was collective equipoise, with

perceived uncertainty about the intervention, and systematic review of the literature suggested a benefit, but with recognised lack of reliable data(180). In an open, unblinded study, it should be recognised that it is possible that this collective equipoise is not shared by individual investigators which may affect recruitment.

The dangers of premature cessation of a study must be recognised. Terminating RCTs early due to apparent benefit has been shown by a simulation study published in 1989 by Pocock et al to lead to an overestimate of treatment effects(231). The role of chance must be appreciated as well, as famously demonstrated by a 'double-blind' clinical trial where patients with chronic disease were randomised between treatment with prayer compared to control. The first 6 results showed an advantage to the group treated with prayer, and this could have led to the termination of the study (232). However, five of the next six showed an advantage to the 'control' group.

The dilemma regarding stopping a trial early due to potential harm can be summarise as:

- Stopping too soon with only modest evidence of harm, thereby risking abandonment of a treatment that might have proved beneficial had additional longer-term data been obtained.
- Permitting a trial to continue in the face of growing evidence of harm, thereby risking further patient exposure to a harmful treatment(233).

3.6.7.   Outcome of Hi-SPEC trial steering committee

During the TSC the individual AEs were examined. It was recognised that out of the 13 patients receiving a pleural vent, 5 become non-functioning and 2 become dislodged. This was felt to be an unacceptably high risk of failure for study participants. A retrospective analysis of the risk of requiring additional chest drain insertion in patients with pleural vents versus standard care, suggested an increased risk signal as the study progressed (see Figure 19). Here I calculated the Hazard ratio for patients requiring additional chest drain at 6 monthly interims in Pleural vents versus standard care. This was to determine if this increase risk had been present earlier on in the trial. As figure 19 illustrates, the HR at 6 months was 0.693 (95% CI 0.043,11.16), 12 months was 0.745 (95% CI 0.05, 12), 18 months 1.37(95% CI 0.2, 8.2) and 24 months 3.1(95% CI 0.6, 15.4). Whilst the confidence intervals were broad and none of the lower intervals were greater than 1, the trend is clearly one of escalating treatment failure with the Pleural Vent as the trial progressed.
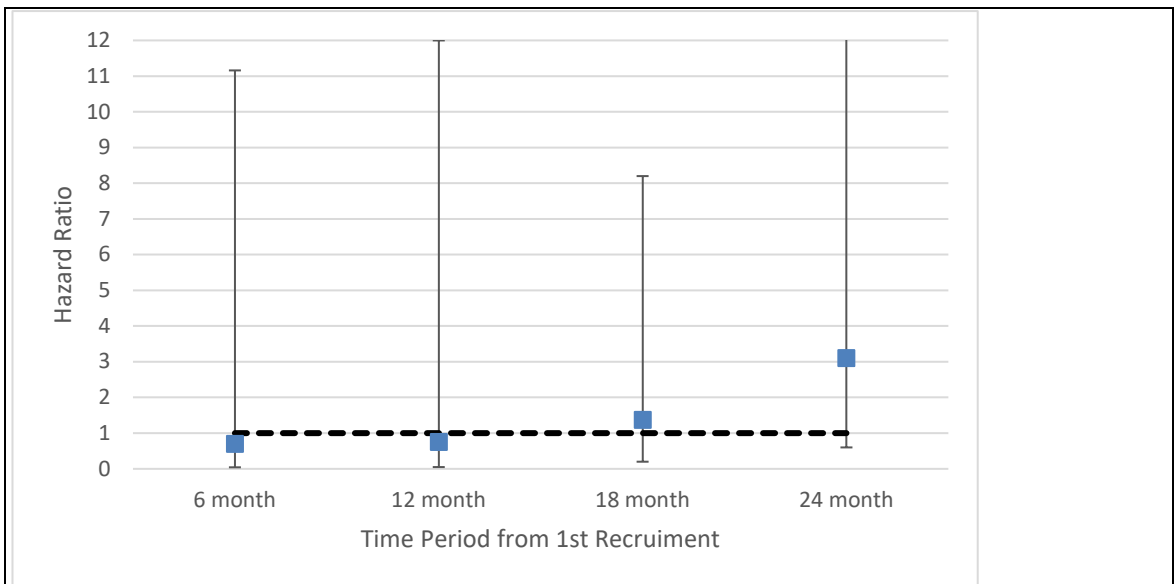
Figure 19. ***Hazard ratio and 95% CI for patients requiring additional chest drain at 6 monthly interims in Pleural vents versus standard care***

With the increasing evidence that Pleural Vents were more prone to treatment failure and with an alternative device available in the intervention arm (Atrium Pneumostat) a decision was made to withdraw the Rocket Pleural Vent and continue with just the Atrium Pneumostat in the intervention arm. This would mitigate the potential risk posed by continuing use of the Rocket Pleural Vent, whilst allowing the overall trial on ambulatory management of SSP to continue.

An urgent safety measure written by myself and sent to the HRA. All recruiting sites were notified and asked to acknowledge receipt of notification. Personal correspondence was made with all sites PI to answer and queries.

We were aware that another currently recruiting trial was using the Rocket Pleural Vent on a differing patient's population (patients with PSP). The chief investigator of this trial was notified.

CHAPTER 4.   DISCUSSION

4.1.   Refractory transudative effusions

Non-malignant pleural effusions are not a benign process and represent a significant mortality risk. The results obtain via the survival cohort study demonstrates that patients with effusions secondary to organ failure (heart, liver, and kidney) are at significantly higher risk than those related to a local disease process, whether this be infection or inflammation. Correspondingly, the transudative, bilateral effusions that often accompany organ failure are independently associated with a worse prognosis., with 43% and 18% 1-year mortality in transudative and exudative effusions respectively and a 57% and 20% 1-year mortality rates in bilateral vs unilateral effusion. This supports the findings that pleural effusions secondary to organ (heart, renal and liver) dysfunction, as opposed to an exudative effusion secondary to localised inflammation are an indicator of poorer prognosis. This supports the findings of an earlier paper demonstrating high mortality rates in CHF, liver and renal failure(62). These mortality rates are not dissimilar to that seen in some malignant disease. Effusions refractory to medical therapy and repeated aspiration may require more definitive management strategies. This may involve disease specific procedures, including transjugular intrahepatic portosystemic shunt (TIPS) procedure or liver transplantation in liver disease, or pleural interventions including pleurodesis or indwelling pleural catheter placement.

The one year-mortality rate for patients with an effusion secondary to heart failure in this cohort was found to be 50%, similar to the 1- year mortality rate (46%) of patients with acute decompensated heart failure admitted to intensive and coronary care units(234) and significantly more than the 1 year mortality for outpatients with NYHA class IV CHF (28%)(235). Hepatic hydrothorax was also a predictor of significant mortality, with a quarter of patients dying within a year. This is higher than patients with chronic alcoholic liver disease (16.4%)(236) and equivalent to a high MELD (Model For End-Stage Liver Disease) score of 20-29(236) which would be considered an indication for liver transplant. The renal cohort in our study had a high 1-year mortality rate (46%) which is triple the one-year mortality (15.6%) of patients on dialysis (237). The increased hazard ratio associated with renal failure does not, however, reach significance, presumably due to low numbers in the cohort.

To my knowledge this is the largest prospective study to date examining the mortality rates in NMPE. It included approximately equal inpatient and outpatient numbers and involved patients managed by a range of specialities. All patients presenting with an undiagnosed pleural effusion were eligible aside from those excluded if they could not give informed consent, declined to participate in the trial or were pregnant or lactating. The findings are consistent with a previous study demonstrating high mortality rates in patients with CHF and bilateral effusions(62). A limitation of this study is that it was performed at a single centre. All these patients required pleural aspiration, either for diagnostic or therapeutic purposes. A diagnostic aspirate would not usually be indicated for an effusion with a high pre-test probability of cardiac aetiology and a low probability for an alternative cause. Hence it is likely that the CHF effusions aspirated were either refractory to medical management or there was a level of concern in the treating physician that warranted further invasive investigation. This is the likely explanation for pleural infection representing the commonest cause of NMPE in our cohort, as opposed to CHF worldwide(19). We cannot comment on the mortality rate amongst patients that did not require a pleural procedure, and it is likely that requiring an aspiration in NMPE is an indicator of disease severity.

This study demonstrated that pleural effusions secondary to organ dysfunction, in particular cardiac, have an extremely high 1-year mortality and the presence of an effusion requiring aspiration is a marker of severe disease and poor prognosis. The median survival in these patients was not dissimilar to some malignancies, and it supports the idea that these patients should be managed in a symptom-based approach, and to minimise hospital length of stay.

The follow-on study examined a cohort of 105 patients with cardiogenic pleural effusions. This cohort were predominantly outpatients (69%), with a high proportion (45%) with persevered LV function. The mean NT-proBNP was high as 7797 pg/L, however this value is likely positively skewed, as only 36 values available to this analysis, based on clinical decision at the time to perform the test. The mean diuretic dose, at 60mg, was a lower dose one might expect for patients failing to respond to diuretics management. This may be because higher doses of diuretics were contraindicated due to other comorbidities or side-effects. Eight patients were not on diuretics at time of enrolment to study. This may be because of diagnostic uncertainty of the underlying cause of the effusion at time of enrolment, with 5 of these patients having unilateral effusions. All these patients had a pleural aspirate to enter the study, the majority of which (62/105) were diagnostic.

The overall proportion of patients who needed a further therapeutic pleural procedure (24%), is higher than the previously cited figure of 10% (20). The population studied may be more prone to re-accumulation, having already required one pleural procedure. No single variable studied was

predictive of re-accumulation. It may be with the small absolute numbers of patients experiencing re-accumulation (n 23), with a large number of variables studies (9), that the study was underpowered to detect a significant determinate. There are no previous studies examining factors associated with reoccurrence of cardiogenic pleural effusions. Morales-Rull et al examined factors associated with initial formation of pleural fluid in patients with CHF, finding that male gender, NT-pro-BNP levels >3500pg/ml, systolic pulmonary artery pressure (sPAP) >55mmHg and a serum prealbumin <15 were associated with pleural effusion development in a multivariate analysis(29). It must be noted that hypoalbuminaemia was uncommon in our patient cohort, with no patients with an albumin less than 15, and only one patient with an albumin less than 20mg/l.

The study has its limitations. The original study design, a prospective cohort of patients with undifferentiated pleural effusions was not designed explicitly for patient with heart failure. Whist the majority of patients diagnosed with CHF had an echocardiogram, these were not reported in a standardised manner. Additionally, the collection of NT-proNBP was not standardised or consistent. As mentioned previously, the study may have been underpowered to detect a significant variable in determining recurrence.

Overall, these studies have demonstrated that nearly a quarter of patients with cardiogenic effusions will have a symptomatic re-accumulation of their pleural effusion and have a poor prognosis. With this in mind, the REDUCE trial, a randomised control trial examining the use of IPCs in non-malignant pleural effusion to alleviate symptoms in this cohort of patients, will add much needed evidence. The trial process was difficult, with recruitment slower than anticipated. In patients with pleural effusions caused by heart failure, screening demonstrated that there was a significant lag between identifying potentially eligible patients and recruitment. This was mainly due to ensure patients were medically optimised by their treating cardiologist. During this time, the patients could either be successfully medically optimised, in which case this was a useful finding, but rendered them ineligible to the trial, or they deteriorated to a point where insertion of an IPC was not recommended. Several patients also elected of immediate IPC insertion. As this is a commercially available device, with U.S. Food and Drug Administration (FDA) 510(k) clearance for the use in specific non-malignant recurrent pleural effusions aetiologies, including congestive heart failure, the IPC is an available option. In patients with liver failure there were various recruitment challenges. Liver transplant is a definitive and curative option for eligible patients with hepatic hydrothorax. There is clinical equipoise as to whether IPCs should be inserted as bridge to transplant due to perceived increased infections risks, with transplant centre taking diametrically differing view. This partially reflects the sparsity of prospective research on the matter. A prospective study on IPC in hepatic hydrothorax demonstrated a high infection rate

(16%) however, there was no mortality related to IPC infection, with all three patients treated for pleural infection ultimately successfully undergoing liver transplantation (238). A retrospective case series demonstrated a higher rate of infectious complications in 18% (n 11) of patients, three of whom died of related sepsis(50). Of the 19 patients listed for transplant, 8 patients died prior to the procedure, including 2 of sepsis secondary to IPC-related empyema. Another recent retrospective study had a 10% rate of pleural infection (n 8), two of whom died secondary to sepsis(75). The situation is further complicated by the phenomenon of 'spontaneous bacterial empyema', secondary to intrathoracic translocation of infected ascites fluid (spontaneous bacterial peritonitis), with can occur in 13% of hepatic hydrothoraces. This is distinct from a genuine infected pleural space, and may explain why the reported rates of pleural infection are so high(239).

Despite the recruitment challenges, recruitment rate increased as the trial proceeded. This was likely because of increased trial awareness amongst researchers and their sub-speciality colleagues. Increasing the numbers of sites, and the pool of potentially eligible patient also contributed to the increased recruitment.

4.2.   Pneumothorax

4.2.1.   Recurrence rates

This thesis describes the first systematic review of the literature on recurrence rates in adults with PSP who have been medically managed. Meta-analysis of data from 29 studies, totalling over 13,000 patients showed that 32% of patients will experience PSP recurrence, with most occurring within the first year.   Furthermore, it outlined several factors which increased the risk of recurrence. There was strong evidence that female gender was a risk factor for recurrence. This is consistent with an epidemiological study that found an increased rate of pneumothorax recurrence in female patients, particularly in the age group 31-50 years of age, with re-hospitalisation rates of 54% compared with 46% in males (127). It is recognised that a proportion of pneumothoraces in women are secondary to underlying gender-specific pathophysiology, including lymphangioleiomyomatosis (LAM) and catamenial (endometriosis and non-endometriosis related) pneumothoraces.   Whilst catamenial pneumothoraces were historically thought to be a rare entity, with an early study attributing only characterising 1% of PSPs as such(240), a recent retrospective study demonstrated that up to 25% of women referred to

surgery for recurrent pneumothoraces had evidence of thoracic endometriosis (241). The presence of these underlying conditions may explain the higher risk of recurrence seen in women.

Low BMI is an established risk factor for the initial development of PSP (105, 242). Whilst two studies (158, 201) demonstrated increased risk of recurrence with low weight and BMI respectively, differing classifications precluded meta-analysis. The hypothesis that PSP recurrence is linked with low body weight, either due to nutritional deficiencies affecting α_1-antitrypsin levels or due to unbalanced physical development was supported by two papers (158, 201, 243-245).

There is strong evidence supporting the link between smoking and developing a pneumothorax, with a clear dose-response relationship (105, 246). However, only one study in this review demonstrated an association between smoking and recurrence,(210) with several studies demonstrating a trend towards increased recurrence in non-smokers (156, 158, 159, 164, 201, 210). It has been suggested that there is a difference in aetiology between PSP in smokers and non-smokers, with 'never smokers' suffering from a genetic predisposition to pulmonary bullae, regardless of smoking habit. However, a more likely explanation is that the detrimental effect of smoking was obscured by the high base-line rates of cigarette smoking in the included studies and the heterogeneous classifications used to define smoking status. The fact that smoking cessation reduced the risk of PSP recurrence adds further weight to the relationship between smoking and PSP. Interestingly, this finding also suggests that smoking-related risk is reversible, at least in terms of early PSP recurrence (156, 210).

There were insufficient number of studies included to determine if the choice of medical interventions (NA vs ICD) for PSP influenced recurrence rates. A recent meta-analysis comparing RCTS of NA versus ICD insertion found no difference of recurrence at one year between the interventions (247). There was no randomised data comparing conservative management to NA or ICD, but non-randomised data demonstrated no difference in recurrence between conservative management and intervention. It has been hypothesised that conservative management decreases the risk of recurrence, as slow re-expansion of the lung enables healing of the pleural defect (89, 165). However, conversely, it has been postulated that chest drain insertion may inflame the pleural surfaces, promoting pleural symphysis and preventing long-term recurrence (210). An RCT comparing standard and conservative management is currently recruiting and may offer clarification(89).

The presence of bullae on imaging has been postulated as a predictor of recurrence, however, this theory was not supported by the findings of this review. The lack of standardised radiographic

scoring system may explain the conflicting results, although the hypothesis that rupture of bullae causes PSP is also debated (174, 244). The modified dystrophic severity score (DSS), which assessed both blebs and bullae, appeared to be the most useful radiographic scoring system, however with a negative predictive value of over 90% but a positive predictive value of just 68%, it is of greatest value as a rule-out test (163). The DSS has been used in one small subsequent study, but further prospective validation is required(173).

The recurrence rates reported in the included studies varied widely, likely as a result of differences in study design and population, with no single identifiable study characteristics which explained the variation.

This is the first systematic review of PSP recurrence rates, and it provides the most reliable estimate of overall recurrence to date, based on comprehensive evaluation of existing data. Having an accurate estimate for recurrence will enable clinicians to provide better counselling for patients who have experienced their first PSP. Sub-group analysis identified factors associated with higher recurrence rates, including female gender and continued cigarette smoking. This finding will facilitate communication with patients and could be useful in guiding further treatment or investigations. For example, if a patient is thought to be at high risk of recurrence, early referral for surgery may be considered. Thus, this systematic review has clear clinical relevance and immediate potential for impact.

The methodology of the review was rigorous, with dual, independent screening of abstracts, review of papers, data extraction and assessment of study quality. Hence, I feel the result of this review is a reliable summation of the existing literature. Nonetheless, the review does have limitations. There was significant heterogeneity between the included studies, and although a random effects meta-analysis model was used, this heterogeneity may have reduced the precision of the final estimated recurrence rate. Some of this heterogeneity is likely to be a result of differing study populations, and it should be acknowledged that for specific populations their true recurrence rate might appreciably differ from the estimates given. The inclusion of studies with heterogeneous populations means the resultant estimate for recurrence rate can be considered representative of the population at large, at the expense, however, of more accurate estimates for specific populations. This review is also limited by the quality of the data in the included studies. RCT data was limited, and all included studies were at high risk of bias in at least one domain. Non-randomised observational studies are at risk of selection bias and confounding by indication, and since many of the studies were also retrospective, there was a high risk of reporting and ascertainment bias.

4.2.2.   Conservative management

This thesis has outlined an increasing interest in conservative management of spontaneous pneumothorax, including the hypothesis that this encourages optimate pleural defect healing and reduce the risk of future recurrence. In patients with traumatic pneumothorax, there is similar uncertainty on the role of conservative approach. Chest drain insertion is not without risk of complication, with documented complications rates ranging from 15-30% (133, 248-250). Current guidelines recommends chest tube placement for traumatic pneumothorax, particularly in patients on PPV(137), with a caveat that asymptomatic non-ventilated patients can be managed with observation or aspiration at the treating clinician's discretion. Existing literature has examined whether occult pneumothoraces can be managed conservatively (133, 134). Scoring systems, to determine whether chest tube intervention is required for occult pneumothoraces, are in their infancy and have not been prospectively validated (251). We sought to determine whether traumatic pneumothoraces can be treated conservatively and examine factors that safely identify patients who could avoid chest tube insertion. Here we show the majority of patients managed conservatively did not require further invasive intervention, including patients requiring PPV.

Recent studies(133, 134) have focused on whether there is a role for conservative management for 'occult' pneumothoraces not initially visible on chest radiograph. The resultant positive findings, including patients on PPV, have been incorporated into clinical guidelines(252). Whilst these studies have been useful in establishing management pathways for traumatic pneumothoraces, they do have limitations. It is difficult to translate these findings into a clinical practice where CT is becoming the first line investigation, with the majority of patients (70%) in our study having a CT scan as their initial imaging. Furthermore, the distinction between overt and occult can be misleading; whether a pneumothorax is seen on chest film, is not solely related to its size, and can be influenced by other factors, e.g. use of supine chest radiograph has decreased sensitivity (140), with 'occult' pneumothoraces in our study reaching over 80mm in size.

With this is mind we looked at the outcomes for traumatic pneumothoraces as a whole. Nearly half (46%) of the patients included were managed conservatively, with the majority of these, 252/277 (90%), not requiring subsequent invasive treatment for their pneumothorax. This included 56/62 (90%) of patients who received immediate PPV. Multivariable analysis supported that immediate or subsequent PPV did not confer an additional risk of failure of conservative

management. This is consistent with the most recent study on occult pneumothoraces, with Moore et al demonstrating a failure rate of 14% of patients on PPV managed with observation. Whilst this was higher than their 4.5% failure rate for those not on PPV, PPV was not identified as an independent predicator of failed management on multivariate analysis (133) and no patient developed tension pneumothorax related to delayed tube insertion. Smaller, earlier studies found conflicting results. Wilson et al conducted a retrospective review of a Canadian trauma registry, identifying 68 occult pneumothoraces, comparing tube thoracostomy group to a without tube thoracostomy group. Both cohorts had patients who received PPV, 83% in the tube thoracostomy group and 48% in observed group. Mortality was similar at approximately 10% in each group. Importantly, there were no instances of tension pneumothorax or pneumothorax progression requiring tube thoracostomy in the observation group, including patients who received PPV(134). Brasel et al(143) and Enderson et al (141) demonstrated a 22% (2 out of 9) and 53% (8 of 15) failure rate respectively for patients with occult pneumothoraces on PPV managed with observation. In Brasel's(143) paper, no patients developed tension and they concluded that observation was safe in these patient, whilst Enderson(141) et al, found that 3 patients developed tension and recommended tube thoracostomy for all patients requiring PPV. It is possible that this failure rates may be related the ventilated settings over 20 years ago. This has led to ongoing debate regarding the management of occult pneumothorax on PPV. The East Practice Management Guidelines (2011) on occult pneumothoraces (252) recommend that occult pneumothoraces may be observed in stable patients regardless of PPV.

The currently recruiting OPTICC trial (NCT00530725) which is randomising occult pneumothoraces on PPV between chest tube insertion in ventilated patients. The primary outcome was a composite of respiratory distress (RD) (need for urgent pleural drainage, acute/sustained increases in O2 requirements, ventilator dysynchrony, and/or charted respiratory events). An interim analysis from the OPTICC trial was published in 2013, including 90 patients, 40 were randomized to tube thoracostomy, and 50 were randomized to observation. There was no difference in mortality or ICU, ventilator, or hospital days between groups. In those observed, 20% required subsequent pleural drainage, predominantly for pleural fluid (60%). One patient (2%) in the observation group developed tension. There was a high degree of complications associated with tube thoracostomy, occurring in 15% of patients, with suboptimal tube thoracostomy position occurred in an additional 15% (253).

There were limitations in these earlier studies, particularly selection bias. In Brasel at al's study only 39 of 86 eligible patients were enrolled, with physician judgement, patient refusal, and

"enrolled but not randomized" listed reasons for exclusion. The OPTICC trial is also excluding patients if the physician believed drainage was necessary.

In my study, the size of pneumothorax was not associated with failed observation on univariate and multivariate analysis, with non-significant differences in size of pneumothorax between the successful and failed observed groups. Pneumothorax size had previously been thought to be a predictor of progression(254), with De Moya et al(251) proposing a scoring system using size of occult pneumothorax and its relationship to the hilum to guide management. However this has not been successfully validated(133), with Moore et al demonstrating that pneumothorax size was not an independent predicator of failed observation (133).

The presence of a haemothorax appears to be associated with failure of conservative management in both overt and occult pneumothoraces(133). This is consistent with clinical practice. A significant haemothorax is an indication for chest tube insertion, to evacuate blood from the pleural space and avoid complication such as infection and a fibrothorax and when combined with the presence of pneumothorax, this provides a strong incentive for intervention.

When this information is combined with previous trials on traumatic pneumothoraces it appears that there is a subpopulation that can be managed conservatively. Certainly, when there is no significant haemopneumothorax (<2cm in size) there can be consideration for expectant management. Mechanism of injury, ISS or size of pneumothorax do not appear to provide a strong indication for intervention. Additionally in our study, clinical condition did not confer an adverse prognosis, although in other studies respiratory distress has (133). Although the use of ventilation has been controversial, it appears from our findings and previous studies that pneumothoraces can be managed conservatively with careful observation on PPV with no increased risk of harm(133, 134).

This is an observational trial and as such will be subject to the inherent limitations of such a study. Selection bias may have been introduced by physician selection, and the decision to intervene may have affected the conservatively treated cohort characteristics and it is likely that the high-risk unwell patients were underrepresented in the conservatively treated arm. It is recognised that the outcomes are measuring clinical behaviour (non-protocolised management).

The 'negative' outcome of interest in our study was, treatment failure, as defined as the requirement for an invasive pleural intervention. This only occurred in 25 of the 277 patients managed conservatively. With 11 potential predictors of treatment failures, the statistical model used was underpowered to detect whether these variables could predict treatment failure, and it's possible that some of these factors are in fact valid predictors. Those treated with an

immediate intervention, despite similar ISS, likely represented a more unwell population, with higher rates of cardiorespiratory compromise, PPV use and higher mortality rates. The length of stay criteria (length of stay is 3 days or more or admitted to a High Dependency Area regardless of length of stay) is likely to have biased against patients successfully conservatively managed and not requiring a prolonged hospital admission, suggesting that the overall rate of effective conservative management is probably greater. Efforts were made to minimise bias, by including large number of consecutive unselected patients into the analysis and careful documentation and comparison of cohort characteristics.

This study represents the largest observational study on traumatic pneumothoraces to date. It demonstrates that the majority of conservatively managed patients were successfully managed without requiring a chest drain. This includes the majority of patients on positive pressure ventilation (PPV), the use of which did not present an increased risk of failure of expectant management. This study provides support for an observed, expectant approach if the treating physician does not feel an immediate chest drain is warranted in the patient with a traumatic pneumothorax. However, this is a highly selected patient group and at present there isn't strong randomised evidence to support a conservative approach over chest tube thoracostomy in ventilated patients. Future prospective randomised trials examining the outcomes of a conservative approach in traumatic pneumothorax, regardless of pneumothorax size or use of PPV would help clarify which patients are best managed expectantly. The OPTICC trial is expected to be published soon, as should be a fully powered noninferiority trial studying management of mechanically ventilated patients with occult pneumothorax.

4.2.3.   Ambulatory management

The Hi-SPEC trial is the first randomised control trial of Heimlich Valves in patients with secondary spontaneous pneumothorax. There were various challenges during the trial process with recruitment slower than anticipated. Examination of the screening log demonstrated multiple explanations for this. A proportion of patients presented out of hours when there was no delegated individual available to consent or insert the intervention. Patients with SSP are often unwell, and the screening log demonstrated that a significant proportion were felt to be too unwell to consent. Additionally, the lung in the SSP often does not collapse circumferentially and is often tethered to the chest wall. This made several patients ineligible for the trial, particularly as the protocol dictated that the two different interventions were inserted into two specific locations in the chest wall, and both options had to be feasible in order to be eligible.

The study was impeded by slow study set-up. There was an initial decision to set the principle centre (Bristol) up first for a period, to ensure the device worked safely, with additional sites set-up later. However, there was a significant delay from centres between the date the local information pack was sent out and the study green-light. The sending of the local information pack should initiate a 70-day recruitment team-frame. This delay likely reflected the pressure on local research and innovation (R&I) departments, limiting the ability for prompt site set- up. An earlier approach to sites, and an inclusion of R&I capacity in the feasibility assessment may have improved the timeliness of site set- up.

Ultimately, recruitment rate increased, aided by substantial amendments that were initiated and enhanced recruitment strategies. This included broadening the inclusion criteria to allow the pleural interventions to be inserted where the operator felt appropriate, which reflects standard practice, and enabling patients with drains already in-situ to be potentially eligible by the attachment of the Atrium Pneumostat chest drain valve.

As part of ongoing review of adverse events in the trial, it was noted that there was an imbalance in the rate of serious adverse events in the intervention arm. These SAEs were similar in nature and described either an enlarging pneumothorax or increasing subcutaneous emphysema in patients with the Rocket Pleural Vent. In these patients a conventional chest drain needed to be inserted to manage the pneumothorax, which resulted in a more prolonged admission. Feasible explanations for this were that the 8Fr cannula in the Rocket Pleural Vent was not of sufficient calibre to manage the large air-leaks that can occur with SSP, or there was increased propensity for luminal debris to collect within the vent in patients with SSP. This situation was closely monitored, and after two similar episodes occurred in January 2019, an urgent Trial Steering Committee was organised the following week.

As discussed previously, it was felt that the nature of these events raised sufficient level of concern regarding the use of the Rocket Pleural Vent in the study participants and it was agreed that use of the device be discontinued with immediate effect. However, there was consensus that the trial should continue, with the Atrium Pneumostat Valve as the sole intervention arm.

4.3.   Recruitment

Both RCTs conducted during this thesis recruited slower than anticipated. The differing trial designs posed their own unique enrolment challenges. Difficulty in recruiting to RCTs it not uncommon, with more than 50% of trials requiring a funding extension because of recruitment

issues and more than at third of trials not meeting recruitment targets(255). This leads to excessive costs, unrepresentative study samples and equivocal results due to under-recruitment. Statistically non-significant findings can increase the risk that a potentially effective interventions being abandoned prior their true value being established or lead to a delay in demonstrating their value whilst more trials are carried out(256). It has been calculated that there were as many as 10 000 unnecessary deaths in the USA due to recruitment delays to an RCT of streptokinase in acute myocardial infarctions(257).

Barriers to recruitment can be found at various levels: the patients, the recruiting clinician and team, the trial centre, the trial organisation and the trial design(258). Factors that can influence recruitment at each of these levels and can be summarised as(259):

i)   Competition for research participants (e.g. competition with similar studies);

ii)   Intersections between clinical care and research (e.g. proximity of team to clinical areas);

iii)   Patient costs and benefits (e.g. access to additional extra service resources for participants)

iv)   The clinical research team (e.g. commitment of research team to the particular study).

4.3.1.   The Hi-SPEC Trial

There were multiple barriers to recruitment identified during the Hi-SPEC trial. These were predominately regarding the intersections between clinical care and research. Physical barriers were identified, with a geographical distance between the research team and the clinical area where the patient presented. This was addressed by maintaining a presence within the A&E department, liaison with A&E research nurses and presentations at governance meetings. Time barriers, such as out of hours presentations, affected recruitment, with screening data demonstrating that patients often presented outside core working hours. Research personnel were available out of hours, however despite this there was still reduced uptake. The introduction of the option of attaching the Atrium Pneumostat valve to a pre-existing chest drain, maintained the eligibility of patients who had chest drain inserted out of hours. Resource barriers, particularly in A&E, where non-research staff have limited resources to undertake research tasks were also likely to have influenced recruitment. A&E staff were incentivised with training opportunities. Protocol barriers were considered, for example the rigid criteria for pleural intervention placement site was loosened, balancing internal and external trial validity.

4.3.2.   The REDUCE trial

The recruitment barriers for the REDUCE trial were typically at the point of consent. With more specialities involved, there was a higher probability of the responsible clinicians deciding the trial was not acceptable for the patient, i.e. lack of individual research equipoise. This was particularly true for patients with hepatic hydrothorax, where some clinicians had views on the acceptability of IPC use in this population. Conversely certain patients, particularly with heart failure found the idea of repeated aspiration less acceptable. Time was spent forming links with colleagues from different specialities (i.e. cardiology, hepatology and nephrology) and explaining the rationale of the trial and the collective research equipoise that exists. Time was also spent communicating with patients and addressing perceived patient barriers.

4.3.3.   Feasibility assessment

Recruitment for both studies was below projected figures. I have discussed various possible reasons and the measures taken to address the under-recruitment. A key element of trial design is trial feasibility, and a major aspect of this is whether the trial will be able to recruit to target. When determining feasibility, there are several factors which need to be examined. The patient population of interest must be assessed to determine how many potential patients there are with the aetiology of interest within a defined time-period. The potential patient population should be reviewed to determine whether they meet the specific trial inclusion and exclusion criteria. Furthermore, recruitment confounding factors need to be examined to determine how feasible it is to recruit this patient population, i.e. where and when do these patient present, and are there referral networks in place to facilitate recruitment.

When assessing feasibility, the acceptability of the trial to patients, clinicians and research teams needs to be determined. Other factors to consider are the availability of qualified site personnel and equipment as well as the investigator and site experience in conducting similar trials. Whilst these factors are all important when designing a trial, they are equally applicable to the feasibility assessment when assessing individual sites interest in recruiting to the study.

An in-depth study feasibility assessment would enable more accurate predictions in recruitment rates and number of sites required, enabling the use of targeted strategies to optimise recruitment. Likewise, a thorough site feasibility assessment would determine whether the anticipated recruitment figures are achievable at a given site and facilitate discussion regarding site-specific barriers to recruitment.

CHAPTER 5.   CONCLUSION

In this thesis I sought to examine the role of ambulatory management of non-malignant pleural disease. My hypothesis was ambulatory management of non-malignant pleural disease will lead to improved patient-related outcomes and shorter length of hospitalisation. The two populations of interest were patients with pleural effusions secondary to organ dysfunction (heart, liver and renal) and patients with pneumothorax secondary to underlying lung disease (secondary spontaneous pneumothorax).

I sought to answer this hypothesis in 6 studies, with a range of research methodologies. Firstly, I examined in a prospective non-randomised study the survival of patients in NMPE using time-to-event statistical analysis. This demonstrated, in the largest study of its kind, that patients with NMPE have a poor prognosis, and patients with pleural effusion secondary to heart failure demonstrating a particularly high 1-year mortality. Features associated with pleural effusion secondary to organ dysfunction, i.e. transudative and bilateral effusions, conferred a poorer prognosis. The presence of an effusion requiring aspiration in patients with heart, liver and renal failure was shown to be a marker of severe decompensated disease and ultimately poor prognosis. These findings are important as they have changed the narrative that these effusions are benign, indeed they are still commonly referred to as benign pleural effusion. This has implications on what we tell our patients and how we manage them. It supports an approach which focuses on symptom improvement and minimisation of hospital stay in these patients who have limited survival. A significant proportion of cardiac pleural effusions require repeated therapeutic procedures after their initial aspirate. This thesis has shown that 24% of cardiac pleural effusions require a further invasive procedure, which is more the double to the previously citied figure.

Management of patient with malignant effusions has moved towards an ambulatory approach to facilitate these aims, with the use of IPCs as a first line option in patients with MPE. Whilst, there have been care-series examining their use in patients with organ dysfunction, there are presently no randomised trials. As part of this PhD, I managed the REDUCE trial, facilitating the study process, initiating site-setup and trial amendments.   This randomised controlled trial was chosen to examine whether ambulatory IPC was superior to the current standard of care, repeated needle thoracentesis. The primary outcome, breathlessness as measured by VAS score, was chosen as this was felt to be the most relevant patient-related outcome. There were several challenges with

recruitment to a study which involved several different specialties and required their buy-in to enrol patients into the study. The patient cohort was typically an unwell population, and there was often a narrow recruitment window before the patients decompensated to the point where trial participation was no longer appropriate. Another barrier was a lack of individual equipoise in a proportion of clinicians involved. This was particularly apparent in patients with hepatic hydrothorax, regarding the decision to use IPCs as a bridge to transplant. Some centres, i.e. Cambridge, use IPCs so routinely as a bridge to transport that they were not prepared to consider the use of simple aspiration. A polar approach was taken by other centres, where some transplant surgeons considered IPC placement a contra-indication to transplant due to perceived infection risk. Whilst recruitment was undeniably affected by these opinions, it highlights the importance of the trial, to provide randomised control data on the use of IPCs in this population. The study has recruited 65 of the target 86 patients, and is due to be completed in August 2019. After analysis of the results, I aim to submit for publication in 2020.

In patients with pneumothorax I felt it was important to examine several aspects of the natural history and management. There is no consensus on recurrence rates in patients with PSP, with recurrence rates frequently cited between 16 and 52%, with more extreme outlying figures also published. This makes counselling about future risk difficult and creates uncertainty regarding the optimal management. To address this question, a systematic review was performed of all studies, both randomised and non-randomised, examining the recurrence rates in medically managed patients with PSP. This demonstrated, for the first time, a pooled recurrence rate of all the available literature. It demonstrates that 32% of patients will develop a recurrence, with most of the risk in the first year. Recurrence rates did not differ based on the initial intervention for PSP. Several factors were associated with a higher risk of recurrence, including female sex, lower BMI and radiological evidence of dystrophic lungs, whilst smoking cessation was associated with lower recurrence rates. With this data we can more confidently discuss recurrence rates with our patients and make more evidence-based decisions on the requirement for definitive surgical management. Furthermore, we identified factors that were associated with recurrence, such as smoking. This enable clinicians to give pragmatic advice on minimising risk of recurrence, although there was insufficient data to consider development of a risk stratification system.

The second study on pneumothorax examined outcomes of patients with a traumatic pneumothorax who were managed without invasive intervention. There is increasing interest in managing patients with pneumothorax conservatively, based on the theory that allowing the lung to re-expand without the aid of invasive management results in optimal healing of the pleural defect and lowers risk of recurrence. It is also recognised that drain insertion is not without

potential complications. There has been increasing interest in traumatic pneumothoraces, due to increased use of CT imaging identifying small 'occult' pneumothoraces that would have previously not been identified by chest x-ray, and therefor presumably have gone untreated. The aim of our study was to use a large trauma patient cohort to create a profile of consecutive patients presenting with traumatic pneumothoraces to examine the outcomes of conservatively managed patients and determine whether there are factors that can help predict whether a chest tube is required. The study, the largest of its kind, demonstrated that the majority of patients who were treated conservatively initially, were successfully managed without requiring a subsequent chest drain. This, importantly, included a high-risk group of patients that required positive pressure ventilation. It is likely that a proportion of traumatic pneumothoraces can be managed conservatively, however further randomised trials are needed to verify these findings and further delineate which patients are most suitable for this approach.

Finally, to test the hypothesis of ambulatory management in patients with pneumothorax, a randomised controlled trial design was chosen to examine whether the ambulatory Heimlich valve system was superior to the current standard of care of chest tube insertion attached to underwater seal, in patients with SSP. Recruitment was slower than expected, with challenges in recruiting patients who were acutely unwell, often presented out of hours and can be technically difficult to manage. Strategies were put in place to maximise enrolment, including an amendment that allowed an ambulatory flutter valve to be attached to a pre-existing chest drain in the intervention arm. Further challenges were noted, with reports of difficulties with the interventional device, the Rocket Pleural Vent. There were several reports of problems with the devices, centred around the device not adequately managing the air-leak, resulting in enlarging pneumothorax or subcutaneous emphysema developing. The situation was observed closely, however in January 2019, with 2 similar events occurring in the space of a week, the decision was to hold a TSC to examine the events. The ultimate decision was to discontinue use of the Rocket Pleural Vent in the trial, and to continue with Atrium Pneumostat Valve, compared to standard care. These finding suggest that the Rocket Pleural vent in its current form is not suitable for the management of SSP, either due to the greater air-leak produced, or an increased propensity of the device to block. The Hi-SPEC trial is expected the complete in June 2019, with publication in 2020.

5.1.   Overall Summary

Non-malignant pleural disease is a common cause of morbidity and mortality, with few high-quality studies available to support management. This thesis aimed by way of robust non-randomised and randomised trials to provide an evidence base to improve patient care.

It showed, in the largest study of its kind that transudative pleural effusions secondary to organ dysfunction should not be regarded as 'benign pleural effusions'. These complicated transudates are instead associated with a poor prognosis, comparable with certain malignant pleurisies. Approximately a quarter of patients with a cardiogenic pleural effusions, require further pleural procedures.   These finding have important implications for the management of these conditions where there should be an emphasis on improving quality of life, with freedom from procedures and shortening length of hospitalisations. The REDUCE trial, the first randomised control trial examining IPCs in this population, is recruiting well in a challenging study population and will guide subsequent management for these patients.

Using meta-analysis, we have determined a pooled recurrence rate of PSP, combining rates from a broad range of sources to provide a pooled overall risk. This will inform discussions with patients post pneumothorax and help determine the utility of definitive surgical treatment. Our study on conservative management of traumatic pneumothoraces provides support for an observed, expectant approach if the treating physician does not feel an immediate chest drain is warranted in the patient with a traumatic pneumothorax. Finally, the Hi-SPEC study examines the role of ambulatory management of SSP with a flutter valve. This study faced recruitment difficulties in an acutely unwell patient cohort who often need urgent management out of hours. Careful consideration has been made regarding continuation of the trial in the light of adverse events noted in the study intervention group.

Involvement in the coordination of two clinical trials has been an invaluable learning experience, with the lessons learned in trial design, management and analysis forming a platform for future academic work.

CHAPTER 6.   FUTURE DIRECTIONS

The results of the Hi-SPEC and REDUCE trials are awaited with interest and after submission of the PhD thesis I will analysis and disseminate the results. The following sections will outline potential for further research in areas addressed by this thesis.

6.1.1.   Prognostication of non-malignant pleural effusion

Whilst this thesis has demonstrated that patient with a NMPE have a poor prognosis, and certain features such as transudative and bilateral effusions are associated with a worse prognosis, we could not develop a prognostic score to predict outcomes for individual patients. With the LENT and PROMISE score we have clinical risk scores to help predict survival and guide management for patients with MPE(58, 59). Although we know that age, left atrial dilatation low systolic blood pressure, renal impairment, anaemia and certain biomarkers (CRP, CA-125 NT-proBNP) are associated with poor prognosis in patients with heart failure, we do not have a prognostic scoring system for cardiogenic pleural effusion to predict response to treatments or survival(61, 260-262). Development of a scoring system could help deliver a more personalised approach for patients with a complicated transudate.

6.1.2.   The REDUCE trial

If the REDUCE trial demonstrates that IPCs are a safe method of managing non-malignant effusions, then further work should focus on investigating how best to optimise this method. It is recognised that a proportion of patients with IPCs achieve self-pleurodesis, with 42% of patient with IPCs for cardiogenic effusions achieving spontaneous self-pleurodesis. This thesis has demonstrated that non-malignant pleural effusions have a poor prognosis, with 50% of patients with refractory cardiogenic pleural effusions dying within a year (263). As the mean duration until pleurodesis in CHF ranges from 56 to 150 days(66, 264) there is a strong incentive to achieve a more accelerated pleurodesis. There has been increased interest about how to achieve a more rapid pleurodesis effect in MPE, including instillation a talc preparation into the IPC(265). This would combine the pleurodesis effect of talc, with the outpatient management of the IPC. The IPC Plus study demonstrated the safety and efficacy using the IPC as a port to instill a talc slurry preparation in patients with malignant pleural effusions, demonstrating significantly higher rates of pleurodesis in the talc arm (43%) at day 35 compared with 23% in the placebo group, with no

difference in mortality, adverse events or days in hospital. This technique has not been investigated in patients with heart failure.

A recent retrospective cohort study of 36 patients (43 IPCs placements) with cardiogenic effusions examined 15 patients undergoing talc poudrage (Group 1) with subsequent IPC placement and 26 patients receiving only IPC placement (Group 2)(73). Pleurodesis rates were higher in Group 1, with 80% achieving pleurodesis at a median time 11.5 days, compared to a 25% pleurodesis rate at a median time of 66 days. The shorter time to pleurodesis and subsequent drain removal is likely to have reduced the risk of IPC infection, with only 2 cases of pleural infection, both in Group 2, who did not receive pleurodesis. This study suggests that treating patient with talc pleurodesis and then placing an IPC is safe; leads to increased rates of pleurodesis and is associated with decreased rates of infection.

More studies are needed to examine the use of an accelerated pleurodesis regime. I have written a draft protocol for A Randomised Controlled Trial Evaluating the Efficacy of Indwelling Pleural Catheters Plus Sclerosant in Persistent Symptomatic Pleural Effusions Secondary to Heart Failure (REDUCE 2) , examining whether the use of talc as a sclerosant in conjunction with an indwelling pleural catheter (IPC) increase the number of patients achieving successful pleurodesis in patients with CHF when compared to using an IPC alone. All enrolled patients will have an IPC inserted, and then invited back after 7 days, during which they will have community drainages. If there is no evidence of significant trapped lung, then participants will be assigned randomly (1:1) to either receive talc slurry sclerosant via the IPC, or to receive a pleural placebo instillation of 0.9% sterile saline.
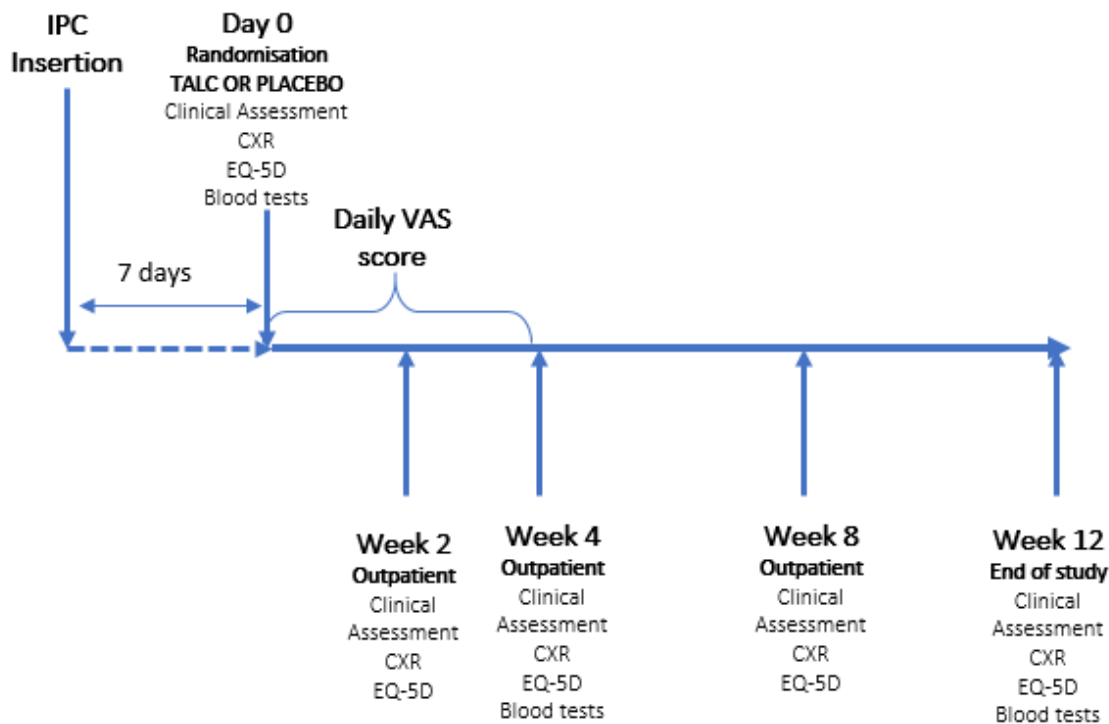
Figure 20. **REDUCE 2 study schedule**

An alternative trial design would be to compare IPCs to talc slurry pleurodesis in patients with heart failure. This study would provide needed head to head comparison between two definitive forms of treatment and is a possible future research project.

6.1.3. Conservative management of traumatic pneumothorax

The observational work on traumatic pneumothorax outlined in this thesis suggests there is a role for conservative approach in certain patients. Work needs to be carried out to determine which patient would be most suited to this approach. Additionally, a randomised clinical trial is required to established whether these observational findings are valid. The OPTICC trial (NCT00530725) is currently recruiting and randomising patients with occult pneumothoraces in mechanically ventilated patients between chest tube insertion and observation and should contribute to this evidence base.

6.1.4. Systematic review of PSP recurrence rates

The systematic review of studies examining recurrence rates in PSP was helpful in determining a pooled average recurrence rate. Whilst it identified certain factors associated with increased risk

(i.e. smoking, female gender), it was unable to create a risk model to identify risk recurrence in the individual patient. Further work needs to be done to determine if radiographic markers, such as bleb scores, or other parameters, such as air-leak data can help determine recurrence risk and help create a risk calculator, which would guide management.

6.1.5. The Hi-SPEC trial

For the Hi-SPEC trial it seems likely, due to the adverse safety signal, that the Rocket Pleural Vent is not an appropriate intervention for managing SSP. The results from the alternative ambulatory intervention, the Atrium Pneumostat, will be useful in determining a power calculation for future trials on ambulatory management of SSP. Future research could also examine whether we can characterise which patients are most suited to ambulatory management, either using radiological parameters or airflow data from digital air-leak devices. It is also increasingly recognised that conservative management is a suitable option in certain patients with PSP(165). There is little research on whether conservative management is suitable in patients with SSP.

CHAPTER 7.   PUBLICATIONS   AND CONTRIBUTIONS

The following is a list of publications that have arisen directly from, or have contributed significantly to, sections of this thesis.

Walker SP, Bibby AC, Halford P, Stadon L, White P, Maskell NA. Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis. European Respiratory Journal. 2018 Sep 1;52(3):1800864.

- SW and NAM conceived trial design. SW designed search strategy and performed meta-analysis. Data was extracted independently by two SW and PH. Risk of bias was assessed independently by SW and AB. Differences of opinion were resolved by discussion or by NAM. PW reviewed statistical analysis. SW drafted the manuscript. All authors reviewed manuscript prior to publication.

Impact: cited in Thorax Journal as an article of interest in the 'What's Hot that the other lots got'

Walker SP, Barratt SL, Thompson J, Maskell NA. Conservative Management in Traumatic Pneumothoraces: An Observational Study. Chest. 2018 Apr 1;153(4):946-53

- SW, SB, JT and NAM conceived trial design. SW collected the data and performed the statistical analysis. SW drafted the manuscript. All authors reviewed manuscript prior to publication

Impact: Nominated as one Top 10 trauma papers 2017-2018: http://www.stemlynsblog.org/top-10-trauma-papers-2017-2018-for-traumacareuk-conference-st-emlyns/

Walker SP, Morley AJ, Stadon L, De Fonseka D, Arnold DT, Medford AR, Maskell NA. Nonmalignant pleural effusions: a prospective study of 356 consecutive unselected patients. Chest. 2017 May 1;151(5):1099-105.

- SW and NAM conceived trial design. SW collected the data and performed the statistical analysis. SW drafted the manuscript. All authors reviewed manuscript prior to publication

Impact: cited in Thorax Journal as an article of interest in the 'What's Hot that the other lots got' and reviewed in NEJM Journal Watch Hospital Medicine Alert for June 5, 2017

Walker S, Maldonado F. Indwelling Pleural Catheter for Refractory Hepatic Hydrothorax: The Evidence Is Still Fluid. Chest. 2019 Feb 1;155(2):251-3.

- SW and FM conceived the article. SW drafted the initial manuscript, which was revised by the other co-authors.

Walker SP, Maskell N. Pneumothorax management—chest drain or needle aspiration?. Journal of thoracic disease. 2017 Oct;9(10):3463.

- SW and NAM conceived the article. SW drafted the initial manuscript, which was revised by the other co-authors.

Walker S, Adamali H, Bhatt N, Maskell N, Barratt SL. Pleuroparenchymal sarcoidosis-A recognised but rare manifestation of disease. Respiratory medicine case reports. 2018 Dec 31;23:110-4.

- SW, HA and SB conceived the article. SW, SB and NB drafted the initial manuscript, which was revised by the other co-authors.

Walker S, Maskell N. Identification and management of pleural effusions of multiple aetiologies. Current Opinion in Pulmonary Medicine. 2017 Jul 1;23(4):339-45.

- SW and NAM conceived the article. SW drafted the initial manuscript, which was revised by the other co-authors.

Walker S, Maskell N. Pneumothorax, ERS Monograph 2016; 74: 1–14. DOI: 10.1183/2312508X.10001116

- SW and NAM conceived the article. SW drafted the initial manuscript, which was revised by the other co-authors.

I hereby declare that the statements of contribution given above are accurate to the best of my knowledge.

Prof. Nick Maskell (Primary PhD Supervisor)

15th May 2019

CHAPTER 8.   REFERENCES

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3.   Fysh E, Thomas R, Smith N, Lee P, Kwan B, Yap E, et al. Australasian Malignant Pleural Effusion (ample) Trial: A Multicentre Randomised Study Comparing Indwelling Pleural Catheter Versus Talc Pleurodesis. Hospital. 2016;6(7):8.

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APPENDIX A: ADDITIONAL MATERIAL FOR PSP RECURRENCE META-ANALYSIS

Search Strategy for PSP Recurrence meta-analysis

MEDLINE (Ovid SP) search strategy

#1 ((pneumothor*[Title]) AND recurr*[Title/Abstract])

#2 (((pneumothor*) AND recurrence[MeSH Terms]))

#3 (pneumothorax[Title]) AND epidemiology[Title/Abstract]

#4 (#1 OR #2 OR #3)

Embase (Ovid SP) search strategy

#1 pneumothor*.ti and recurr*.ab

#2 (pnuemothor* and recurr*).ti

#3 pneumothor*.ti and recurrence.kw

#4 (pneumothor* and epidemiology).ti

#5 (1 or 2 or 3 or 4)

Data collection Sheet for PSP Recurrence meta-analysis

Name of study	
Authors	
Date	
Type of study	
Interventions	
N (PSP)	
M:F	
Excluded patients	
1st or 2nd recurrence included	

Overall recurrence	
Follow-up period (months)	
1 year recurrence	
2 year recurrence	
weight categories	
Weight Recurrence	
Gender Recurrence	
Smoking Recurrence	
Proportion Surgery	
Proportion pleurodesis	
Conservative Recurrence	
Aspiration Recurrence	
ICD Recurrence	
Ipsilateral/contralateral	

Figure 21. ***Risk of bias summary: review authors' judgements about each risk of bias item for each included study.***
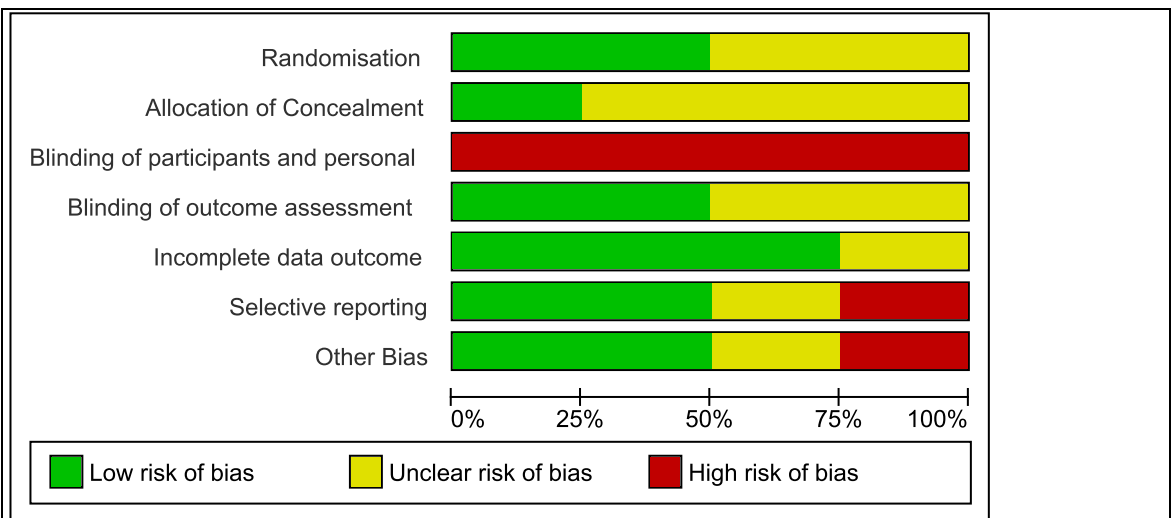
Figure 22. ***Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included study***

APPENDIX B: SITE SET UP FOR REDUCE STUDY

Eight centres were recruiting by March 2016 when I began my academic placement. A decision was made to increase. the number of recruiting centres up to 14, to increase the available pool of eligible patients. Potential sites were assessed using a feasibility form, which assessed whether the sites had used IPCs for NMPE, their views on using them for this indication, and whether the cardiologist and hepatologists would refer their patients for this procedure. Once a site was chosen as a recruitment site, the green-light process was commenced. Once the site was sent the local information pack, the site had 70 days to recruit their first patient.

Table 19 shows the sites recruiting for the REDUCE trial.

Table 19. *REDUCE trial sites*	
Site	**PI name**
North Bristol	Prof Nick Maskell
London	Dr Alex West
North Tees & Hartlepool	Dr Ben Prudon
Middlesbrough	Dr Rehan Mustafa
Oxford	Prof Najib Rahman
North Midlands	Dr Mohammed Haris
South Manchester	Dr Matt Evison
Cambridge	Dr Jurgen Herre
Ayrshire	Dr Anur Guhan
Newport	Dr Alina Ionescu
Essex, Chelmsford	Dr Keith Hattotuwa
Blackpool	Dr Adeel Ashraf

Macclesfield	Dr Thapas Nagarajan
Bath	Dr James Walters

Appendix C: Recruitment up for REDUCE study

The first patient was recruited for the REDUCE trial on the 7th April 2015. The trial is currently recruiting, with an end-recruitment date of 1st August 2019. Currently 65 patients have been recruited.

Recruitment was slower than anticipated. Screening logs demonstrated several common reasons for screen failures:

1. Patients were optimised with medical management (i.e. diuretics)

2. Patient preferred to be managed with recurrent aspirations

3. Patients were too unwell for study

In order to maximise recruitments, several strategies were implemented including two substantial amendments, in order to increase the number of patients potentially eligible. These included:

1. <u>Regular Newsletter circulated around the research team</u>

Newsletters were sent to every site, detailing current recruitment by site, overall recruitment, congratulating sites on recent participant enrolments and providing advice in a 'Top Tips' section. Initially the newsletters were sent out quarterly, then every other month from 2018. From November 2018 a newsletter was sent out with every randomisation to enhance communication.

Figure 23. *Example of REDUCE trial newsletter*

2. Investigator meetings at British Thoracic Society

An investigator meeting was held at the BTS Winter meeting 2017, to raise awareness, encourage recruitment and trouble-shoot.

Figure 24.   *BTS Winter meeting REDUCE trial update*

3. <u>Increased communication between respiratory/pleural team and cardiologists, hepatologists and nephrologists.</u>

   Regular communication was encouraged between the sub-speciality teams to facilitate identification of potential patients. This also ensures prompt medical optimisation.

4. <u>Incentivised prizes for recruiting teams at study landmarks (at 45,50,55,60,75 and 80)</u>

   A decision was made to provide incentivised prizes for recruiting team at study landmarks. These were well-received.

5. <u>Teleconferences with trial team</u>

Teleconferences were arranged with the trial teams to discuss trial issues and recruitment

6. <u>Investigating the set-up of a WhatsApp group</u>

We approached sites about joining a WhatsApp group to encourage discussion of trial issues and recruitment. Only 5 research staff entered their details on the log and there were several replies from investigators who were not receptive to the idea. One example given was 'while this is a nice idea it means that one can never separate from work so no thank you'.

7. <u>Pens distributed as aide-memoire.</u>

8. <u>Evaluated individual site targets in August 2018 to enable sites to re-set a realistic target, to incentivise recruitment.</u>

A decision was made to increase the number of sites from 9 to 14 to increase the pool of eligible patients.

The trial was extended twice:

- Recruitment extension 1: Extend trial 2 years to 01/08/2018

- Recruitment extension 2: Extend trial 1 years to 01/08/2019

Figure 25. **REDUCE Trial Cumulative Randomisations**

Figure 26. **REDUCE recruitment per site (+ screening in grey)**
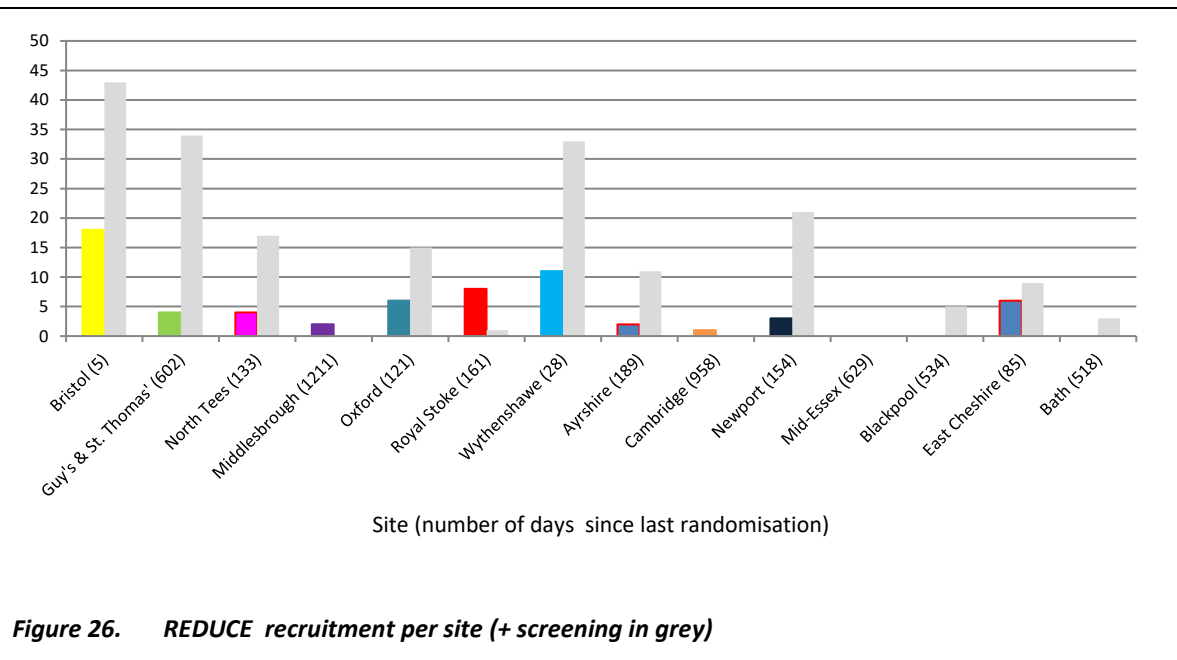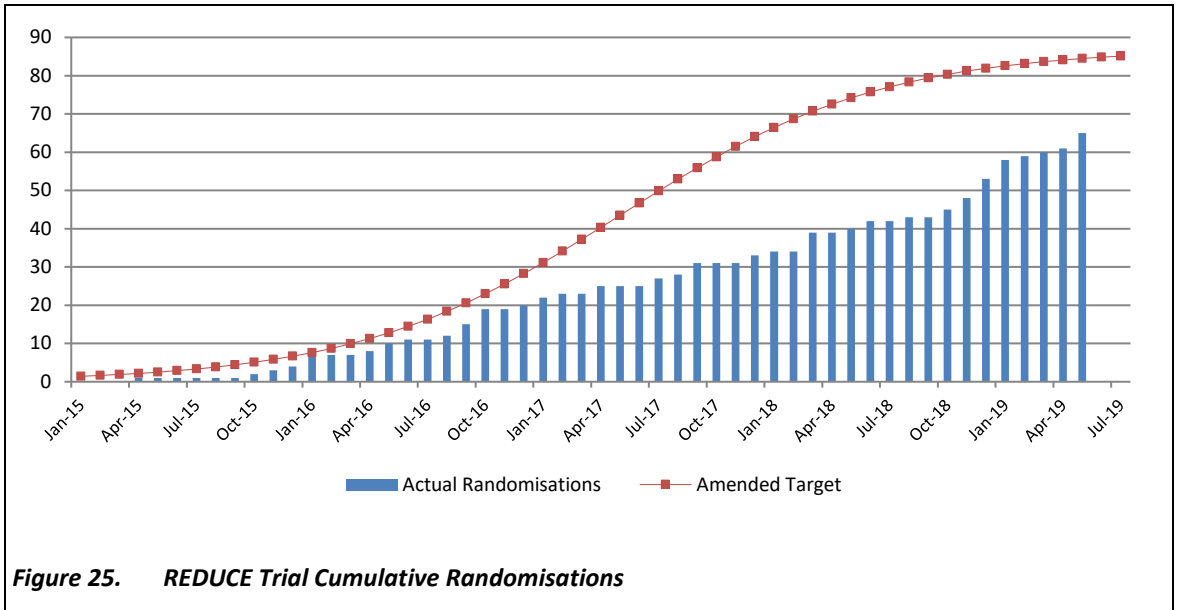
APPENDIX D: AMENDMENTS FOR REDUCE STUDY

Changes to the protocol after trial commencement

Several amendments were made to the trial protocol after initial ethical approval was granted. At discussion at the trial steering committee (TSC) on 15/1/16 a decision was made to include patients with pleural effusions secondary to renal failure. A substantial amendment, with amended protocol and associated documents, was submitted to ethics committee to allow the inclusion of pleural effusion secondary to renal failure. It was felt that including the renal subgroup of patients into the trial would help answer the question of how best to manage patients with pleural effusions secondary to renal failure and make our study more generalizable to patients with transudative effusion of differing aetiologies.

A further amendment was made to the inclusion criteria in order to address exclusion of participants with a non-malignant pleural effusion, who are currently incorrectly excluded due to a focus on Light's criteria in determining the aetiology. We proposed to include participants with pleural effusions classified as an exudate by Light's criteria, where malignancy and infection had confidently been excluded as a cause and the primary cause as assessed by the treating physician was felt to be cardiac, liver or renal failure. This reflects the well-recognised limitation of Light's criteria, when used to classify pleural effusions, which is highly weighted towards sensitivity in identifying exudative processes and suffers in sensitivity in identifying transudates. This can lead to over-diagnosis of transudative effusions as exudates in up to 20% of cases. By amending the inclusion criteria in this manner, the inclusion criteria of the trial will better reflect standard clinical practice.

The other amendments were non-substantial in nature and involved the change of primary investigators and extension to the recruitment.

Amendment Date (on IRAS)	Substantial or Non-Substantial	Amendment No	Documents Reviewed	Details of Amendment
30/09/2014	Substantial	SA1	Protocol v1.1	Secondary resarch questions added, inclusion & exclusion criteria amended, SF-36 removed, error in power calculation corrected, minimisation factors updated

			PIS v1.1`	minor spelling and formatting changes
			VAS booklet cover v1.0	original
			VAS booklet v1.0	original
			VAS for hospital FU v1.0	original
			Procedure and Drainage Record v1.0	original
			IRAS amendment form v1.0	original
11/05/2015	Substantial	SA2	Trial Summary v 1.0	original
			Contact details v 1	original
			EQ-5D-5L v 2.1	Addition of boxes to include patient ID number
			Consent form 1.1	Removal of one box for patient ID number to be consitent with rest of documentation
			Protocol v1.2	The protocol has been edited in respect of the sections on prerandomisation and randomisation to clarify to intended patient flow through the trial. We have specified that blood tests and chest radiographs do not need to be repeated if they have been performed in the 10 days prior to randomisation to minimise the number of procedures undertaken by patients in circumstances in which they can be avoided. Within the appendix, the trial schedule has been updated to provide a more comprehensive overview of data collection points.
16.07.2015	Substantial	SA3	Protocol v3.0	update version numbers
			PIS v3.0	update version numbers & include radiation risk statement
			Consent form v2.0	update version numbers
			REDUCE EQ-5D-5L v 2.0	update version numbers
21/09/2015	non-substantial	MA01	Consent v2b	change wording of NHS recrds to be applicable to Scottish systems
11/04/2016	Substantial	SA4	Protocol v4.0	add Steve Walker as trial coordinator & include renal patients
			Poster for clinicians	include renal patients
			PIS v4.0	include renal patients
			GP letter v2.0	include renal patients
			Trial Summary v2.0	include renal patients
				extend to 01/08/2018
05/12/2016	non-substantial	MA02	NA	change of PI at North Tees from Richard Harrison to Ben Prudon
13/01/2017	NA - request for HRA approval	NA	NA	request for pre-HRA Approval study to come under HRA Approval
01/06/2017	Substantial	SA05	Protocol v5.0 01/06/2017	amend the inclusion criteria in order to minimise exclusion of potential participants with a nonmalignant pleural effusion, who are currently incorrectly excluded due to a focus on the Light's criteria in determining aetiology of the effusion.
12/07/2017	non-substantial	MA03	NA	Addition of Royal Gwent Hospital, Newport and Broomfield Hospital, Chelmsford, Essex as a new site
29/09/2017	non-substantial	MA04	NA	Addition of Royal United Hospital, Bath and Macclesfield General Hospital, East Cheshire NHS Trust as a new site

30/10/2017	non-substantial	MA05	NA	Addition of Blackpool
02/03/2018	non-substantial	MA06	NA	Change the PI from Dr Said Isse to Dr Keith Hattotuwa at Broomfield Hospital, Mid Essex.
24/07/2018	non-substantial	MA07	NA	One year extension (01/08/2019)
25/06/2018	non-substantial	MA08	NA	Addition of Queen Margaret Hospital, Dunfermline as a new site
11/07/2018	non-substantial	MA09	NA	Addition of RoyalFree Hospital, London as a new site

APPENDIX E: SET-UP FOR HI-SPEC STUDY

The initial decision of 9 recruiting sites was based on a recruitment projection of 4 patients recruited per site per year. As recruitment figures were below these projections, a decision was made to increase the number of recruiting sites to 13.

Potential sites were assessed using a feasibility form, which assessed whether the sites had experience of using HV for pneumothoraces and views on their use for this indication.

Table 20 shows the sites recruiting for the Hi-SPEC trial.

Table 20. *Hi-SPEC sites*	
Site	**PI name**
Bristol	Prof. Nick Maskell
Oxford	Prof. Najib Rahman
Taunton	Dr Justin Pepperell
London (St Thomas)	Dr Alex west
Blackpool	Dr Amrithraj Bhatta
Swindon	Dr Andrew Stanton
North Midlands	Dr Nadeem Maddekar
Watford	Dr Matthew Knight
Reading	Dr Edward McKeown
Mansfield	Dr Mark Roberts
Bath	Dr James Walters
London (Royal Free)	Dr James Goldring
Fife	Dr Ian Fairburn

Once a site was chosen as a recruitment site, the green-light process was commenced. Once the site was sent the local information pack, the site had 70 days to recruit their first patient. Site set up time was highly variable, though invariably was longer than 70 days (Mean 155 days ±87), which impacted on recruitment (see table 21)

Table 21. *Hi-SPEC Site Set-up*				
Site	Date site pack sent	SIV	Green Light	Total duration
Oxford	08/10/2016	11/11/2016	16/03/2017	159
Taunton	10/11/2016	13/12/2016	03/07/2017	235
London	22/11/2016	21/11/2016	01/03/2017	99
Blackpool	18/10/2016	15/12/2016	21/02/2017	126
Swindon	11/11/2016	24/02/2017	24/02/2017	105
North Midlands	24/11/2016	19/05/2017	23/05/2017	180
West Hartfordshire (Watford)	09/07/2017	10/10/2017	11/10/2017	94
Reading	30/05/2017	02/10/2017	08/02/2018	254
King's Mill	08/03/2018	3/6/18	10/05/2018	63
Royal Free	14/03/2018	12/8/18	21/09/2018	191
Bath	12/04/2018	1/5/18	10/05/2018	28
Fife	03/04/2018	21/1/19	27/02/2019	330

APPENDIX F: Recruitment for HI-SPEC study

The first patient was recruited for the Hi-SPEC trial on the 21st March 2017. The trial is currently recruiting, with an end-recruitment date of 12th June 2019. Currently 35 patients have been recruited.

Recruitment was slower than anticipated. Screening logs demonstrated several common reasons for screen failures:

- Chest drain already inserted

- Technical (broad range): some which may be addressed by amendment

- Out of hours (these patients will often have chest drain inserted)

Table 22. *Reasons for screen failure*	
Reason for screen fail	**Strategy addressing this:**
Chest drain already inserted	Amendment to include patients with chest drain previously inserted
Technical	Amendment to remove stipulation that chest drain insertion is restricted to both second intercostal space in the mid-clavicular line and safe triangle
Not SSP	CT inclusion criteria may increase this
Out of hours	Amendment to include patients with chest drain previously inserted
Too unwell at initial presentation	Amendment to include patients with chest drain previously inserted
Patient factors	
Was not aware of patient	Amendment to include patients with chest drain previously inserted

Other strategies to encourage recruitment included:

- Regular Newsletter circulated around the research team

- Teleconferences with trial team

- Pens distributed as aide-memoire.

- Implementation of training sessions to each site

- Investigator meetings at British Thoracic Society

A decision was made to increase the number of sites from 9 to 14 to increase the pool of eligible patients.

The trial was extended once:

- Recruitment extension 1: Extend trial 2 years to 12/06/2018 to 12/6/19

Overall recruitment is displayed in figure 27, with recruitment per site displayed in figure 28.

Figure 27.   Hi-SPEC Recruitment graph

Figure 28. *Hi-SPEC recruitment per site*
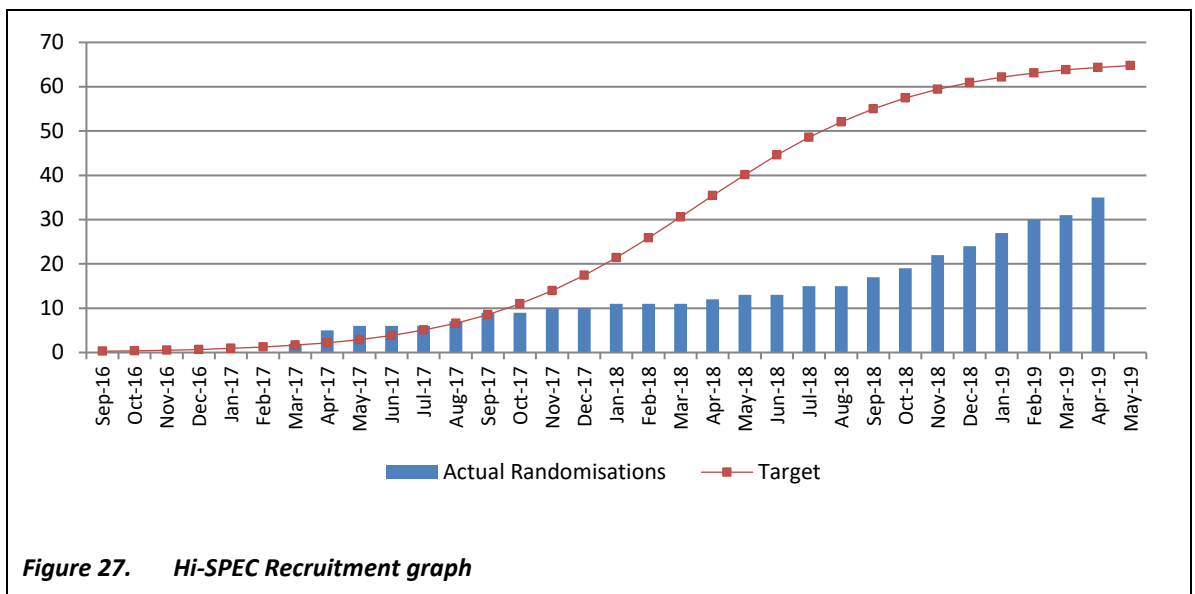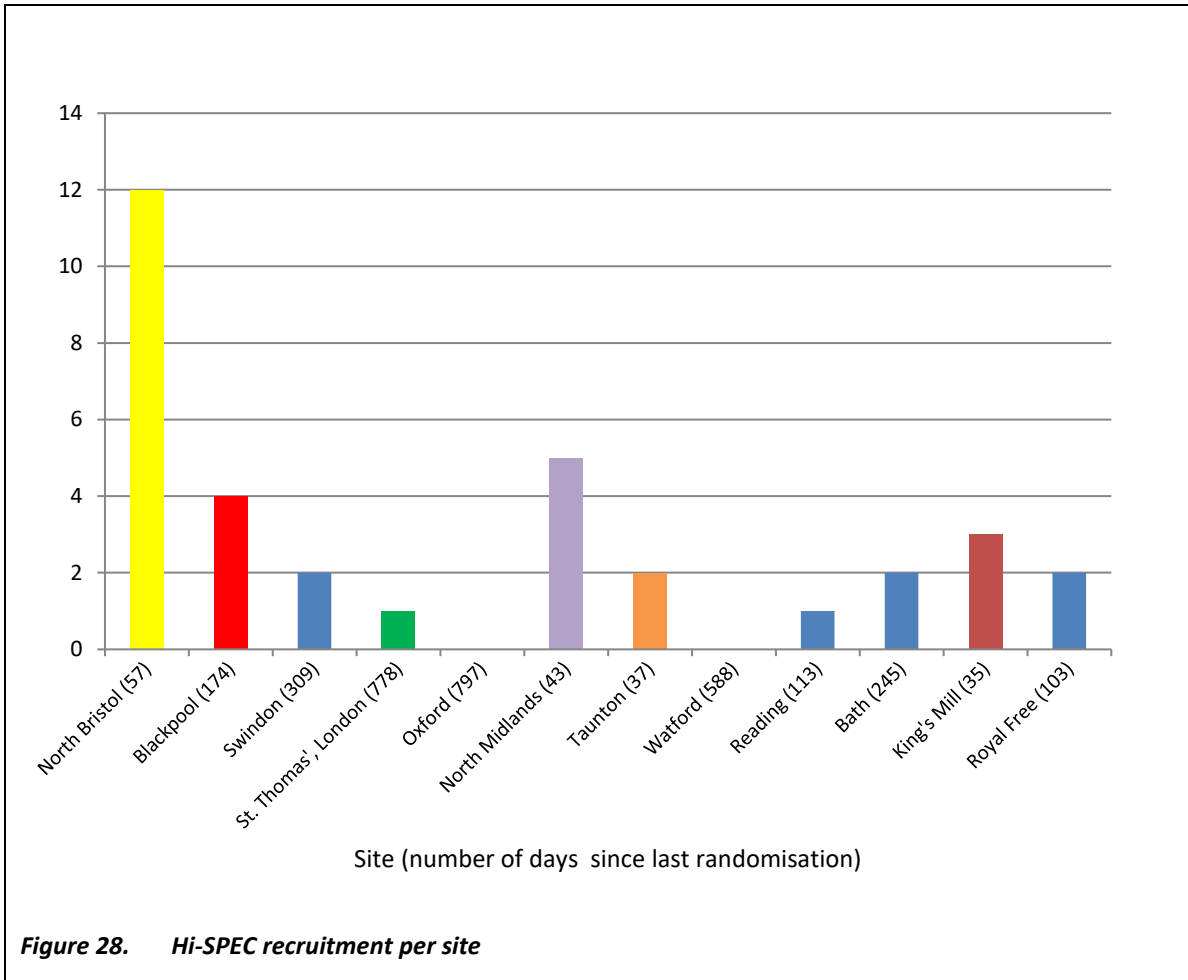
APPENDIX G: AMENDMENTS FOR HI-SPEC STUDY

Several amendments were made to the trial protocol after initial ethical approval was made. The reference of '> 20 pack years' was removed from inclusion criteria, as this was deemed arbitrary and not reflective of BTS guidelines. The exclusion criteria were amended to only exclude patients with significant hydropneumothorax or haemopneumothorax (≥25 lung field), as it was recognised that a third of patients with a pneumothorax will develop a small effusion secondary to blood from bleb rupture. A secondary research question was added and corresponding outcome measure to ascertain whether Heimlich valves lead to a shorter duration of admission until patient is deemed medically fit for discharge, to determine if factors independent of pneumothorax confounded length of stay.

After a trial steering committee on 27th September 2017, slow recruitment was identified as an issue. Screening data was interrogated to identify reasons for screen fails (see Table 23). The commonest reason for screen fail was a drain was already in-situ, typically inserted out of hours or due to an emergency. It was also recognised that patient population was sufficient with 89 SSP identified in 1 year. During discussions regarding how to address this, an amendment was proposed to allow the attachment of a Heimlich valve device i.e. the Atrium Pneumostat chest drain valve, to the end of a previously inserted chest drain. We felt the introduction of the Heimlich valve chest drain (HVCD) would improve the trial in various aspects. As a pneumothorax is a potential medical emergency, a chest drain is frequently inserted as a matter of urgency, and there is therefore limited consent to an interventional trial. Allowing the option of randomising patients after chest drain insertion will enable us to recruit in a more controlled environment. Secondly, the Pneumostat valve is widely used throughout the UK, and by including its use in the intervention arm, we will be increasing the generalisability of the study, and ensuring the trial is evaluating use of Heimlich valves in secondary spontaneous pneumothorax in general, as opposed to with only one device.

To facilitate this amendment, changes were made to protocol, PIS, discharge letter and trial summary. The inclusion criteria were also broadened to extend the definition of secondary spontaneous pneumothorax, to include evidence of smoking-related emphysema on CT scan as part of the definition of secondary spontaneous pneumothorax to ensure we were able to recruit patients with undiagnosed emphysema. The inclusion criteria 4) 'Chest drain insertion possible at both 2nd intercostal space in the mid-clavicular line and the mid axillary line (safe triangle)' was

also removed to be in line with clinical practice and British Thoracic Society (BTS) guidance and replaced with 'Chest drain insertion indicated and technically possible for treatment of pneumothorax according to current BTS guidelines'.

Table 23. *Screen fails for Hi-SPEC trial*	
Reason for screen fail	**N**
Chest drain already inserted (out of hours presentation)	18
Chest drain already inserted (missed)	15
Technical	15
Not SSP	16
Too unwell	6
Patient factors	4
Not documented	5
Total screened	**92**

The Trial Management Team held a Trial Steering Committee on 5th February 2019 in light of 7 adverse events associated with the Rocket Pleural Vent, two of which occurred in the previous week. All events were expected events and related to the device either blocking or becoming dislodged and the majority of patients subsequently had a chest drain inserted. There were no concerns regarding the Atrium Pneumostat. Various options were discussed, including stopping the trial completely based on safety to participants; continuing the trial in its current form with advice on increasing number of flushes; or thirdly continuing the trial with only the Atrium Pneumostat Valve available in the ambulatory arm. Ultimately, it was agreed that the nature of these events raised sufficient level of concern regarding the use of the Rocket Pleural Vent in the study participants and that continued use of the device was not recommended. However, the consensus was that the trial should continue with the Atrium Pneumostat Valve as the sole intervention arm. This would address safety concerns, as the trial would no longer be using the Rocket Pleural vent, and would enable the trial to continue evaluating ambulatory management of SSP. This change would also have the additional benefit of increasing the number of trial participants receiving the Atrium Pneumostat and might inform on future trials.

An urgent safety notification was sent to the trial teams on the 7th February 2019, and substantial amendments were made, removing the option of the Rocket Pleural Vent from the intervention arm, and instead limiting management to the Atrium Pneumostat chest drain valve. To facilitate this the protocol, PIS, consent form, discharge letter and trial summary were amended.

A table of all the amendments made during the Hi-SPEC trial is displayed in the Appendix C.

Amendment Date (on IRAS)	Substantial or Non-Substantial	Amendment No	Category	Documents Reviewed	Details of Amendment
21/09/2016	Minor	1	B (20/10/2016)	NA	Addition of Taunton, Swindon & London
24/10/2016	Substantial	1	A (02/12/2016)	Protocol v3.0 24/10/2016 Patient booklet v1.0 13/10/2016 Trial Summary v2.0 01/09/2016	Trial questionnaires combined into booklet QoL measurments clarified in text as illustrated in appendix 2 contact details for SAE reporting Blackpool added as a site
13/01/2017	Minor	2	C (18/01/2017)	Patient booklet v1.1 13/01/2017	wording error corrected
05/04/2017	Substantial	2	A (13/06/2017)	Protocol v4.0 05/04/2017	remove reference of '> 20 pack years' from inclusion criteria 2 exclusion criteria 5: only exclude significant hydropneumothorax or haemopneumothorax (≥25 lung field) add a secondary research question and corresponding outcome measure to ascertain whether Heimlich valves lead to a shorter duration of admission until patient classified medically fit for discharge
18/05/2017	Minor	3	B (23/05/2017)	CV and GCP for PI at Stoke	change of PI at Stoke
16/06/2017	Minor	4	NA	NA	Addition of Watford General Hospital and Royal Berkshire Hospital
14/08/2017	Minor	5	Category B	NA	Change of PI from Patricia Yunger to Matthew Knight at Watford General Hospital
19/12/2017	Substantial	3	Category A	Protocol v5.0 with tracked changes Hi-SPEC discharge letter v2 0 19/12/2017 – trackedHi-SPEC Trial Summary v3.0 19/12/2017 – tracked Hi-SPEC_Patient_Information_Sheet_v3 0 19/12/17 - tracked	Added another Heimlich valve to allow patients with a drain already inserted (within the previous 36 hours) to participate Secondary spontaneous pneumothorax defined can also be defined by evidence of smoking-related emphysema on CT scan Removed Chest drain insertion possible at both 2nd intercostal space in the mid-clavicular line and the mid axillary line (safe triangle) Approval for up to 14 sites Extention of recruitment end date to 12/06/2019
20/03/2018	Minor	6		NA	Addition of Royal United Hospital, Bath; King's Mill Hospital, Mansfield and Royal Free Hospital, London as new sites to Hi-SPEC trial.

01/04/2018	Minor	7	C (17/04/2018)	Consent form v2.0 06/02/2018	Updated consent to v2.0 in line with PIS v3.0
25/06/2018	Minor	8	NA	NA	Addition of Queen Margaret Hospital, Dunfermline as new site to Hi-SPEC trial.
11//7/18	minor	9	NA	NA	Addition of Royal Free london as new site
14/01/2019	minor	10	Category B	NA	Change of PI at Swindon
05/02/2019	Substantial	4		Cover letter to REC Protocol v6.0 Patient Information sheet v4.0 Trial Summary v4.0 Discharge letter v3.0	Removing the use of the Rocket Pleural vent for the remainder of the study in relation to an urgent safety measure prompted by a high ocurrance of Aes of issues with the vent becoming blocked or dislodged.