Which factors predict early discontinuation of antifibrotics in idiopathic pulmonary fibrosis?

By

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Abstract

Introduction

Pirfenidone and nintedanib are recommended in idiopathic pulmonary fibrosis (IPF). Randomised controlled trials have shown discontinuation rates of 14-33%; clinical audit in our regional centre showed a rate of 18.4%. I aimed to establish the main factors, which predict early discontinuation of antifibrotics using a mixed methodology approach.

Methods

I collected data on 170 patients with IPF (2012-16) prescribed pirfenidone (n=139) or nintedanib (n=31). Retrospective data was collected including demographics, social factors, diagnostics, antifibrotic prescribed, treatment duration and side-effects. We undertook focus groups and patient interviews, which were analysed thematically.

Results

Commonest side-effects were nausea/vomiting (50%) and appetite loss (40%; pirfenidone) and diarrhoea (79%) and weight loss (25%; nintedanib). DL_{CO} ≤40% (OR=2.46) increased risk of early discontinuation at 30-days, with males (OR=0.41) and skin side-effects (OR=0.09) associated with reduced risk. At 90-days, deconditioning side effects (OR=2.58) increased risk of early discontinuation, whereas males (OR=0.39) and gastrointestinal side effects (OR=0.40) reduced risk. Thematic analysis suggested side-effects were tolerable and social factors were not considered barriers by patients.

Conclusion

Female gender and DL_{CO} ≤40% were predictors of early discontinuation, compared with social factors. Low DL_{CO} has been shown to predict increased mortality therefore progressive disease would increase risk of early discontinuation.

Dedication

This work is dedicated to my parents.

To my mother who has shown unconditional love and dedication to my happiness however frustrated and moody I may be.

And to my father, who continues to push me in every aspect of my life and inspire me to be the best that I can be. Both graduates of the University of Birmingham, it's in his footsteps I aim to follow.

Finally, to my wife Jaskiren, who is my love, support and strength. We continue to strive through life together.

Acknowledgements

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I would also like to thank Professor Sherwood Burge, Sister Geraldine Burge, Sister Helen Alldrick, Timothy Smith and all other staff at the Birmingham Chest Clinic for their accommodating nature and expertise, which helped to complete this thesis. To all the patients at the Birmingham Chest Clinic and at the IPF support group who took time out of their day to participate in interviews and focus groups.

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1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease of unknown cause. Traditionally referred to as Cryptogenic Fibrosing Alveolitis (CFA), it represents a clear disease entity characterised by Usual Interstitial Pneumonitis (UIP) found either on radiology or histopathology (1). It is a relentlessly progressive condition with variable natural history and an average prognosis of 3-5 years from diagnosis, with only 20% of patients surviving longer than 5 years (2).

1.1 Presenting features of IPF

Common symptoms of IPF consist of exertional breathlessness and cough, which is mostly non-productive. Examination is likely to reveal bibasilar inspiratory crackles and finger clubbing. The incidence of IPF increases with age, with the majority of patients diagnosed in their 60's and 70's and men tend to be more affected than women.

IPF is characterised by the appearance of UIP on High Resolution Computed Tomography (HRCT) or surgical lung biopsy (SLB). A clear history from an Interstitial Lung Disease (ILD) specialist is required to rule out other causes of ILD such as connective tissue disease, occupational, environmental and drug related. Characteristic radiological UIP pattern is shown by evidence of subpleural reticulation with a basal predominance, traction bronchiectasis and honeycombing.

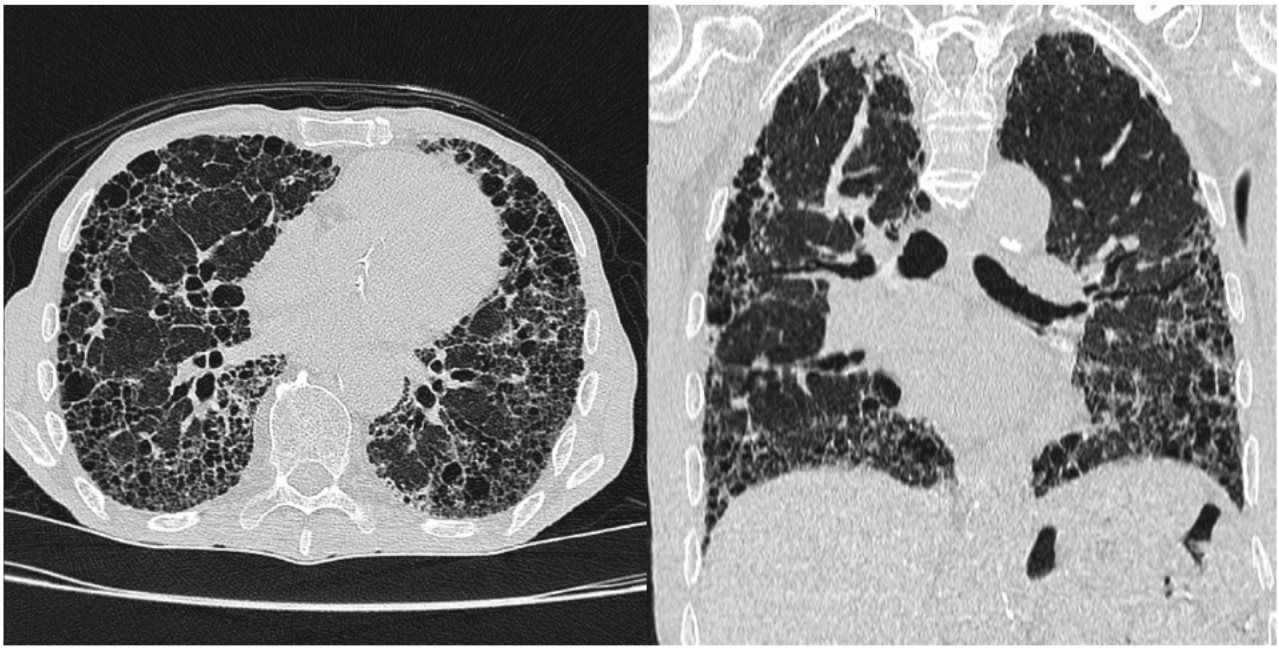

Figure 1-1 Typical case of Usual Interstitial Pneumonitis with sub-pleural reticulation with a basal predominance, traction bronchiectasis and honeycombing. Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 33436.

HRCT has been shown to have a positive predictive value of between 90-100% of diagnosing UIP and therefore in a change from the original American Thoracic Society/European Respiratory Society (ATS/ERS) statement, surgical biopsy is no longer required for a definitive diagnosis in those who have a typical HRCT appearance (Figure 1-1) (1).

With regards to exclusion of other causes of ILD, a careful history and examination is required to exclude asbestos or historical inhaled antigenic exposure (as in hypersensitivity pneumonitis (HP)). Autoimmune serology and specific IgG testing has been recommended for ruling out connective tissue disease and HP (3). Recommendations are made in the ATS/ERS statement that particular care is taken to search for causes of chronic hypersensitivity pneumonitis as it may mimic IPF (4). Bronchoalveolar lavage (BAL) is advocated for investigation of other causes of ILD, particularly chronic HP, where >40% lymphocytes in the BAL would increase the likelihood of an alternative diagnosis. It can also be useful when the HRCT is not typical of UIP. However, at present, it is not clear whether the use of BAL and differential cell count aids in the diagnosis of IPF. BAL has not been

mentioned in the ERS/ATS guidelines as a requirement in the diagnosis of IPF, but other organisations such as Tzilas et al in Greece advocate the use of BAL as an important diagnostic tool in other diseases too (connective tissue associated ILD, fibrotic Non Specific Interstitial Pneumonitis (NSIP)) (5).

Those patients with an HRCT that does not show honeycombing (classed as 'possible' UIP) or where the HRCT does not show UIP, may go onto surgical lung biopsy, performed either by open or video assisted thoracoscopic (VATS) access. Typical features of UIP on the surgical lung biopsy include a heterogeneous appearance at low magnification with fibrosis and honeycombing mixed with normal lung. Fibrosis is usually characterised by dense collagen and fibroblastic foci. Figure 1-2, which is from the review paper by Tolle et al., shows the typical features of definite UIP (6).

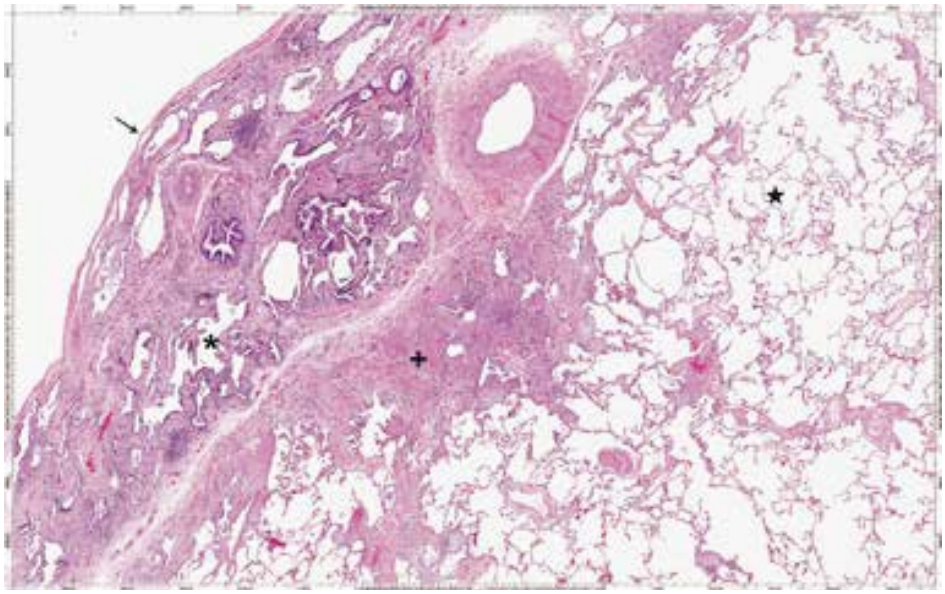

Figure 1-2 Histological slide showing definite pattern of UIP with dense fibrosis (plus sign) and honeycomb change (star sign) next to the pleural surface (arrow). Figure from Tolle et al review paper on IPF (6).

Pulmonary function testing in IPF shows a restrictive pattern. There is roughly equal reduction of both Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC), with an FEV_1/FVC ratio of more than 0.7. Gas transfer is also significantly affected and by definition there is reduction in the Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO}). With regards to prediction of prognosis and disease staging, FVC currently is of unclear value, whereas the value of DL_{CO} less than

40% has shown to have an increased risk of mortality (4, 7, 8). Longitudinal measurements of FVC however and rate of decline over 6 to 12 months has been associated with decreased survival (7-10). This is important as currently the criteria for treatment with antifibrotics in the United Kingdom are based on FVC level. There are composite scores such as the Composite Physiologic Index (CPI), which take into account FEV_1, FVC and DL_{CO} that are available for use. This has shown to predict mortality more accurately compared to individual lung function testing, but as of yet have not been used in any prospective clinical trials with treatment (11).

1.2 Diagnosing IPF

In 2015 the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) statement clearly outlined the criteria required for making a diagnosis of IPF in patients with ILD (1). The diagnostic criteria put forward are as follows:

1. Exclusion of other known causes of ILD, such as occupational or environmental exposures, drugs and connective tissue disease.
2. Presence of UIP either on HRCT or surgical lung biopsy.

They state that the accuracy of diagnosis increases with a multidisciplinary approach between Respiratory Physicians, Radiologists and Histopathologists with an expertise in ILD. The current ILD service at University Hospitals Birmingham Foundation Trust (Heartlands, Good Hope, Solihull Sites) (UHB (HGS)) is set up to have a monthly ILD Multidisciplinary Team (MDT) meeting to discuss cases and aid in diagnosis and further management. This is usually attended by core members as written above, but also by the ILD specialist nurses who are involved in early instigation of antifibrotic drugs and symptom management. Research teams are also present to help identify patients that could be approached for recruitment into future studies. Due to the value of an MDT with a specialist interest in ILD to help rule out other causes and aid in the diagnosis of IPF, healthcare systems where an ILD MDT is not available should refer their patients to their nearest ILD specialist service. This is the case

with the UHB (HGS) ILD service, which acts as a Hub and Spoke model taking referrals throughout the West Midlands, including Herefordshire. Figure 1-3 shows the catchment area of the UHB (HGS) tertiary ILD service.

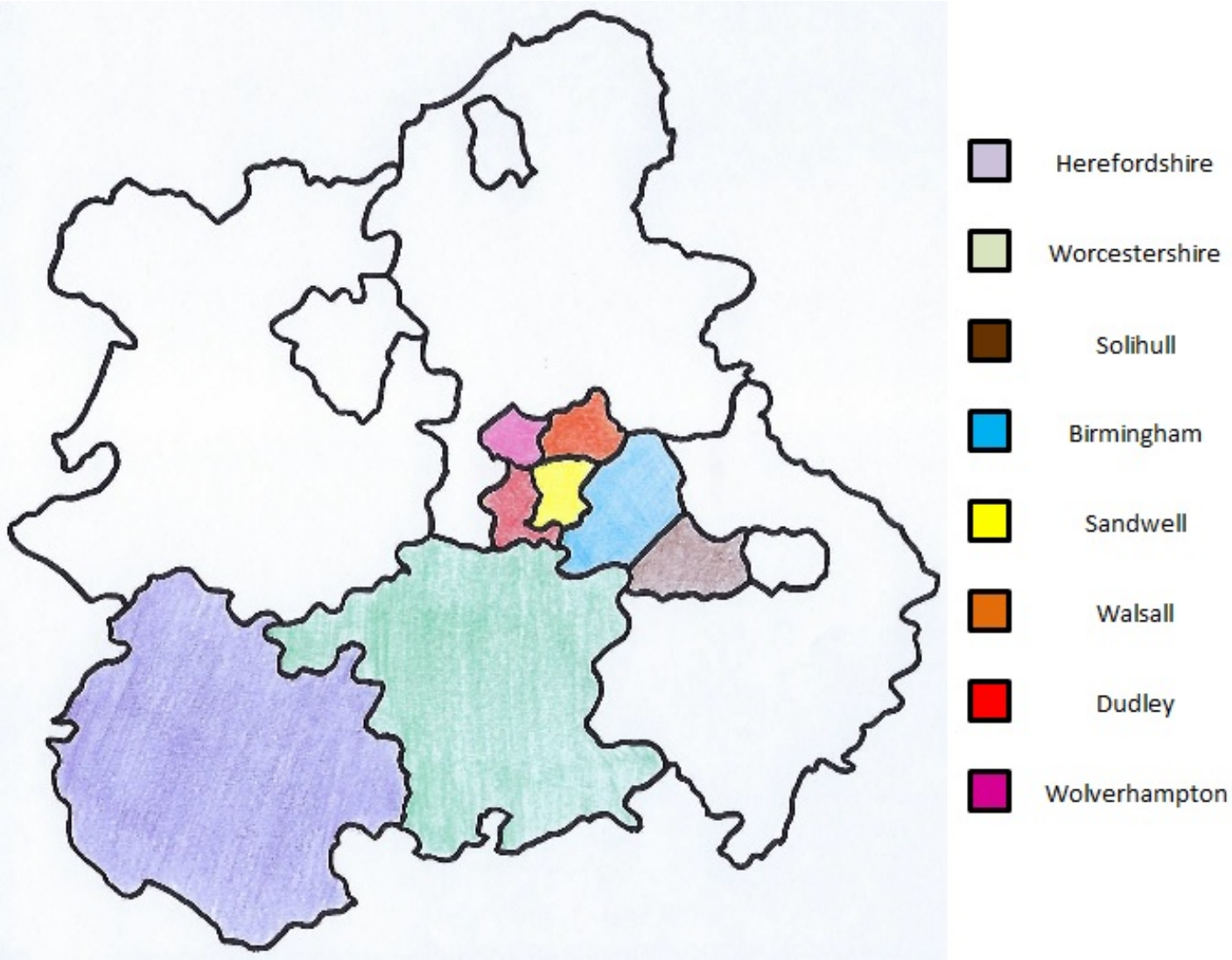

Figure 1-3 Figure to show the catchment area of UHB (HGS) ILD service. Shown are the counties that will refer patients to the tertiary ILD service at UHB (HGS) in the West Midlands.

1.3 Management of IPF

Current management of IPF can be divided into pharmacological and non-pharmacological treatments. Pharmacological treatments currently available consist of the antifibrotics, Pirfenidone and Nintedanib (1). Currently, the prescription of antifibrotics in the United Kingdom (UK) is only

available to patients with an MDT diagnosis of IPF and an FVC between 50 and 80% (12, 13). Non pharmacological therapies that are strongly advocated include long term and ambulatory oxygen therapy in those with clinically significant resting hypoxia and lung transplantation (2, 4). The recommendation for long term oxygen therapy in those with resting hypoxaemia has been taken from low quality evidence and draws on conclusions in studies of long term oxygen therapy in obstructive airways diseases. Additionally, there are weak recommendations such as the use of pulmonary rehabilitation, corticosteroid therapy in acute exacerbations and treating asymptomatic gastroesophageal reflux. Lee et al. looked at two hundred and forty two patients from the placebo arms of three IPFnet randomised control trials (14-16) and showed that in the 51% of patients taking anti acid therapy there was a slower decline of FVC (0.07 litres difference between the two groups at 30 weeks (95% CI 0.00, 0.14)) compared with those not taking anti acid therapy leading to the conclusion that gastro-oesophageal reflux (GORD) contributes to disease progression and these patients may benefit from anti acid therapy (14). Pulmonary rehabilitation has been shown to significantly increase the exercise tolerance and quality of life; Vainshelboim et al showed a significant increase in exercise tolerance, functional capacity, dyspnoea and quality of life in their study with albeit small numbers of 32 patients with IPF (17). These results are mirrored in the paper by Holland et. al (18) demonstrating significant improvements in physiological and quality of life measures, but also showed that these were not sustained 6 months following intervention. A systematic review showed that mechanical ventilation in IPF patients reported a high mortality of 87% of 135 reported cases, which has led to the statement recommending only a minority of patients with IPF receiving mechanical ventilation (19). The statement stresses that this decision is best made by the clinician after discussion with the patient and their caregivers. In some situations, mechanical ventilation may be used as a bridge to transplant (4). The non-pharmacological treatment guidelines stated above are also mirrored in the National Institute for Health and Care Excellence (NICE) guidelines for IPF in the UK (2).

Given that at present, idiopathic pulmonary fibrosis has no cure; treatment of the condition takes a holistic approach. There is a multi-disciplinary approach to management with focus being on prolonging survival, maintaining a good quality of life and slowing disease progression. This is demonstrated visually in Figure 1-4, which is adapted from Raghu et al.'s review paper in 2017 and does well to show that although antifibrotics are currently the hot topic, there is a whole host of other management issues that need to be addressed for optimum patient care (20), including good palliative care, transplantation and patient education.

Figure 1-4 Multidisciplinary approach to IPF management. GORD – Gastro-oesophageal reflux disease. IHD – Ischaemic heart disease. COPD – Chronic obstructive pulmonary disease. SBOT – Short burst oxygen therapy. LTOT – Long term oxygen therapy. Adapted from review paper Raghu et al 2017.

Emotional support of patients with IPF is quickly becoming recognised as a major factor in the optimum management of these patients. The gold standard locally is a system where the patient diagnosed with IPF is introduced to an ILD nurse, who will be their first point of contact in many instances. This will not only be to do with pharmacological management (and management of complications/side effects etc.), but also with symptomatic management and to facilitate continued care in the community. This support and continued education system is also extended towards support groups run by the ILD nurses and relatives of ILD patients, along with the patients themselves, which ties into the emotional support offered by the service. There have been qualitative studies examining the feelings and perceptions of patients with IPF towards the disease. Post diagnosis there have been three separate phases identified; coming to terms with the diagnosis, reactive coping (acceptance) and proactive coping (ownership of condition), all of which require separate emotional support (21). UHB (HGS) has set up support groups for IPF patients to aid them through the initial phases of diagnosis and starting treatment with antifibrotics. Locally it is felt that this group will help patients to understand their condition better and cope with the initial side effects of antifibrotics.

Education of healthcare providers is still lacking in IPF, such that referral to a tertiary centre such as UHB (HGS) can be delayed by dismissal of symptoms and lack of knowledge of disease. The delay in referral then leads to patients who have further advanced disease, more co-morbidities and are potentially frailer than those referred earlier, which could lead to delay in starting antifibrotics or deterioration to the point where they are out of the 50-80% range currently set by UK NICE guidelines. It could also be a factor in increasing the risk of early discontinuation with patients being much further along in the disease process than seen in the clinical trials as shown in section 1.4. In a qualitative study in the European Union (EU), 58% of cases had protracted diagnosis due to dismissal of symptoms and misdiagnosis (22). This evidence is compounded by a more recent American survey, conducted by Cosgrove et al. who used an online survey to obtain information on time frames between initial symptoms and first physician assessment, initial symptoms and referral to a

specialist centre, initial symptoms and diagnosis, type and number of diagnostic tests and misdiagnoses (23). The first point to consider is the insidious onset of symptoms for IPF, which the patient may not realise the importance of when compared to an acute illness; in this survey the median time to initial assessment from start of symptoms was 3 months. 72% of the respondents put the delay down to perceptions of their symptoms as part of the aging process. Initial symptoms most commonly consisted of shortness of breath, cough and fatigue. 89% of patients saw their primary care physician initially and perhaps the most striking result here is that 30.4% reported that they had 4 or more visits to the primary care physician before referral to a specialist. Compounded by this was the misdiagnosis rate, with 55% reporting 1 or more misdiagnosis and 38% reporting 2 or more. The median time frame from initial symptoms to final diagnosis was 7 months. Astonishingly only 34.7% of patients had their diagnosis made by a recognised ILD centre, but 68% of patients felt that consulting a specialist with expertise in ILD was the most important contributory factor in obtaining a diagnosis. Needless to say with the misdiagnoses, there were treatments instigated such as corticosteroids, which have been shown to be detrimental in IPF and the use of which is currently strongly recommended against (1).

Whilst these findings show that although knowledge and expertise around IPF is currently improving, there is still a fair way to go to increase the awareness of the disease in primary care and even amongst general physicians to prompt early referral to a specialist ILD centre with expertise in diagnosing IPF. Shortening this delay will likely help the patient start on antifibrotics earlier in their disease process, which may prolong life expectancy and perhaps reduce the risk of early discontinuation from treatment.

1.4 Clinical Trials in IPF

Previous management of IPF was largely supportive with prognosis being rapid and poor. ‘Triple therapy’, which was a combination of three drugs; namely: Azathioprine, Prednisolone and N-Acetylcysteine were originally thought to be beneficial in IPF (24). The PANTHER trial showed that triple therapy was actually increasing mortality compared to placebo and the pathophysiology of IPF

had to be revisited (16). This then paved the way for the discovery of the antifibrotics, Pirfenidone and Nintedanib.

1.4.1 Pirfenidone

A placebo controlled, double blind, randomised control trial was conducted in Japan in 2004 looking at the use of pirfenidone for treatment of IPF (25). Although their primary endpoint was the change in oxygen saturations (SpO_2) during a 6 minute steady state exercise test, the study was terminated early due to an increased number of exacerbations in the placebo group compared to the pirfenidone group. In relation to the studies reported in this thesis, there were a number of adverse events (AE's), which were significantly different in the pirfenidone group compared to the placebo group, which included photosensitivity, stomach discomfort, anorexia, nausea and fatigue. Study drug discontinuation in the pirfenidone group was caused by adverse events in 11 of the patients (15%), namely photosensitivity (most commonly), vomiting, fever, abnormality of liver function, dizziness, facial paralysis and hepatoma compared with headache and bradycardia in the placebo group. A pre-specified reduction in dosing was used to deal with adverse events. Approximately half of the patients managed to tolerate the full dose of 1800mg/day and of those who could not tolerate the full dose, half were able to tolerate the reduced dose of 1200mg/day.

A follow on phase III trial conducted in Japan looked at the effect of two doses of Pirfenidone (1800mg and 1200mg per day) on a primary endpoint of change in Vital Capacity (VC) over 12 months. They showed significantly less decline in VC compared with placebo in both high dose and low dose groups (26). With regards to adverse events, the most common in the Pirfenidone group included photosensitivity, anorexia, dizziness, asteatotic eczema, abdominal discomfort and reduction in white cell count. Of the 86 out of 267 total patients that discontinued the study medication, 40 were in the high dose group and 15 in the low dose group. 15 out of 40 in the high dose and 9 out of 15 in the low dose discontinued due to adverse events, excluding acute exacerbations or progression of disease. The authors commented that most of the adverse events disappeared with a decrease in the dose or temporary holding of the medication, which agrees with

previous phase II studies conducted by Azuma et al. Around 50% of patients in both high and low dose groups suffered with photosensitivity, however, only 5 of these discontinued the drug because of this. The conclusions drawn from this therefore state that Pirfenidone was well tolerated in this study. However, limitations of this study include the change in primary endpoint from lowest oxygen saturation (SpO_2) during 6 minute walk test (6MWT) to the change in VC over 12 months, which was due to the lack of validation of the use of 6MWT as a predictor of mortality in IPF. Selection bias therefore plays a role here with the patients being enrolled in the study needing to be able to complete the 6MWT at baseline resulting in a cohort of patients with mild functional impairment. It is therefore not possible to extrapolate the tolerability of Pirfenidone to current practice of patients who may have increased frailty and co-morbidities affecting their ability to cope with the significant side effects.

Following on from this were the results of two further multinational phase 3 trials across northern America and Europe. The CAPACITY trials (004 and 006) by Noble et al. showed a pirfenidone treatment effect on the change in percentage predicted FVC at 72 weeks and at earlier time points before (27). In trial 004 at week 72, the mean FVC change in the pirfenidone group was -8.0% compared with -12.4% in the placebo group. The change in FVC was significant in the first trial (004), but not in the second (006). There was also a treatment effect vs placebo in progression free survival time and categorical FVC change. One of the studies, CAPACITY 004 demonstrated a dose response relationship with testing of FVC change in both high dose (2403mg per day) and low dose (1197mg per day) groups. 15% of patients in the pooled pirfenidone group from both studies discontinued due to adverse events, of which the most common event was IPF itself with other notable groups including rash and nausea. The inclusion criteria required an FVC threshold of at least 50%, which is comparable to current National Health Service (NHS) prescribing guidelines in the UK and either FVC or DL_{CO} of 90% or less. The latter point here demonstrates that although one measure of lung function may be in the range of current UK guidelines for prescribing pirfenidone (FVC between 50-80%), there is still the possibility of inclusion of patients in the study with mild functional

impairment, which again may correlate with less frailty, disease burden and increased ability to cope with side effects.

To further validate the use of pirfenidone, another phase three clinical trial was requested to support the results of the CAPACITY study. The ASCEND study by King et al. went on to show that treatment with pirfenidone over a period of 52 weeks significantly reduced the rate of FVC decline (primary endpoint), 6MWT distance and progression free survival (28). There was a 47.9% relative reduction in the proportion of patients who had an absolute decline of 10% in FVC in the pirfenidone group compared to the placebo group. In this study, they also pooled the data from the three trials and significantly showed a reduction in the all cause and IPF related deaths. Discontinuation of study treatment due to adverse events occurred in 14.4% of patients in the pirfenidone group with the most common reason being the worsening of IPF, deranged liver function, pneumonia, rash and weight loss. The paper does mention that gastrointestinal (GI) and skin related adverse events were the most common in those that did suffer, but only around 2-3% of patients would drop out because of these.

Noble went on to analyse the pooled data from both CAPACITY and ASCEND trials (three multinational phase 3 trials), which confirmed the results from previous with significant improvement in FVC decline in the pooled date with pirfenidone compared with placebo (29). Figure 1-5 demonstrates this data below.

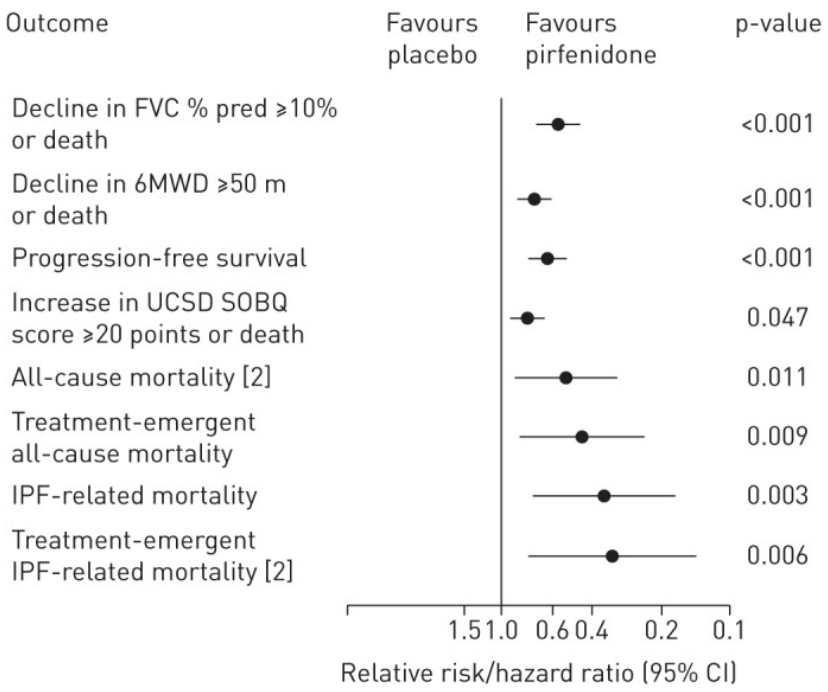

Figure 1-5 Forest plot to show clinical efficacy outcomes at 1 year in pooled population as demonstrated by Noble et al. FVC – Forced vital capacity. 6MWD – 6 minute walk distance. UCSD SOBQ - University of California San Diego Shortness of Breath Questionnaire.

With regards to the safety profile within the data, in line with previous data 99% of patients in the pirfenidone group had at least one adverse event. When compared to placebo, the most common with larger effects included nausea, diarrhoea, fatigue, headache, rash, dizziness, dyspepsia, vomiting, anorexia and gastro-oesophageal reflux disease. 12% of patients in the pirfenidone group compared to 9% in the placebo group had an adverse event leading to early discontinuation, however, 'early' is not defined in the write up. Interestingly, using the pooled data patients with worse physiological function at baseline defined by an FVC less than 65% predicted, DL_{CO} less than 40% predicted and 6 minute walk distance less than 350m had a higher rate of adverse events leading to treatment discontinuation. The pooled data did show that the magnitude of treatment effect is consistent across subpopulations with different baseline measure of disease status, which further emphasises the need for early recognition and management of adverse events to enable patients to reap the benefit of pirfenidone.

Following on from the phase 3 trials, the RECAP trial was an extension open label study looking at the safety profile of pirfenidone (30). It was offered to all patients who had completed either the CAPACITY trials or ASCEND trials; all patients regardless of high dose/low dose prescription or placebo were put on the high dose of pirfenidone. The open label study supports the ongoing use of pirfenidone in patients with IPF with a tolerable safety profile comparable to the results from the phase 3 trials. 33.8% of patients discontinued RECAP due to AE's over the course of the study, of which 23% were not related to IPF progression. The most common AE's that caused discontinuation included nausea and rash. Of those patients that discontinued in the first year of treatment, 44% were due to AE's not related to IPF progression. This was the most common time frame for discontinuation from treatment and although the data is not shown, the authors also state it was common in those patients newly initiating pirfenidone treatment. This suggests that most patients newly initiating pirfenidone will require close monitoring and management in the initial phases of treatment and within the first year. A limitation from using an extension study includes the survival bias, since to be included, patients must have survived the first CAPACITY/ASCEND trials, which then implies that they would be again physiologically better than some of the patients we tend to see in clinical practice. This then impacts the number of people who would discontinue early theoretically as they may well be worse physiologically.

In a similar type of study, looking at the integrated results of the CAPACITY trials, and interim results of two ongoing open label studies (002 and 012) the safety and tolerability of Pirfenidone was again demonstrated as above (31). Interestingly analysis of adverse events in 6 month intervals showed that gastrointestinal and skin related side effects declined rapidly after the initial 6 months of treatment. As these are the adverse events that are most commonly reported in patients taking pirfenidone in these phase 3 trials, and although the reported discontinuation rate secondary to these side effects is pretty low, it does show again that the initiating phase of pirfenidone and the management of side effects in the first 6 months of treatment may be important in keeping patients on pirfenidone. Figure 1-6 is a graph taken from Dominique et al. demonstrating the rapid decline of

side effects after six months of treatment, highlighting the importance of close monitoring in the initiating phase of pirfenidone (31).

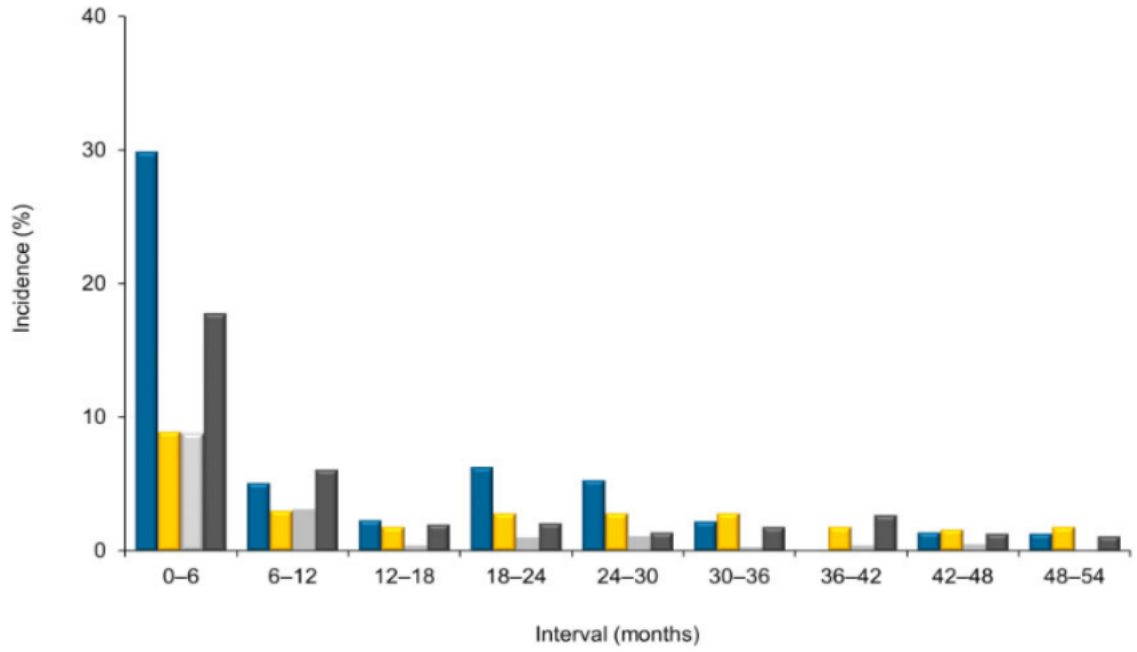

Figure 2 Incidence of new-onset treatment-emergent gastrointestinal and skin-related adverse events by 6-month intervals in the integrated patient population. (■) Nausea, (■) vomiting, (■) photosensitivity, (■) rash.

Figure 1-6 Figure to show rapid decline of side effects within the first six months of initiating treatment with Pirfenidone. Figure taken from Dominique et al.

The above is supported by another study which integrates the safety data of five phase 3 trials including the two CAPACITY trials, ASCEND trial and interim results of the two open label RECAP trials (32). Again common AE's causing early discontinuation other than progression of IPF were nausea and rash. The dataset used in this study however also included patients with baseline data of a broad range, which were not originally seen in the CAPACITY criteria for example and therefore may be more representative of the general population of patients with IPF.

Data from the CAPACITY and ASCEND trials showed a greater proportion of patients treated with pirfenidone vs placebo reported adverse events of nausea, rash, abdominal pain, upper respiratory

tract infection and diarrhoea. It also mentions that most adverse events were responsive to dose modification (20).

Due to the nature of clinical trials, there is an inherent selection bias, which will lead to a difference between real world and clinical trial data. Tzouvelekis et al. conduct a real world longitudinal study of patients with IPF taking pirfenidone in Greece (33). It reveals data on the safety and efficacy of pirfenidone which is comparable to the large multicentre trials. For the relevance to our study, the discontinuation rate was 22.5%, which is higher than the rates reported in the large phase 3 and extension studies. The reasons for discontinuation included photosensitivity/rash (11.2%), gastrointestinal side effects (7.5%), liver toxicity (5%) and other (2.5%). It is important to note that 72% of those that discontinued did so during the first 6 months of treatment. This is an important point to notice as it highlights again the need for close monitoring in the initial phases of treatment with Pirfenidone. If these side effects can be reduced or managed effectively, it will help to prolong treatment time and therefore the life of the patient.

1.4.2 Nintedanib

Nintedanib (BIBF 1120) is a tyrosine kinase inhibitor acting on the platelet derived growth factor receptors (PDGFR), vascular endothelial growth factor receptors (VEGFR) and fibroblast growth factor receptors (FGFR). The phase 2 trial on its use was conducted in 2011 by Richeldi et al, which looked at its treatment of patients with a diagnosis of IPF and FVC of more than 50% over the course of 52 weeks (34). It failed to show a significant improvement in the predefined endpoint, which was the annual rate of decline of FVC. However, the results did show a trend towards improvement and also showed a possible dose response relationship with many of the secondary endpoints being favourable for higher doses of 100mg twice a day and 150mg twice a day (compared to 50mg once a day and 50mg twice a day). For example, the number of acute exacerbations was significantly reduced in those taking the higher dose of 150mg twice a day compared to placebo (RR 0.16, CI 0.03 to 0.70, 95%), and the doses between showing a trend to improvement, but not being significant. With regards to the safety profile, 112 out of 428 patients prematurely discontinued the study

treatment, of which 96 were secondary to adverse events. 30.6% of patients in the highest dose group discontinued due to adverse events, which was higher than placebo at 25.9%. In the 32 (out of 112) patients taking 150mg twice a day that had discontinued early, 11 had tried a dose reduction but still required early discontinuation. The most common adverse events leading to early discontinuation included diarrhoea, nausea and vomiting in the group with the highest dose. In this same group, 5% had serious gastrointestinal events and 6% had severe gastrointestinal events. Of note, the median FVC for all patients recruited into the TOMORROW trial was 80.2% with median DL_{CO} 3.6, again suggesting that these patients were healthier than those we see in clinical practice at present.

Richeldi et al. then went on to set up two phase 3 trials called INPULSIS 1 and INPULSIS 2, which were replicates and ran parallel to each other in a multinational setting looking at the treatment of IPF with Nintedanib 150mg twice a day compared to placebo (35). In INPULSIS 1, the adjusted annual rate of FVC decline was 114.7ml compared to 239.9ml with placebo. In INPULSIS 2, the adjusted annual rate of FVC decline was 113.6ml compared to 207.3ml with placebo. Both of these changes were significant. Some of the secondary endpoints were inconsistent between the two trials, such as INPULSIS 2 showing a significant increase in time to first exacerbation, but not in INPULSIS 1. Although there were pre-specified criteria for an acute exacerbation, this remained an investigator based assessment of the patient having met said criteria, however, as mentioned by Richeldi et al. the acute exacerbation of IPF is difficult to characterise and diagnose and therefore may have produced the inconsistencies seen between the two trials. 78 (25.2%) out of 309 patients in the nintedanib group of INPULSIS-1 discontinued medication prematurely, of which 65 were secondary to adverse events. This compared to 36 (17.6%) patients in the placebo group discontinuing study treatment early. In INPULSIS-2, the numbers are similar with 78 (23.7%) out of 329 patients in the nintedanib group discontinuing early compared with 44 (20.1%) in the placebo group. Again of the 78 that discontinued early, 62 were due to at least one adverse event. Of the adverse events in both trials, the most common was diarrhoea, of which 93.7% and 95.2% in INPULSIS-1 and INPULSIS-2

were mild to moderate in intensity and in only 4.5% and 4.3% (in the Nintedanib group) in 1 and 2 respectively did diarrhoea cause early discontinuation of nintedanib. Only descriptive analyses are available in the dataset and write up, but other adverse events demonstrated to be higher in the nintedanib groups compared to placebo included nausea, decreased appetite, vomiting and weight loss. There was a higher proportion of patients in the nintedanib groups compared to placebo where adverse events led to discontinuation, of which again, the majority were gastrointestinal in nature.

In the nintedanib trials, more than 10% of patients treated with nintedanib and a greater proportion of patients treated with nintedanib vs placebo reported adverse events of diarrhoea, nausea, abdominal pain, vomiting and liver enzyme elevations. It is mentioned that most of these adverse events were managed by dose reduction or treatment interruption (20).

Trial	Drug	Total discontinuation of patients in treatment arm	Percentage due to adverse events (%)	Which adverse events?
Azuma et al.	Pirfenidone	21.9%	15.1	1. Photosensitivity (6.8%) 2. Vomiting (1.4%) 3. Fever (1.4%) 4. Liver function abnormality (1.4%) 5. Dizziness (1.4%) 6. Facial Paralysis (1.4%) 7. Hepatoma (1.4%)
Taniguchi et al.	Pirfenidone	High dose (1800mg/day) – 37.0% Low dose (1200mg/day) – 27.3%	25.0	1. Progression of disease (7.4%) 2. Acute exacerbation (3.7%) 3. Photosensitivity (2.8%) 4. Lung Carcinoma (1.8%) 5. Fever (1.8%) 6. Respiratory Failure (1.8%) 7. Rash (0.9%) 8. Liver function abnormality (0.9%) 9. Gastric ulcer (0.9%) 10. Anorexia (0.9%) 11. Muscle pain (0.9%) 12. Dysgeusia (0.9%) 13. Loss of consciousness (0.9%)
CAPACITY	Pirfenidone	Pooled pirfenidone group – 15%	Not stated	1. Idiopathic pulmonary fibrosis (3%) 2. Nausea (1%) 3. Rash (1%)
ASCEND	Pirfenidone	Not stated	14.4	1. Worsening IPF (1.1%) 2. Liver function abnormality (1.1%) 3. Pneumonia (1.1%) 4. Rash (1.1%) 5. Weight loss (1.1%)
RECAP	Pirfenidone	42%	33.8	1. IPF progression (10.9%) 2. Rash (1.1%) 3. Nausea (1.0%) 4. Other (20.9%)
Tsouvelekis et al.	Pirfenidone	Not stated	22.5	1. Photosensitivity/rash (11.2%) 2. Gastrointestinal disorders (7.5%) 3. Liver toxicity (5%) 4. Other (2.5%)
TOMORROW	Nintedanib	50mg OD – 27.9% 50mg BD – 20.9% 100mg BD – 16.3% 150mg BD – 37.6%	50mg OD – 23.3 50mg BD – 16.3 100mg BD – 14.0 150mg BD – 30.6	Cumulative percentages across treatment groups: 1. Respiratory, thoracic and mediastinal disorders (4.0%) 2. Gastrointestinal disorders (4.7%) 3. Infections and infestations (1.6%) 4. Cardiac disorders (1.2%)
INPULSIS	Nintedanib	INPULSIS-1 – 25.2% INPULSIS-2 – 23.7%	INPULSIS-1 – 21.0 INPULSIS-2 – 18.8	INPULSIS-1: 1. Respiratory, thoracic and mediastinal disorders (3.9%) 2. Gastrointestinal disorders (8.4%) 3. Investigation results (3.2%) 4. Cardiac disorders (1.6%) 5. General disorders (2.6%) INPULSIS-2: 1. Respiratory, thoracic and mediastinal disorders (2.4%) 2. Gastrointestinal disorders (6.4%) 3. Investigation results (2.4%) 4. Cardiac disorders (0.6%) 5. General disorders (0.6%)

Table 1-1 Table to show discontinuation rates due to adverse events for each trial using both pirfenidone and nintedanib and which adverse events caused discontinuation.

1.4.3 Application of drugs used in major trials in our locality

Prescribing history of antifibrotics in the past 6 years has progressed from clinical trials, to a named patient programme (NPP) and then to NHS licence for prescription. The criteria for prescribing under the three circumstances are different. Current NHS guidelines for prescribing antifibrotics are following an MDT diagnosis of IPF. The patient then has to fit into the narrow FVC range of 50-80%. Before this, the NPP did not put an emphasis on the criteria like the NHS prescribing does; patients were eligible for prescription despite normal FVC or an FVC lower than 50%.

The current practice at UHB (HGS) can be divided into patients referred from UHB (HGS) hospitals and patients referred from outside of the three UHB (HGS) hospitals. Within Birmingham, Solihull and Sutton Coldfield, there are three hospitals, each with their own ILD team with an interest in IPF. These are Heartlands Hospital, Solihull Hospital and Good Hope Hospital. Patients would usually be referred by their general practitioner (GP) to a respiratory physician for further investigation of chronic cough or shortness of breath or whatever the initial symptoms may be. Assessment would then take place at one of the three hospitals within the trust and an initial management plan by a general respiratory physician takes place. This may be sending for further investigations such as HRCT, bronchoscopy or biopsy. Once the results of these are available, the general respiratory consultants would then refer to the ILD team for further investigation, confirmation of diagnosis or treatment. The catchment area that the patient falls under will determine which hospital he or she will be referred to. Outside of UHB (HGS), again initial review is most commonly by the GP with referral to secondary care. Once ILD is confirmed then the patient is referred to the ILD team at UHB (HGS) and will see an ILD specialist at the Birmingham Chest Clinic (BCC), which acts as a hub in a hub and spoke model.

Following review in the ILD service, the case is then discussed at the ILD MDT, of which there is one at each site. Each site has a specialist interest in aspects of ILD. Solihull hospital will have a rheumatologist present and will aim to discuss possible connective tissue disease related ILD. At Heartlands hospital, there is availability of a histopathologist, and therefore all patients who have

had a biopsy should be discussed at Heartlands. All three sites will discuss general cases of ILD not requiring Rheumatology/Histopathology input.

Once a diagnosis of IPF is confirmed via MDT, the patient is followed up in their respective hospitals. Each site will have at least one ILD specialist nurse, who will act as the initial point of contact for these IPF patients and will help with initiating antifibrotics, dealing with side effects and managing the patient as a whole. NICE guidelines for IPF in the UK recommend availability of an ILD nurse at all stages of the care pathway to help with support and information; this would be important for those on and off antifibrotic treatment (2). This is especially important in the first few months as during the titration of pirfenidone and the starting of nintedanib, patients have experienced the highest rate of adverse events as discussed earlier. Once started on antifibrotics, current NHS standard of care and local policy, is for monthly monitoring with blood tests to ensure liver function is stable and then move onto 3 monthly reviews after 6 months to ensure stability and coping with diagnosis and side effects.

1.5 Adverse events in real world studies of antifibrotics

Clinical trial data is clearly not always representative of the general population and so is the case with antifibrotics. It is likely that patients in the real world will have more co-morbidities, increased frailty and worse lung function than those in clinical trials. Certainly, the average for patients starting nintedanib in the INPULSIS trials was 80% predicted FVC, however, clinical guidelines in the UK only allow prescription of antifibrotics between 50-80% FVC. Toellner et al in Northern England took data from three tertiary centres in the UK prescribing nintedanib as part of the Patient In Need (PIN) programme (36). Retrospective analysis showed that Nintedanib in their experience has an acceptable AE profile and is tolerated by the majority of patients. 723 AE's were identified in total in 187 patients with the majority (49.7%) of patients reporting diarrhoea as the most common side effect. Other common side effects reported included nausea (36.4%), reduced appetite (23.5%), tiredness (20.3%), gastro-oesophageal reflux (18.2%), abdominal pain and bloating (24.1%) and weight loss 14.4%). The team employed treatment adjustment strategies as previously mentioned in

the INPULSIS trials and showed that 64% of all AE's were managed with no change to treatment, 21% by dose reduction, 7% with temporary discontinuation and 6% permanently stopped treatment. In total at the end of the monitoring period 21% had permanently discontinued treatment, which is lower than the 25.2% and 23.7% in the INPULSIS trials. It should be noted that of those who developed diarrhoea, only 8% led to treatment discontinuation which is comparable to the 5% quoted in the INPULSIS trials. The major limitation in this study is that all of the patients enrolled would have been on the PIN programme, which would mean that enrolment would commonly be due to an FVC of less than 50% or more than 80% (otherwise pirfenidone would be the evidence based choice ethically), have had previous adverse events with pirfenidone, or make an informed decision to take nintedanib due to the side effect profile of pirfenidone. The average FVC percentage for all patients in this study was 81.1%, which is higher than would be allowed for prescription on the NHS.

This contrasts to a similar review from Germany where Bonella et al. report insights from the German Compassionate Use Program (CUP), which is similar in design to the PIN, in that immediately following the positive results from the INPULSIS trials, nintedanib was commercially available and therefore prescribable under CUP in Germany (37). Again, exclusion criteria included previous intolerability of or disease progression on pirfenidone. The majority of patients from this study in comparison to the PIN program had received treatment with pirfenidone (77%). A total of 62 patients were assessed. Mean predicted FVC percentage in this cohort however was slightly lower than that of previous trials at 64%. The total rate of discontinuation however is lower than that of Toellner et al. and the INPULSIS trials at 11%. It is also reported that diarrhoea led to treatment discontinuation in 11% of patients, which when compared to the 5% in the INPULSIS trials is slightly higher and may be reflected by the increased severity of lung function with a lower average FVC and also lower average DL_{CO} (40% in CUP and 47% in INPULSIS). Other common side effects that are reported are similar to other studies with gastrointestinal being most common (diarrhoea, nausea,

anorexia and heartburn) along with weight loss in 50% of patients (which is significantly higher than the number reported in INPULSIS) and fatigue (38.7%).

The above is comparable to the extension from the TOMORROW trial, which continued to show reduction in FVC decline (38). It also showed again that the most common adverse event was diarrhoea at 74.1% in the nintedanib group compared with 40% in the comparator group (which included placebo/nintedanib 50mg once daily in periods 1 or 2 of TOMORROW), which then led to treatment discontinuation in 17.6% of patients. Other causes of treatment discontinuation in the nintedanib group include nausea, abdominal pain and weight loss.

1.6 Side effects of antifibrotics and their management

In the CAPACITY and ASCEND trials proactive management of adverse events was pre specified prior to the start of the studies. This was based on previous knowledge of common adverse events commonly associated with pirfenidone namely gastro-intestinal and skin related side effects. The success of these pre-specified proactive management strategies are reflected in the lower incidence of treatment discontinuation due to gastrointestinal and skin related side effects in the CAPACITY studies compared to the Japanese phase 3 trials. A panel of industry funded (InterMune International AG) experts including Pulmonologists, Gastroenterologists and Dermatologists across Europe convened in Basel, Switzerland to discuss and set recommendations for the management of gastrointestinal and skin related side effects of pirfenidone (39). Literature to date was reviewed by the panel and recommendations made based on the latest evidence. Pirfenidone has been shown to reduce gastrointestinal motility and small bowel transit, thereby causing nausea (39). It also has the propensity to cause photo-toxic or erythematous rash in exposed areas of skin. The absorption of Ultra Violet (UV) light has been suggested as the underlying mechanism for this (40). Both GI and skin related side effects have been demonstrated to show a possible dose-dependent relationship. A large part of management of these side effects starts from the education given to the patient when they are making an informed decision about which antifibrotic they would prefer to take and then again once the decision has been made. Education should extend to the benefit of the medication

and then the potential side effects, prophylaxis available and precautions advised during treatment. For example, in the management of nausea, a prokinetic could be considered in the short term to manage the initial effect. Other strategies that could be explored include splitting of the medication; for example splitting three capsules throughout a meal, or advising patients to take the capsules after food to minimise the effect of nausea.

Using a high sun protection factor (SPF) sun cream should be advised or prescribed and adequate education about the risk of sunburn despite a cloudy environment or thick clothing due to the ability of UV light to penetrate this. If despite adequate avoidance measures and prophylactic measures, the side effects are still an issue, then dose reduction to 2 capsules three times a day has been advocated. If the nausea or photosensitivity still persists then a dose interruption/holiday has been advocated to alleviate symptoms. A slower re-titration to maximum dosing would then be an option to allow patients to develop an alternative strategy for coping with these side effects. To help manage these side effects, management in a specialist centre with experience with antifibrotics, making use of regular specialist ILD nurse review in the first 6 months of treatment has been recommended. Although these discussions were organised for management of side effects of pirfenidone, a similar strategy can be adopted for nintedanib. Figure 1-7 shows a possible treatment algorithm for the management of adverse events adapted from Costabel et al., which can be used for both pirfenidone and nintedanib (39). There is currently no systematic approach locally in UHB (HGS) and this algorithm is not followed currently.

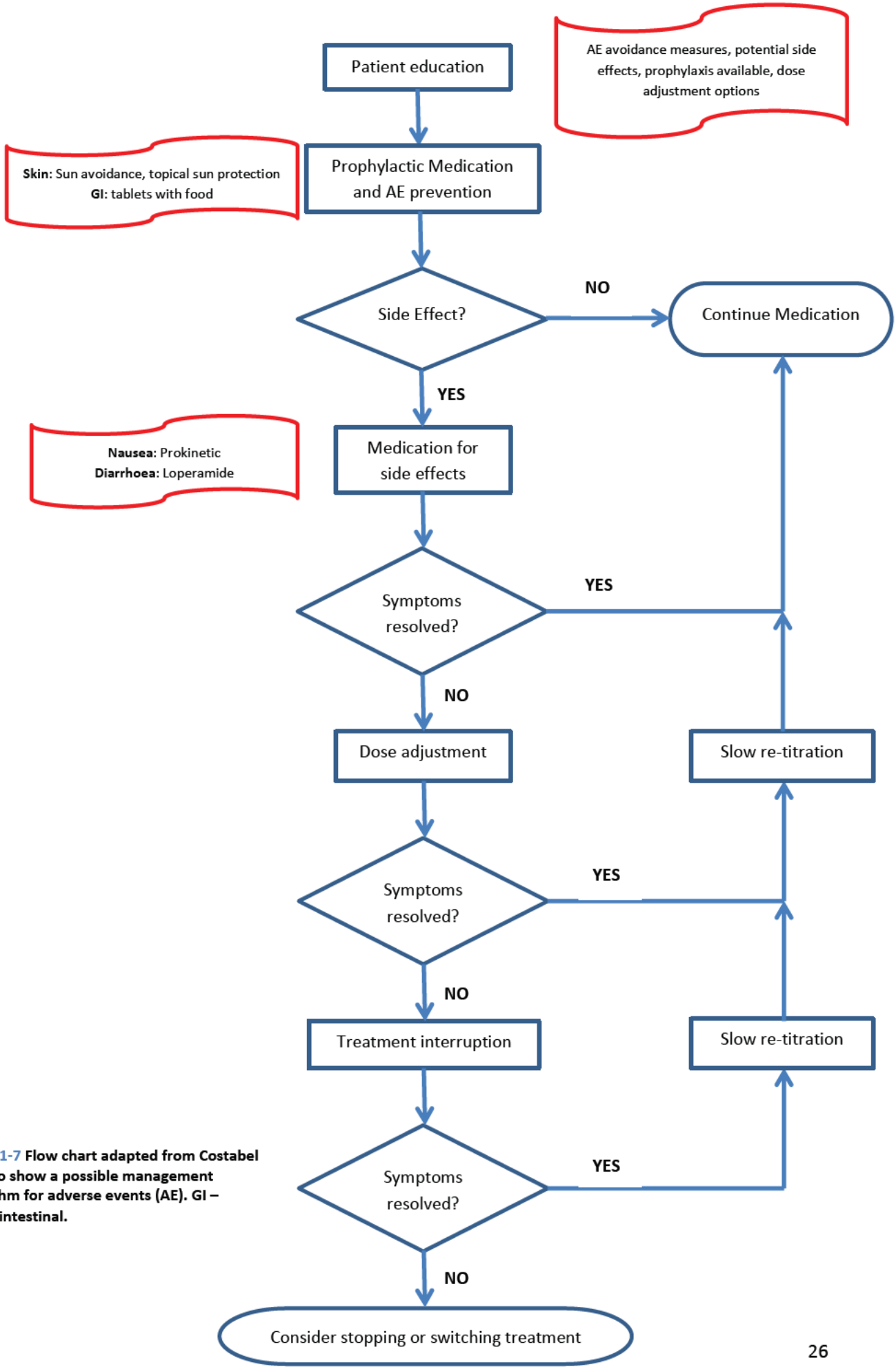

Figure 1-7 Flow chart adapted from Costabel et al. to show a possible management algorithm for adverse events (AE). GI – Gastrointestinal.

1.6.1 Role of the clinician in management of side effects

Lately, there has been much more knowledge and exposure to clinicians around IPF and the emphasis has been on early diagnosis and referral, not on adherence to treatment. This enhances the ability of a specialist ILD centre to see these patients early and be able to instigate investigation, formal diagnosis and treatment early, which will benefit the patient greatly. Fischer states in an editorial that the identification of IPF begins with the primary care giver, which in the UK would be the GP (41). Furthermore, Fischer comments on the role of the primary care giver in contributing to longitudinal management of IPF, including management of side effects of antifibrotics such as nausea with pirfenidone and diarrhoea with nintedanib. They are also best placed to facilitate passage through to palliative care – with good access to hospices and community services.

1.7 Aims of this thesis

The overall aim of my study is to look at a population of patients prescribed antifibrotics between 2012 and 2016 and investigate which features would predict early discontinuation from antifibrotic therapy. The specific objectives are as follows:

1. **Understand the demographics of the population being prescribed antifibrotics at UHB (HGS).**

Using data between 2012 and 2016 I will use retrospective electronic databases and telephone interviews with patients and/or patients' next of kin to help describe the group of patients taking antifibrotics for IPF.

2. **Identify the reasons for discontinuation of antifibrotics in UHB (HGS).**

By using retrospective data collection via clinical records I aim to show the different reasons for discontinuation of antifibrotics and how this relates to published literature. By achieving this objective, we will be able to identify management options tailored specifically at the reasons for discontinuation and how to prevent this. It will allow me to create a predictive model to investigate which variables (such as baseline investigations, adverse events etc.) are likely to influence early

discontinuation. This will help in decisions to initiate therapy in those patients where clinical judgement is difficult.

3. **Describe the referral pathway and identify areas of delay in referral and subsequent treatment.**

Using both retrospective electronic data and qualitative methods such as focus group and individual interviews, I aim to illustrate the possible areas for delay in the referral pathway to UHB (HGS), which can then result in poor baseline function as the IPF progresses and may contribute to early discontinuation of therapy. With this knowledge, we can aim further interventions at reducing the delays in referrals and perhaps the risk of discontinuation.

4. **Describe the patterns of adverse events on IPF patients on antifibrotics in UHB (HGS).**

Understanding the prevalence and characteristics of AE's in our population will allow us to tailor our services effectively. Identifying groups of patients at increased risk of developing certain AE's will allow targeted strategies for adherence in those at high risk of discontinuation. It may also help to identify patients that may not tolerate initiating medication and therefore aid in the decision not to start treatment. This objective will be achieved by retrospective viewing of clinical letters on an electronic database, supplemented with patient or patient's relatives' telephone calls. Qualitative interviews will also help to identify which adverse events are more important from the patient perspective.

5. **Understand the patient perspective on managing IPF with antifibrotics.**

A qualitative research arm of the project should aid to demonstrate the patient's perspective of managing IPF with antifibrotics. This will be done with individual and focus group interviews. A patient perspective will allow us to reinforce findings that we may find in this study and may highlight other areas of the patient pathway, experience with disease and management of antifibrotics, which may be useful in understanding patient compliance on these medications.

2 Methods

This was a Service Evaluation, performed in UHB (HGS) looking at factors predicting early discontinuation of antifibrotics in patients with IPF. We used the HRA decision tool and established that the project was service evaluation rather than research. The decision was also discussed with the local R&D department at UHB (Heartlands Hospital), and relevant permission was gained from the Respiratory Medicine Department at Heartlands Hospital to undertake this service evaluation, in line with trust procedure, therefore no formal ethical approval from a National Research Ethic Service (NRES) Research Ethics Committee (REC) was sought. The project was subject to further ethical review at the University of Birmingham and the Research Governance and Integrity Assessment concluded that the project is a Service Evaluation (described in detail in Appendix F). Where patients or their Next of Kin (NOK) were contacted for retrospective data collection, or at focus group/interviews informed consent was obtained for transparency and good practice.

UHB (HGS) is a regional tertiary specialist centre in the West Midlands, UK for ILD. The referral process is as set out in the introduction above (Section 1.4.3). Once patients are referred they are assessed at one of the three sites, Birmingham Chest Clinic, Solihull Hospital and Good Hope Hospital. History, examination and investigations are then discussed at an ILD MDT where a diagnosis can be made. Following diagnosis, IPF patients will then be started on antifibrotics if they meet the criteria as set out in the introduction.

Data was collected using a mixed methodology approach. I looked at a population of 185 patients each with an MDT diagnosis of IPF, who then went on to be prescribed Pirfenidone or Nintedanib between 2012 and 2016. Retrospective data was collected electronically from patient records using clinical letters, discharge summaries, test result reports and pathology results. Qualitative approach was then used via telephone calls with either patients or their relatives if bereaved, followed by individual patient and focus group interviews. Figure 2-1 below shows a flow chart for quantitative data collection and Figure 2-2 shows the process for qualitative data collection.

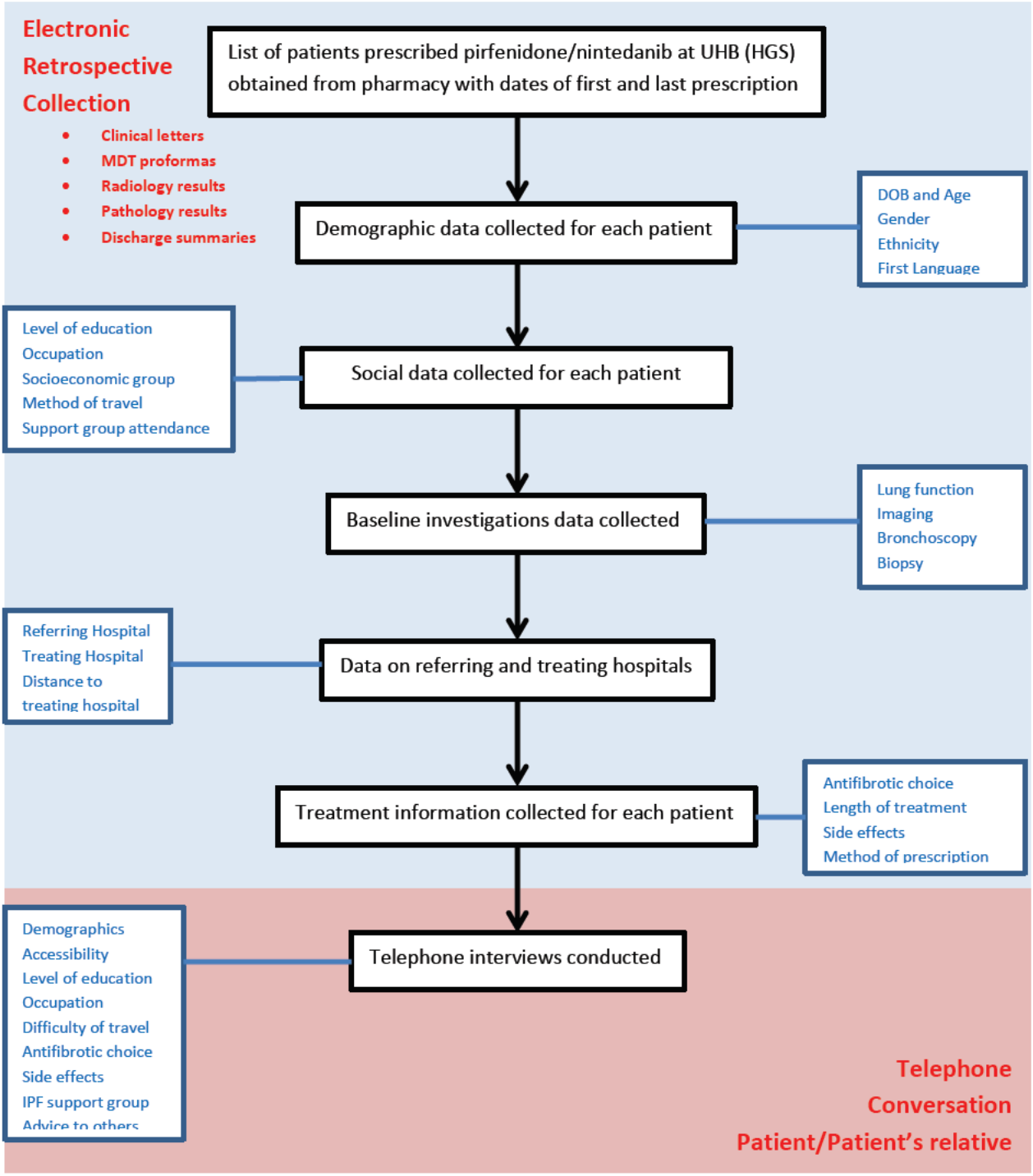

Figure 2-1 Flowchart to show initial data collection for quantitative data.

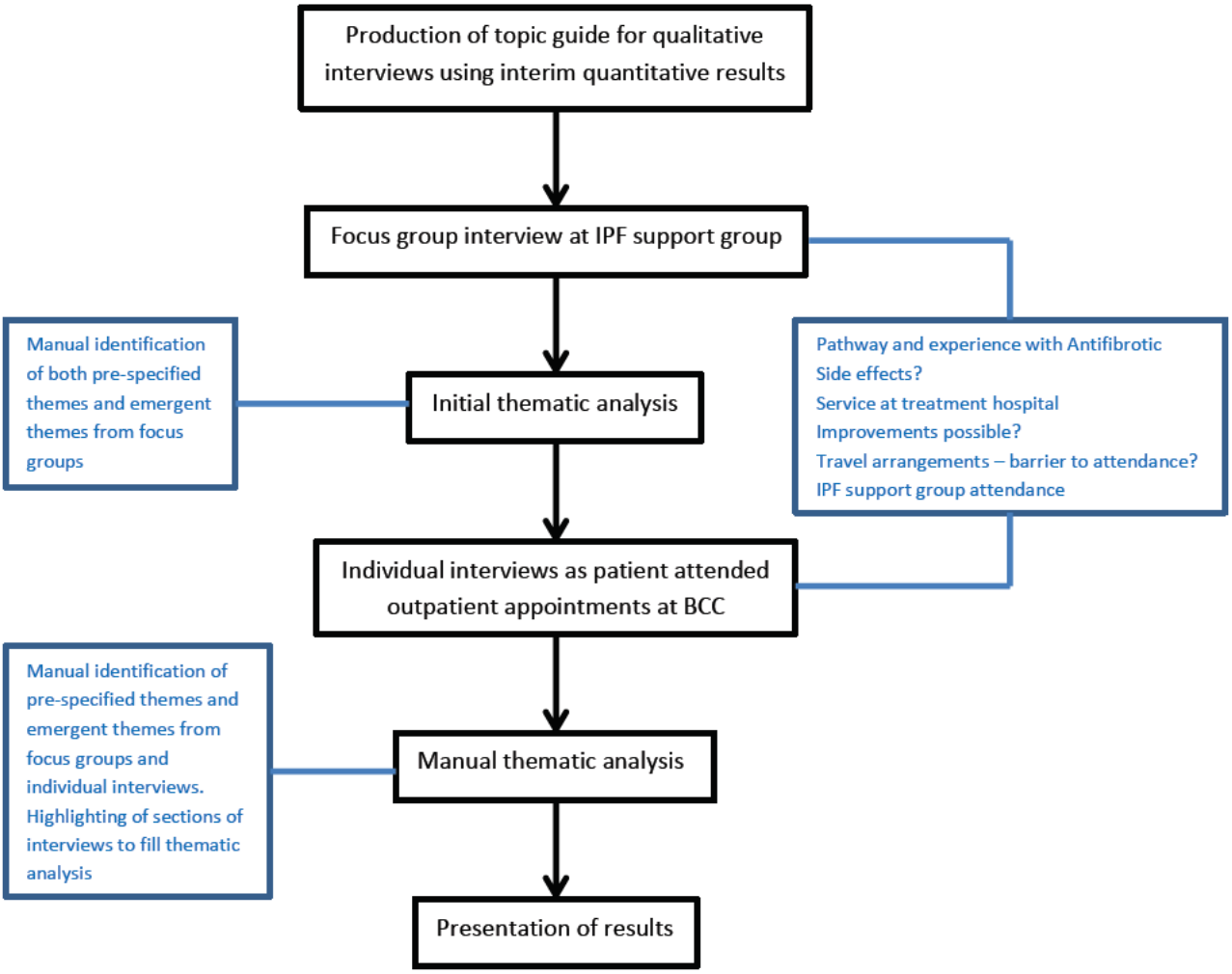

Figure 2-2 Flowchart to show the design for qualitative arm of study. BCC – Birmingham Chest Clinic. For further information see Appendices B-E.

2.1 Quantitative data collection and analysis

2.1.1 Data collection

2.1.1.1 Medical Records

Between 2012 and 2016, 185 patients with an MDT diagnosis of IPF had been started on either pirfenidone or nintedanib at UHB (HGS). UHB (HGS) has an electronic record keeping system called Concerto, which holds information on each patient that comes through UHB (HGS) including demographics, contact information, clinical letters, attendance at appointments, pathology reports, investigation reports and discharge summaries. Initial data collection was done retrospectively using this electronic system. Sources of data collection included those above, but also included MDT proformas for information on investigations used to make a diagnosis. Demographic information collected included patient identifier, date of birth (DOB), age at time of first prescription, gender,

ethnicity and first language. Information regarding the referral pathway was also collected by identifying the referring hospital and then the treating hospital. Along these lines distance to treating hospital was also collected; this was identified a priori as a possible factor for early discontinuation. Information on investigations was then collected, again using the electronic system, and started with pulmonary function testing, including FEV_1, FVC, DL_{CO}, residual volume (RV) and total lung capacity (TLC). The values collected were at the time of diagnosis, which predominantly was at the MDT, and utilised the MDT proforma as the source documentation. The rationale for taking values at this point was that a decision of eligibility for antifibrotics would have been made at, or just after, the MDT. Commonly at UHB (HGS), after assessment and discussion, once the diagnosis is made, the next appointment is usually with the ILD specialist nurse who then initiates the antifibrotic of choice. If the values were not available on the MDT proforma (due to lack of completion) then the closest pulmonary function to the date of the MDT discussion was taken, which could have been from investigation results on Concerto or clinic letters prior. Full pulmonary function testing with the same variables as listed above was then collected after the discontinuation of antifibrotic therapy. This was the first available lung function after stopping the drug, and in the case of those still continuing to take therapy was the last available result prior to the end of data collection (end of September 2017).

Using a combination of the MDT proforma and investigation results on Concerto, the type of imaging used for diagnosis, whether the patient had a BAL to aid in ruling out other diagnoses and whether they required a lung biopsy by either surgical (VATS or open) or transbronchial approach was recorded. The results of these were also recorded. Again, data predominantly was collected from the MDT proformas, but in some cases where it was not clearly completed other sources on Concerto were used.

Using data obtained from the UHB (HGS) pharmacy, the choice of antifibrotic and dates of the first and final prescription were obtained. A lot of patients went onto to a second antifibrotic if a trial of

the first had not been successful. For the purposes of looking at discontinuation, we just looked at the first episode as a previous trial of antifibrotic may bias our results.

With regards to antifibrotic therapy, there have been multiple ways that patients could have been prescribed therapy in the past 4 years, which included prescription via clinical trial or on a named patient basis, both of which did not require a predicted FVC of less than 80% currently required by NICE. The mode of prescription was also recorded to see if this was a predictive factor for early discontinuation.

Treatment experience was then a major part of the data collection, which was comprised of predominantly reading through clinical letters. The majority of these started with an assessment and initiation by a physician and then follow up via the ILD specialist nurses. This enabled us to record healthcare stated reasons for stopping therapy and side effects.

2.1.1.2 Patient reported data

Telephone interviews were then used to complement the retrospective electronic data collection. A proforma was created and is displayed in Appendix A. It predominantly used closed questions as the data we were collecting was specific rather than qualitative. We used the telephone interviews initially to confirm demographic data already collected and also to fill in gaps in those patients were retrospective data was limited. We also used the telephone interviews to collect information on socio-economic factors that may impact a patient's decision to remain on antifibrotic therapy. We collected data on highest level of education and occupation, which allowed us to group patients into socio-economic groups (see proforma). We used the National Statistics Socio-economic classification (NS-SEC) to group patients (Table 2-1).

NS-SEC Class	Occupation
1	Higher Managerial and Professional
2	Intermediate Occupations
3	Small Employers and Account Workers
4	Lower Supervisory and Technical Occupations
5	Semi-Routine Occupations
6	Never Worked or Unemployed

Table 2-1 Table showing the National Statistics Socio-economic classification (NS-SEC) used to group patients using longest occupation held.

Groups used for level of education are shown in Table 2-2.

Highest Level of Education
University Degree
A Levels
GCSE
School
Other

Table 2-2 Table showing the groups used for highest level of education. 'Other' included groups such as apprenticeships and diplomas achieved after school, but not requiring higher education.

Telephone interviews were also used to collect data on travel. As UHB (HGS) receives patients from a variety of centres with a large distance between them, we hypothesised that travel to appointments may influence their decision to continue with antifibrotic therapy. The variables collected in this

regard included method of travel and using an ordinal scale from 1-10 (where 1 = easy travel and 10 = difficult travel), the difficulty of travel. I also asked if the travel ever influenced their decision to attend appointments or start antifibrotic therapy.

A patient perspective on treatment was sought using the telephone interviews and as shown in the proforma, we asked whether patients were given a choice of which antifibrotic to take (as nintedanib was commissioned for use after pirfenidone) and why they chose that particular drug. An open question was inserted at this point to allow patients to comment on compliance and adherence to treatment in an unstructured way. This was further explored if not forthcoming from the patient. Related to these experiences was also whether they had taken a break from treatment, which is advocated in literature for management of adverse events.

We asked patients if they had been made aware of the IPF support group, which in the years involved in the study was run by one of the UHB (HGS) specialist ILD nurses in Solihull and more recently a second support group had been started in Sutton Coldfield by the ILD nurse in Good Hope Hospital. If they had been made aware, they were asked if they had attended.

A final open question was asked to obtain an opinion on starting antifibrotics and what advice they would give to those who were considering doing so.

Patients were contacted by telephone, with their number obtained by their medical records. Verbal consent was gained and the questions asked according to the proforma in Appendix A. Where patients had died, which was not always clear from the medical records, the NOK was consented to answer the questions where willing.

2.1.2 Statistical Analysis

Once all the quantitative data had been collected, it was analysed using IBM SPSS Statistics Version 23. Tests for normality of data were calculated using Shapiro-Wilk testing. Demographic and diagnostic variables are displayed as frequencies and for average, appropriate measures of spread were used; mean with standard deviation (SD) for continuous normal distributed data, median with

interquartile range (IQR) for continuous non-normally distributed data, and percentage for categorical data. Demographics such as age, ethnicity, socioeconomic class and level of education, along with investigations such as imaging, bronchoalveolar lavage results, biopsy results and lung function were grouped by gender. Two tailed independent t-test was conducted for normally distributed data, Mann Whitney U testing used for non-normally distributed data and chi squared for categorical variables.

To look at discontinuation, different variables were sorted into binary outcomes. For example, we created two groups within the age variable; those that are above 60 years old and those that are below 60 years old. Whilst categorising continuous data can result in loss of statistical power we felt it would be more informative for clinical decision making. We grouped the data into those who had less than 30 days between their first and last prescription, thereby only received one prescription and classed this as early discontinuation. Those that had more than 30 days were classed as non early discontinuation. We then applied the binary variables to each outcome to form a univariate analysis and identified those that showed a significant difference. Univariate analysis between those who discontinued medication within 30 days or not, and within 90 days or not, was carried out using chi squared testing for categorical variables. Multivariate analysis was then conducted using a binary logistic regression analysis demonstrating odds ratio (OR) with upper and lower border confidence intervals (CI) for both risk of discontinuation at 30 days and 90 days. All statistical tests were considered significant at the 95% confidence interval.

2.2 Qualitative data collection and analysis

As part of our mixed methodology, we also employed a qualitative approach to data collection in our study, the first of which included individual patient interviews. A topic guide was produced for individual patient interviews after consultation with the clinical team and independent researchers and is attached in Appendix B. This takes into account the use of deductive or pre-specified themes and allowed for semi-structured interviews to introduce further inductive themes. Patients that attended the BCC for follow up appointments were pre-screened and identified to have taken or be

taking antifibrotic therapy, either pirfenidone or nintedanib, for an MDT diagnosed IPF and therefore likely to represent a typical patient within our population. Following attendance at their follow up appointment, they were asked if they would like to participate in an interview on their experiences on antifibrotic therapy. If they agreed they would be introduced to me and written consent was obtained. The written consent form is attached in Appendix C.

2.2.1 Data collection

A series of open questions were asked initially focussing on the referral pathway from the start of symptoms to their prescription of pirfenidone or nintedanib. Themes in this question included recognition of symptoms and assessment by medical professionals, with a rough time to first assessment by an IPF specialist. Once IPF was confirmed, which tablet did they choose (if they had a choice) and the reasons behind making that choice. We then focussed on the experience with the tablets, specifically focussing on tolerability of the tablets, side effects, number of capsules and need for dose reduction or dose holiday (if these were not forthcoming from the patient themselves). We also looked at their experience with service at their relevant treating hospitals as this may well be a reason for early discontinuation in some cases. This was coupled with possible improvements that could be made to the service and support. An open ended question about travel to appointments was asked to highlight possible other reasons in the patient pathway for not attending follow up appointments or continuing with the therapy.

Presence of social support was another factor that we originally hypothesised would have an impact on whether patients would discontinue antifibrotic therapy early or not. Therefore the final part of the individual interview was based on the presence of support in the community and also their attendance to the IPF support group, which may act as an additional emotional and social support to aid in continued understanding of IPF and treatment. Finally, we added a generic question regarding advice that they would give to other patients considering starting pirfenidone or nintedanib, which could highlight other themes that would predict early discontinuation from antifibrotic therapy. We

continued these interviews until we achieved saturation of common themes, and completed ten individual interviews.

Along with the individual interviews, we also utilised patients' presence at the IPF support group to ask if select patients with IPF and experience of antifibrotics would consider participating in a focus group so that their experience could be compared with that of others. An information leaflet was produced and presented to the audience so that they had further information to enable an informed decision to be made, which is attached in Appendix D. Again, similar to the individual interviews we produced a topic guide, which is attached in Appendix E, to use in the focus group sessions. Written consent was gained prior to commencement. The main aim of the focus group interview was to identify themes additional to those already hypothesised that would predict early discontinuation from antifibrotic therapy in patients with IPF. The new inductive themes were then used to adjust structure in the individual interviews if appropriate.

2.2.2 Statistical Analysis

The qualitative interviews and focus groups were audio recorded using a digital dictation device and then manually transcribed onto Microsoft Word 2010 by the chief investigator (PSB). Data was transcribed exactly as heard on audio files including pauses, interruptions, stammers, repetitions, change in voice volume and non-verbal communication cues. Transcription conventions are shown in Table 2-3 and are adapted from Pope et al (42).

Transcription Conventions	
"	Speech from party other than interviewee
_	Change in voice or added sound
thou-	Interruption
and – establish	Pause longer than 1 second
(...)	Inaudible/Incomprehensible speech
- - -	Pause longer than 3 seconds
[...]	Deliberate exclusion by author

Table 2-3 **Table showing transcription conventions used for manual transcription of individual interviews and focus group sessions.**

Thematic analysis was then conducted manually by the chief investigator (PSB) with consultation with co-investigator/co-supervisor (GW) to identify major themes and then subthemes within individual and focus group interviews drawing on both pre-specified deductive themes and newly found inductive themes. Recurring or repetitive themes were identified and coded with the whole dataset then being analysed to ensure all representations of said themes had been identified. These are represented in the results section 3.3.

3 Results

3.1 Descriptive results

3.1.1 Demographic Data

170 patients with MDT diagnosed IPF who were prescribed pirfenidone or nintedanib between the years 2012 and 2016 were included. Of these there were 126 men and 44 women. The median age of all 170 cases at time of data collection was 72.0 (IQR = 12). Most (127 (86%)) patients were British with the majority (133 (96%)) having English as their first language. 77% of cases were from a socioeconomic class of 4-6. Most patients 68 (81%) had only reached school as their highest level of education and had gone on to apprenticeships or straight into work, with only 19% continuing education and obtaining GCSE grade or higher. 24.1% of our population were continuing on therapy by the end of data collection. Table 3-1 shows the demographics of the population used in the study, grouped by men and women. There were no significant differences between men and women in the demographic categories that were identified.

	Total n = 170	Men n = 126 (74.1%)	Women n = 44 (25.9%)	P value
Median age (IQR)	72.0 (12)	72.5 (11)	71.0 (12)	0.179[1]
Ethnicity n(%)[2]				
i. British	127 (86%)	96 (87%)	31 (82%)	0.386[3]
ii. Non British	21 (14%)	14 (13%)	7 (18%)	
a. South Asian	16 (11%)	11 (10%)	5 (13%)	
b. Black African	1 (1%)	1 (1%)	0 (0%)	
c. Black Caribbean	2 (1%)	1 (1%)	1 (3%)	
d. Irish	2 (1%)	1 (1%)	1 (3%)	
First Language n(%)[4]				
i. English	133 (96%)	99 (96%)	34 (94%)	0.671[3]
ii. Non English	6 (4%)	4 (4%)	2 (6%)	
a. Urdu	2 (1%)	1 (1%)	1 (3%)	
b. Punjabi	2 (1%)	1 (1%)	1 (3%)	
c. Bangladeshi	1 (1%)	1 (1%)	0 (0%)	
d. Gujurati	1 (1%)	1 (1%)	0 (0%)	
Socioeconomic class n(%)[5,6]				
i. 1-3	33 (23%)	24 (22%)	9 (25%)	0.731[3]
1. Higher managerial and professional	8 (6%)	7 (7%)	1 (3%)	
2. Intermediate occupations	10 (7%)	4 (4%)	6 (17%)	
3. Small employers and account workers	15 (10%)	13 (12%)	2 (6%)	
ii. 4-6	111 (77%)	84 (78%)	27 (75%)	
4. Lower supervisory and technical occupations	32 (22%)	25 (23%)	7 (19%)	
5. Semi routine occupations	75 (52%)	58 (54%)	17 (47%)	
6. Never worked or unemployed	4 (3%)	1 (1%)	3 (8%)	
Highest level of education n(%)[7]				0.812[3]
i. GCSE and above	16 (19%)	12 (20%)	4 (17%)	
a. University Degree	8 (10%)	8 (13%)	0 (0%)	
b. A Levels	4 (5%)	1 (2%)	3 (13%)	
c. GCSE	4 (5%)	3 (5%)	1 (4%)	
ii. School and Other	68 (81%)	49 (80%)	19 (83%)	
a. School	58 (69%)	41 (67%)	17 (74%)	
b. Other[8]	10 (12%)	8 (13%)	2 (9%)	

Table 3-1 Demographic table to show characteristics of population grouped by gender. ***1.*** *Mann Whitney U test for comparing non-normally distributed data (Shapiro-Wilk 0.001) between males and females* ***2.*** *Data does not take into account 16 males and 6 females with missing data (total 22)* ***3.*** *Calculated via Chi squared statistical analysis* ***4****. Data does not take into account 23 males and 8 females with first language data missing (total 31)* ***5.*** *Data does not take into account 26 missing data required for socioeconomic class identification (18 males and 8 females)* ***6.*** *Socioeconomic class derived from NS-SEC UK.* ***7.*** *Data does not take into account 86 cases with missing data on level of education.* ***8.*** *Other would include NVQ qualification and local apprenticeships.*

3.1.2 Investigations at diagnosis

INVESTIGATION	Total n = 170	Men n = 126	Women n = 44	P value
Imaging via HRCT n(%)				
1. UIP	1. 137 (80.6)	1. 102 (81.0)	1. 35 (79.5)	0.839[1]
2. Not UIP	2. 33 (19.4)	2. 24 (19.0)	2. 9 (20.5)	
a. NSIP	a. 13 (7.6)	a. 9 (7.1)	a. 4 (9.1)	
b. Chronic EAA	b. 1 (0.6)	b. 0 (0)	b. 1 (2.3)	
c. Other	c. 11 (6.5)	c. 7 (5.6)	c. 4 (9.1)	
d. Unclear/not available	d. 8 (4.7)	d. 8 (6.3)	d. 0 (0)	
Bronchoalveolar Lavage n(%)				
1. Had BAL	1. 42 (24.7)	1. 28 (22.2)	1. 14 (31.8)	0.204[1]
2. Did not have BAL	2. 128 (75.3)	2. 98 (77.8)	2. 30 (68.2)	
a. Unclear	a. 4 (2.4)	a. 4 (3.2)	a. 0 (0)	
Bronchoalveolar Lavage Results (missing 3 results) (Median (IQR))				
1. Lymphocytes	1. 5.00 (7)	1. 6.00 (11)	1. 3.50 (5)	1. 0.111[2]
2. Eosinophils	2. 1.50 (4)	2. 3.00 (7)	2. 0.50 (3)	2. 0.235
3. Macrophages	3. 81.0 (30)	3. 76.5 (29)	3. 84.0 (43)	3. 0.260
4. Neutrophils	4. 12.5 (16)	4. 15.0 (19)	4. 10.5 (17)	4. 0.247
Biopsy n(%)				
1. Had Biopsy	1. 42 (24.7)	1. 33 (26.2)	1. 9 (20.5)	0.448[1]
2. Did not have biopsy	2. 128 (75.3)	2. 93 (73.8)	2. 35 (79.5)	
a. Unclear	a. 3 (1.8)	a. 3 (2.4%)	a. 0 (0)	
Biopsy result n(%)	Total n = 43			
1. UIP	1. 35 (81.4)	1. 27 (79.4)	1. 8 (88.9)	0.516[1]
2. Not UIP	2. 8 (18.6)	2. 7 (20.6)	2. 1 (11.1)	
a. NSIP	a. 1 (2.3)	a. 1 (2.9)	a. 0 (0)	
b. Normal	b. 3 (7.0)	b. 2 (5.9)	b. 1 (11.1)	
c. Unsure	c. 4 (9.3)	c. 4 (11.8)	c. 0 (0)	

Table 3-2 Table showing investigations for all 170 cases where information is available grouped by men and women. Lung function results are shown in table 3-3. 1. *Calculated via chi squared testing.* **2.** *Calculated via Mann Whitney U testing.*

165 out of the 170 cases definitely had a HRCT for diagnosis and 5 cases where the imaging could not be traced or there was no documentation of the outcome. Out of these 170 cases, 137 (80.6%) had UIP. 42 (24.7%) of the cases required bronchoalveolar lavage. Biopsy was required in 42 (24.7%) of cases with 81.4% of these showing UIP. As can be seen from Table 3-2 there were no significant differences between male and female with regards to investigations excluding lung function.

3.1.3 Lung function at diagnosis and post antifibrotics

Lung function at diagnosis	Total N = 170	Missing cases (no.)	Men N = 126 (74.1%)	Women N = 44 (25.9%)	P value
FEV_1 *Mean (SD)*	2.10 (0.612)	0	2.30 (0.531)	1.55 (0.481)	0.000[1]
FEV_1 % predicted *Median (IQR)*	78.0 (22.2)	0	78.0 (22.6)	80.2 (21.2)	0.866[2]
FVC *Mean (SD)*	2.61 (0.831)	0	2.90 (0.712)	1.81 (0.589)	0.000[1]
FVC % predicted *Median (IQR)*	74.0 (22.7)	0	73.3 (20.2)	76.8 (28.3)	0.990[2]
DL_{CO} *Median (IQR)*	3.59 (1.79)	7	3.86 (1.64)	2.76 (1.44)	0.000[2]
DL_{CO} % predicted *Median (IQR)*	43.6 (20.2)	7	44.2 (20.8)	40.0 (19.5)	0.019[2]
RV *Median (IQR)*	1.32 (0.54)	51	1.37 (0.540)	1.12 (0.590)	0.001[2]
RV % predicted *Median (IQR)*	53.2 (22.5)	52	53.2 (22.0)	53.2 (28.3)	0.853[2]
TLC *Mean (SD)*	4.18 (1.12)	44	4.59 (0.924)	3.10 (0.830)	0.000[1]
TLC % predicted *Median (IQR)*	65.0 (17.2)	44	66.0 (16.4)	63.0 (22.0)	0.211[2]

Table 3-3 Table showing spirometry, gas exchange and lung volumes at diagnosis, grouped by men and women. 1. Independent t-test for normally distributed data **2.** Mann Whitney U test for non-normally distributed data **3.** Test for normality conducted via Shapiro-Wilkes statistical test

All 170 cases had data on basic spirometry including FEV_1 and FVC. There was missing data on gas transfer and lung volumes as detailed in Table 3-3. The mean FEV_1 for the total population was 2.10 (SD 0.612) and the mean FVC was 2.61 (SD 0.831). Accounting for the missing data, the median DL_{CO} was 3.59 (IQR range 1.79). Although there are significant differences in the raw values for spirometry, gas exchange and lung volumes between men and women, taking into account height, weight and age, the only significant difference between genders is in the DL_{CO} percentage predicted.

PIRFENIDONE N = 139 Lung function over time	**No of cases**	**Missing cases**	**Lung function at diagnosis**	**Spirometry post antifibrotic**
FEV_1 *Mean (SD)*	107	32	2.08 (0.637)	1.85 (0.571)
FEV_1 % predicted *Mean (SD)*	106	33	78.7 (17.4)	72.8 (18.1)
FVC *Median (IQR)*	107	32	2.62 (1.10)	2.33 (0.95)
FVC % predicted *Median (IQR)*	106	33	75.4 (18.4)	71.0 (16.2)
DL_{CO} *Median (IQR)*	81	58	3.82 (1.79)	2.91 (1.67)
DL_{CO} % predicted *Median (IQR)*	82	57	45.5 (20.0)	35.4 (19.4)
RV *Mean (SD)*	8	131	1.14 (0.304)	0.986 (0.189)
RV % predicted *Mean (SD)*	8	131	48.9 (10.0)	41.8 (8.07)
TLC *Mean (SD)*	8	131	4.26 (1.22)	3.67 (1.18)
TLC % predicted *Mean (SD)*	8	131	66.2 (11.7%)	56.6 (12.5)

Table 3-4 Lung function over time for cases taking pirfenidone

NINTEDANIB N = 31 Lung function over time	**No. of cases**	**Missing cases**	**Lung function at diagnosis**	**Spirometry post antifibrotic**
FEV_1 *Mean (SD)*	23	8	2.25 (0.540)	1.93 (0.568)
FEV_1 % predicted *Mean (SD)*	21	10	85.5 (15.4)	74.2 (15.0)
FVC *Mean (SD)*	23	8	2.81 (0.718)	2.43 (0.803)
FVC % predicted *Mean (SD)*	22	9	81.7 (15.8)	71.3 (18.8)
DL_{CO} *Median (IQR)*	17	14	3.70 (2.26)	2.89 (1.38)
DL_{CO} % predicted *Median (IQR)*	17	14	43.0 (27.0)	40.0 (15.0)
RV	1	30	Only one case	
RV % predicted	1	30	Only one case	
TLC	1	30	Only one case	
TLC % predicted	1	30	Only one case	

Table 3-5 Lung function over time for cases taking nintedanib

Table 3-4 and Table 3-5 show the spirometry at diagnosis and post antifibrotic therapy split between pirfenidone and nintedanib. As shown, the mean decline in FVC with pirfenidone was 4.4%, compared with 10.4% with nintedanib. The mean decline in DL_{CO} for pirfenidone was 10.1% compared with 3.0% for nintedanib. The median time on medication was 186 days (IQR 545).

3.1.4 Referral pathway

The majority of referrals to the tertiary ILD service of UHB (HGS) were from secondary care at Good Hope Hospital (22.4%), Birmingham Heartlands Hospital (15.9%), Russells Hall Hospital (15.9%) and Solihull Hospital (15.3%). This is reflected in Table 3-6. The majority of cases within our population of patients had been treated at Birmingham Chest Clinic (62.9%), then Good Hope Hospital (24.7%) and then Solihull Hospital (12.4%). This is displayed in Figure 3-1.

Referring Hospital	Frequency	Percent
GHH	38	22.4
BHH	27	15.9
Dudley	27	15.9
SOH	26	15.3
Hereford	16	9.4
GP	12	7.1
SWBH	8	4.7
Walsall	7	4.1
Private	3	1.8
Nuneaton	2	1.2
Redditch	2	1.2
Wolverhampton	1	.6
Worcester	1	.6
Total	170	100.0

Table 3-6 Frequency of referrals to the tertiary ILD service at UHB (HGS) from different sources

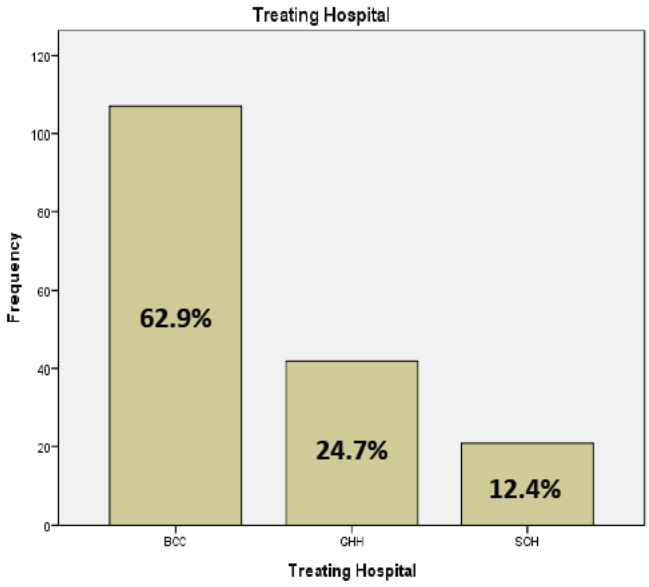

Figure 3-1 Bar chart to show proportion of patients being treated at each site of UHB (HGS).

3.1.5 Side effects during treatment

147 out of 170 patients reported suffering from side effects during treatment. 17 denied having side effects and there was missing data in 6 cases. From healthcare reported side effects, the most commonly reported in those taking pirfenidone were nausea (+/- vomiting) (49.6% of cases), appetite loss (40.3%), fatigue or lethargy (37.0%) and photosensitivity rash (26.9%), whereas the commonest reported side effects for nintedanib included diarrhoea (79.2%), weight loss (25.0%), appetite loss (20.8%) and nausea (+/- vomiting) (20.8%). Table 3-7 and Table 3-8 show the percentage of side effects suffered across all cases of pirfenidone and nintedanib reported by healthcare professionals grouped into gastrointestinal, skin related, deconditioning and other side effects.

Gastrointestinal side effects consisted of appetite loss, reflux, nausea (+/- vomiting), constipation, diarrhoea, abdominal pain and bloating. Skin related side effects included photosensitivity rash, itchiness and non photosensitivity rash. Deconditioning side effects consisted of weight loss, weakness, fatigue, 'generally unwell', muscle ache and painful legs. Other side effects are all those that are not contained within the above groups – namely: dizziness, low mood, headache, joint pains, insomnia, difficulty passing urine, runny nose, liver toxicity, blurred vision, feeling 'spaced out', night sweats, dry mouth, hiccoughs, vivid dreams, blisters in mouth and loss of taste.

Antifibrotic Agent	Side effect		Percent of Cases
Pirfenidone	Gastrointestinal	Nausea (+/- vomiting)	49.6%
		Appetite loss	40.3%
		Diarrhoea	21.8%
		Reflux	12.6%
		Abdominal Pain	11.8%
		Bloating	10.9%
		Constipation	5.9%
	Skin Related	Photosensitivity rash	26.9%
		Non Photosensitive Rash	1.7%
	Deconditioning	Fatigue/Lethargy	37.0%
		Weight loss	10.1%
		Generally Unwell	5.0%
		Muscle Ache	0.8%
		Painful Legs	0.8%
	Other	Dizziness	9.2%
		Headache	4.2%
		Insomnia	3.4%
		Loss of Taste	3.4%
		Low Mood	1.7%
		Spaced out	1.7%
		Joint Pains	0.8%
		Difficulty Passing Urine	0.8%
		Runny Nose	0.8%
		Blurred Vision	0.8%
		Night Sweats	0.8%
		Hiccoughs	0.8%
		Vivid Dreams	0.8%
		Blisters in Mouth	0.8%

Table 3-7 Table to show the percentage of side effects suffered across all cases of pirfenidone as reported by a healthcare professional

Antifibrotic Agent	Side effect		Percent of Cases
Nintedanib	Gastrointestinal	Diarrhoea	79.2%
		Nausea (+/- vomiting)	20.8%
		Appetite loss	20.8%
		Constipation	8.3%
		Abdominal Pain	8.3%
		Reflux	4.2%
		Bloating	4.2%
	Deconditioning	Weight loss	25.0%
		Fatigue/Lethargy	8.3%
	Other	Liver Toxicity	12.5%
		Dry Mouth	4.2%

Table 3-8 Table to show the percentage of side effects suffered across all cases of nintedanib as reported by a healthcare professional

The commonest reported side effects from patient or patient relative telephone interviews for pirfenidone were nausea (+/- vomiting) (35.6%), fatigue or lethargy (26.7%), appetite loss (20.0%) and abdominal pain (17.8%). In those taking nintedanib, the commonest reported were diarrhoea

(90.9%) and abdominal pain (27.3%). Table 3-9 and Table 3-10 show the results grouped into gastrointestinal, skin related, deconditioning and other side effects. We were only able to contact 56 out of 139 patients or patients' relatives taking pirfenidone and 19 out of 31 taking nintedanib, leading to a total 95 missing cases. Out of the cases where data was available 46 (82.1%) taking pirfenidone and 11 (57.9%) taking nintedanib suffered with side effects. Out of those that responded to telephone interviews 35.7% taking pirfenidone and 10.5% taking Nintedanib took a treatment break or had a dose reduction period during their treatment.

Antifibrotic Agent	Side effect		Percent of Cases
Pirfenidone	Gastrointestinal	Nausea (+/- vomiting)	35.6%
		Appetite loss	20.0%
		Abdominal Pain	17.8%
		Diarrhoea	13.3%
		Reflux	4.4%
		Constipation	2.2%
	Skin Related	Photosensitivity rash	11.1%
		Itchiness	4.4%
	Deconditioning	Fatigue/Lethargy	26.7%
		Weight loss	11.1%
		Generally Unwell	8.9%
		Weakness	2.2%
	Other	Dizziness	6.7%
		Low Mood	6.7%
		Headache	4.4%
		Joint Pains	2.2%
		Insomnia	2.2%

Table 3-9 Table showing the percentage of side effects suffered across all cases of pirfenidone as reported by patients or patient's relatives

Antifibrotic Agent	Side effect		Percent of cases
Nintedanib	Gastrointestinal	Diarrhoea	90.9%
		Abdominal Pain	27.3%
		Constipation	9.1%
	Deconditioning	Weight loss	9.1%
		Generally Unwell	9.1%

Table 3-10 Table showing the percentage of side effects suffered across all cases of nintedanib as reported by patients or patient's relatives

Table 3-11 shows the number of patients grouped by each drug that had a dose reduction or break.

Antifibrotic Agent		Number of cases	Percent
Pirfenidone	Had dose reduction or break	20	35.7
	Did not have dose reduction or break	33	58.9
	Unsure	3	5.4
	Total	56	100.0
	Missing	83	n/a
	Total	139	
Nintedanib	Had dose reduction or break	2	10.5
	Did not have dose reduction or break	17	89.5
	Total	19	100.0
	Missing	12	n/a
	Total	31	

Table 3-11 Table showing the number of cases for each antifibrotic that took a break from antifibrotic therapy or had a dose reduction. Missing cases included in table where data not retrievable.

3.1.6 Reasons for discontinuation

According to clinical letters and electronic database results, the commonest reasons for stopping antifibrotic therapy according to healthcare professionals were side effects (47.0%) and death (17.5%). The healthcare stated reasons for discontinuation are shown in Table 3-12 and displayed in Figure 3-2.

Healthcare Professional reason for discontinuation	Number of cases	Percent
Side effects	78	47.0
Continuing Treatment	40	24.1
Death of Patient	29	17.5
Other	9	5.4
Disease progression	6	3.6
Development of Malignancy	2	1.2
Patient Choice	2	1.2
Missing	4	n/a
Total	170	

Table 3-12 Table showing the healthcare stated reason for stopping antifibrotic therapy

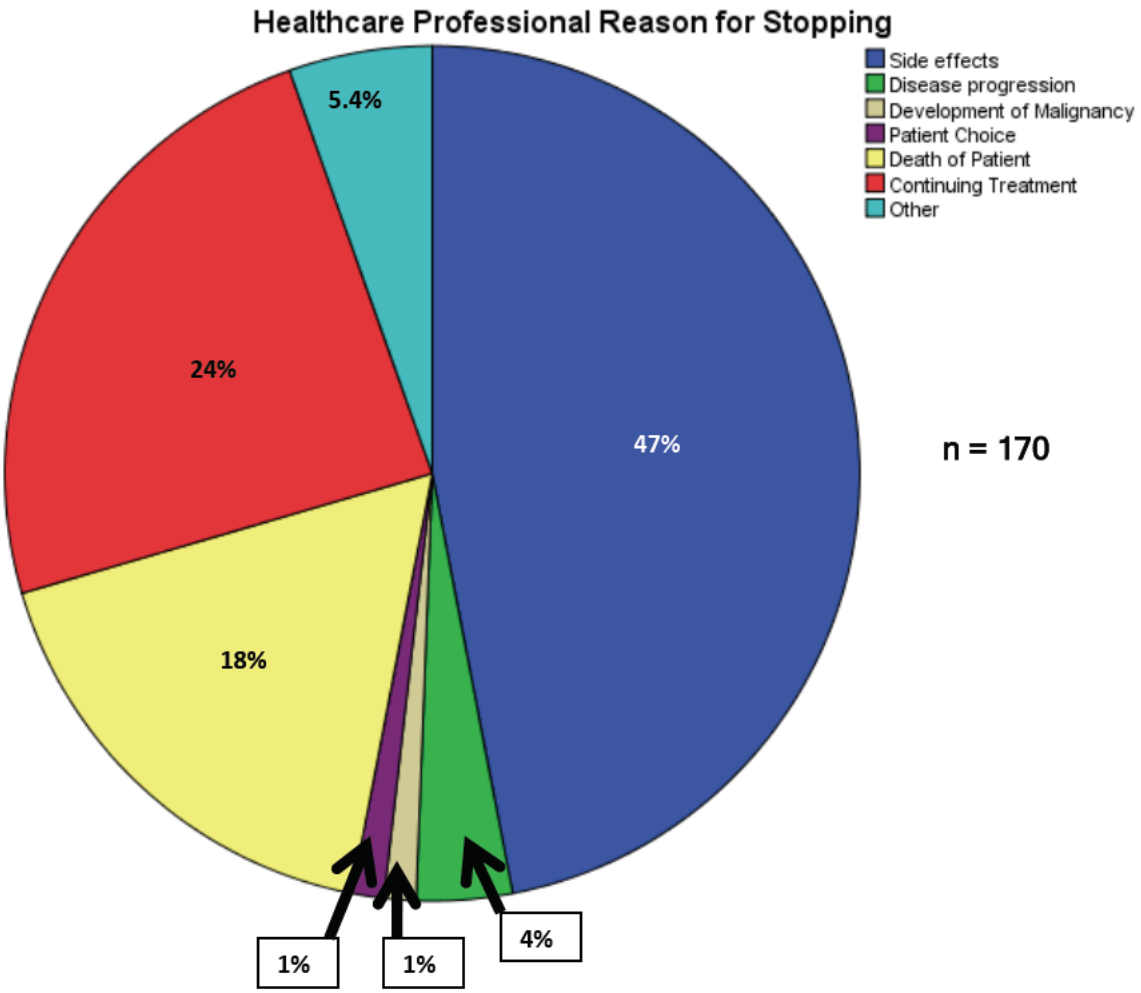

Figure 3-2 **Pie chart to show the healthcare professional stated reason for stopping antifibrotics**

3.2 Univariate and multivariate analysis

3.2.1 30 day discontinuation analysis

As can be seen from Table 3-13 the only variables that showed a significant difference between those with early discontinuation at 30 days and those without were gender ($p > 0.001$), DL_{CO} percentage predicted at diagnosis of above and below 40% ($p = 0.001$), gastrointestinal side effects ($p = 0.007$) and skin related side effects ($p = 0.004$). Referring hospital within and outside of UHB (HGS) was close to significance, but did not quite meet the threshold with a p value of 0.076.

The results of a binary logistic regression, using 30-day cut-off for discontinuation and including variables found to be significant in the univariate analysis are shown in Table 3-14. 95.9% of cases were included in the analysis, with only 7 cases not used due to missing data. The Nagelkerke correlation coefficient was calculated as 0.257 or 25.7%. Once inserted into the multivariate analysis,

only DL_{CO} above and below 40%, gender and the presence of skin related side effects were shown to be significant. A DL_{CO} of less than 40% at diagnosis has been shown to increase the risk of discontinuation at 30 days by 2.46 (CI 1.06 – 5.73). Male gender in our analysis reduces the risk of discontinuation (OR = 0.405 (CI 0.172 – 0.956)), which conversely means that a female gender increases the risk of early discontinuation by 2.47 (1/OR for male gender). The analysis has shown that those with the presence of skin related side effects have a reduced risk of early discontinuation at 30 days with an odds ratio of 0.091 (CI 0.012 – 0.716).

Variable	Total	30 day early discontinuation n = 43 (25.3%)	NOT 30 day early discontinuation n = 127 (74.7%)	Statistic Chi Squared
Age n (%)	N = 170			
1. 65 and below	44 (25.9)	7 (16.3)	37 (29.1)	0.096
2. Above 65	126 (74.1)	36 (83.7)	90 (70.9)	
Age n (%)	N = 170			
1. 60 and below	24 (14.1)	3 (7.0)	21 (16.5)	0.120
2. Above 60	146 (85.9)	40 (93.0)	106 (83.5)	
Gender	N = 170			0.000
1. Male	126 (74.1)	23 (53.5)	103 (81.1)	
2. Female	44 (25.9)	20 (46.5)	24 (18.9)	
Ethnicity	N = 148			0.857
1. British	127 (85.8)	28 (84.8)	99 (86.1)	
2. Non British	21 (14.2)	5 (15.2)	16 (13.9	
First Language	N = 139			0.540
1. English	133 (95.7)	30 (93.8)	103 (96.3)	
2. Non English	6 (4.3)	2 (6.3)	4 (3.7)	
Referring Hospital	N = 170			0.076
1. UHB (HGS)	91 (53.5)	18 (41.9)	73 (57.5)	
2. Non UHB (HGS)	79 (46.5)	25 (58.1)	54 (42.5)	
Dedicated ILD nurse	N = 170			0.451
1. Yes	107 (62.9)	25 (58.1)	82 (64.6)	
2. No	63 (37.1)	18 (41.9)	45 (35.4)	
Distance to Treating Hospital	N = 170			0.291
1. 8 Miles and below	83 (48.8)	18 (41.9)	65 (51.2)	
2. Above 8 Miles	87 (51.2)	25 (58.1)	62 (48.8)	
FVC% at diagnosis	N = 170			0.596
1. 80% and below	113 (66.5)	30 (69.8)	83 (65.4)	
2. Above 80%	57 (33.5)	13 (30.2)	44 (34.6)	
DL_{CO}% at diagnosis	N = 163			0.001
1. 40% and below	64 (39.3)	23 (62.2)	41 (32.5)	
2. Above 40%	99 (60.7)	14 (37.8)	85 (67.5)	
Prescription Method	N = 170			0.969
1. NHS	142 (83.5)	36 (83.7)	106 (83.5)	
2. MPP/NPP	28 (16.5)	7 (16.3)	21 (16.5)	
Socioeconomic level	N = 144			0.192
1. 1-3	33 (22.9)	5 (14.7)	28 (25.5)	
2. 4-6	111 (77.1)	29 (85.3)	82 (74.5)	
Level of education	N = 84			0.282
1. GCSE and above	16 (19.0)	2 (10.5)	14 (21.5)	
2. School and other	68 (81.0)	17 (89.5)	51 (78.5)	
Attended IPF support group	N = 89			0.870
1. Attended	41 (46.1)	10 (47.6)	31 (45.6)	
2. Did not Attend	48 (53.9)	11 (52.4)	37 (54.4)	
Side effects				
1. Yes	147 (86.5)	36 (83.7)	111 (87.4)	0.542
2. No	23 (13.5)	7 (16.3)	16 (12.6)	
a. (Unsure)	(6 cases)			
GI side effects	N = 170			
1. Yes	122 (71.8)	24 (55.8)	98 (77.2)	0.007
2. No	48 (28.2)	19 (44.2)	29 (22.8)	
Skin related side effects	N = 170			
1. Yes	34 (20.0)	2 (4.7)	32 (25.2)	0.004
2. No	136 (80.0)	41 (95.3)	95 (74.8)	
Deconditioning side effects	N = 170			
1. Yes	65 (38.2)	21 (48.8)	44 (34.6)	0.098
2. No	105 (61.8)	22 (51.2)	83 (65.4)	
'Other' Side effects	N = 170			
1. Yes	34 (20.0)	7 (16.3)	27 (21.3)	0.480
2. No	136 (80.0)	36 (83.7)	100 (78.7)	
Combined GI/skin/systemic side effects	N = 170			
1. Yes	142 (83.5)	34 (79.1)	108 (85.0)	0.362
2. No	28 (16.5)	9 (20.9)	19 (15.0)	

Table 3-13 Table showing univariate analyses of variables split between 30 day early discontinuation. The grouping of side effects into gastrointestinal, skin related, deconditioning and other side effects is explained in section 3.1.5.

Variable	P value	Odds Ratio (OR)	95% C.I. for OR	
			Lower	Upper
DL_{CO} of 40% and below	.037	2.46	1.06	5.73
Presence of Gastrointestinal side effects	.101	.485	.204	1.152
Had skin related side effects	.023	.091	.012	.716
Male Gender	.039	.405	.172	.956

Table 3-14 Binary logistic regression multivariate analysis for 30 day discontinuation showing odds ratio for risk of discontinuation and confidence intervals.

3.2.2 90 day discontinuation analysis

Variable	Total	90 day early discontinuation n = 58 (34.1%)	NOT 90 day early discontinuation n = 112 (65.9%)	Statistic Chi Squared
Age n (%)	N = 170			
1. 65 and below	44 (25.9)	10 (17.2)	34 (30.4)	0.064
2. Above 65	126 (74.1)	48 (82.8)	78 (69.6)	
Age n (%)	N = 170			
1. 60 and below	24 (14.1)	4 (6.9)	20 (17.9)	0.052
2. Above 60	146 (85.9)	54 (93.1)	92 (82.1)	
Gender	N = 170			
1. Male	126 (74.1)	34 (58.6)	92 (82.1)	0.001
2. Female	44 (25.9)	24 (41.4)	20 (17.9)	
Ethnicity	N = 148			
1. British	127 (85.8)	41 (87.2)	86 (85.1)	0.735
2. Non British	21 (14.2)	6 (12.8)	15 (14.9)	
First Language	N = 139			
1. English	133 (95.7)	44 (95.7)	89 (95.7)	0.990
2. Non English	6 (4.3)	2 (4.3)	4 (4.3)	
Referring Hospital	N = 170			
1. UHB (HGS)	91 (53.5)	28 (48.3)	63 (56.3)	0.323
2. Non UHB (HGS)	79 (46.5)	30 (51.7)	49 (43.8)	
Dedicated ILD nurse	N = 170			
1. Yes	107 (62.9)	36 (62.1)	71 (63.4)	0.865
2. No	63 (37.1)	22 (37.9)	41 (36.6)	
Distance to Treating Hospital	N = 170			
1. 8 Miles and below	83 (48.8)	30 (51.7)	53 (47.3)	0.586
2. Above 8 Miles	87 (51.2)	28 (48.3)	59 (52.7)	
FVC% at diagnosis	N = 170			
1. 80% and below	113 (66.5)	42 (72.4)	71 (63.4)	0.238
2. Above 80%	57 (33.5)	16 (27.6)	41 (36.6)	
DL_{CO}% at diagnosis	N = 163			
1. 40% and below	64 (39.3)	29 (55.8)	35 (31.5)	0.003
2. Above 40%	99 (60.7)	23 (44.2)	76 (68.5)	
Prescription Method	N = 170			
1. NHS	142 (83.5)	50 (86.2)	92 (82.1)	0.498
2. MPP/NPP	28 (16.5)	8 (13.8)	20 (17.9)	
Socioeconomic level	N = 144			
1. 1-3	33 (22.9)	10 (21.3)	23 (23.7)	0.744
2. 4-6	111 (77.1)	37 (78.7)	74 (76.3)	
Level of education	N = 84			
1. GCSE and above	16 (19.0)	2 (7.4)	14 (24.6)	0.062
2. School and other	68 (81.0)	25 (92.6)	43 (75.4)	
Attended IPF support group	N = 89			
1. Attended	41 (46.1)	12 (40.0)	29 (49.2)	0.413
2. Did not Attend	48 (53.9)	18 (60.0)	30 (50.8)	
Side effects	N = 170			
1. Yes	147 (86.5)	51 (87.9)	96 (85.7)	0.689
2. No	23 (13.5)	7 (12.1)	16 (14.3)	
a. (Unsure)	(6 cases)			
GI side effects				
1. Yes	122 (71.8)	34 (58.6)	88 (78.6)	0.006
2. No	48 (28.2)	24 (41.4)	24 (21.4)	
Skin related side effects				
1. Yes	34 (20.0)	7 (12.1)	27 (24.1)	0.063
2. No	136 (80.0)	51 (87.9)	85 (75.9)	
Deconditioning side effects	N = 170			
1. Yes	65 (38.2)	28 (48.3)	37 (33.0)	0.053
2. No	105 (61.8)	30 (51.7)	75 (67.0)	
'Other' Side effects	N = 170			
1. Yes	34 (20.0)	13 (22.4)	21 (18.8)	0.571
2. No	136 (80.0)	45 (77.6)	91 (81.3)	
Combined GI/skin/systemic side effects	N = 170			
1. Yes	142 (83.5)	47 (81.0)	95 (84.8)	0.528
2. No	28 (16.5)	11 (19.0)	17 (15.2)	

Table 3-15 Table showing univariate analyses of variables split between 90 day early discontinuation. The grouping of side effects into gastrointestinal, skin related, deconditioning and other side effects is explained in section 3.1.5.

Variable	P value	Odds Ratio (OR)	95% C.I. for OR	
			Lower	Upper
Age above 60	.153	2.459	.717	8.437
DL_{CO} 40% predicted and below	.119	1.834	.856	3.929
Presence of gastrointestinal side effects	.030	.400	.175	.915
Had skin related side effects	.126	.453	.164	1.249
Male gender	.026	.392	.173	.892
Presence of deconditioning side effects	.016	2.583	1.196	5.579

Table 3-16 Binary logistic regression multivariate analysis for 90 day discontinuation showing odds ratio for risk of discontinuation and confidence intervals.

As only 43 cases discontinued with less than 30 days between their first and last prescription, we also decided to include a 90-day cut-off for grouping by time to discontinuation. Again, we started with a univariate analysis for each variable and used those that were significant to produce a multivariate analysis to create a prediction model for early discontinuation (90 days in this case). The univariate analysis shown in Table 3-15 shows significant differences in gender (p = 0.001), DL_{CO} percentage predicted at diagnosis above and below 40% (p = 0.003) and presence of gastrointestinal side effects (p = 0.006). Age above and below 60 (p = 0.052) was close to significance.

The variables used in the multivariate analysis are shown in Table 3-16. The inclusion rate of cases was again 95.9%, with only 7 missing cases as per the 30-day analysis. The Nagelkerke correlation coefficient was 0.236 or 23.6%. The significant variables in the 90-day analysis shown to reduce the risk of discontinuation within 90 days include the presence of gastrointestinal side effects (OR = 0.400; CI 0.175 – 0.915) and male gender (OR = 0.392; CI 0.173 – 0.892). The only variable to show a significant increase in risk of discontinuation within 90 days was the presence of deconditioning side effects (OR = 2.58; CI 1.20 – 5.58).

3.3 Qualitative data thematic analysis

The main themes and subthemes found during the qualitative interview and focus group analysis are displayed in Table 3-17, Table 3-18, Table 3-19, Table 3-20 and Table 3-21. These have been grouped into different stages of the patient pathway: diagnosis, management, perception of specialist service, travel and location and health service and community support. Table 3-22 shows the advice given by patients to other patients considering starting antifibrotics.

3.3.1 Diagnostic themes and subthemes

Main Theme		Interview Number	Quotes
Diagnostic Delay	Perception of a slow diagnosis	Individual Interview 1	• 'and I did have a little trouble getting diagnosed in the first place to be honest.'
		Individual Interview 2	• 'constantly getting coughs and colds […] it was occurring every sort of 6 weeks, that sort of time.'
		Individual Interview 10	• 'P: how long did it take from original symptoms to being referred? […] [or] getting a diagnosis? Patient: 6 months'
		Focus Group 1	• 'started having symptoms approximately eight to nine years ago – and after a long time, was referred to a consultant […]they came up with a diagnosis after quite a number of months
	Perception of a quick diagnosis	Individual Interview 6	• 'P: how did you find the referral process? Patient: pretty good'
		Focus Group 3	• 'You were saying about how long it takes for people to be referred […] it was very very quick really.'
Sub - Themes		**Interview Number**	**Quotes**
Delay in Referral	Repeated Healthcare professional visits	Individual Interview 1	• '"Well it could be a bit of damage from previous infections etc etc" and I accepted that for a while'
		Individual Interview 2	• 'My GP prescribed antibiotics and it was occurring every sort of 6 weeks, that sort of time.'
		Individual Interview 3	• 'it was Russell's Hall originally that – (…) - I don't know, I've seen so many doctors.'
		Focus Group 1	• 'eventually I did go and see the doctor and on more than one occasion I had x-rays, showed nothing'
	Lack of healthcare professional knowledge – Chest X-rays	Individual Interview 1	• 'oh you got little patches on your x-ray here, but nothing to worry about' • 'it was very much an "ohh, pff, no no no, u know that's not right" and I don't know in all honesty, whether they knew it was and were trying to protect me for a bit, or whether they genuinely didn't think that it was the diagnosis'
		Individual Interview 2	• 'x-ray […] this just said well you know it's a - you've got a weakness there, you've got a bit of a shadow and so on – and we just carried on really taking antibiotics'
	Lack of healthcare professional knowledge – IPF/disease related	Focus Group 1	• 'I couldn't actually have it, because I wasn't in the right authority […]He didn't think at that point in time it was worth me being referred really' • 'terrible cough, and my doctor, GP, sent me for an x-ray and "nothing wrong with your lungs, you're alright."' • 'GPs do not know enough about IPF' • 'the patient 9/10 knows more about the disease than the medical practitioner' • 'you end up educating them!' • 'what you really need is some form of pro-forma documentation to say this is what I've got doctor.'

		Focus Group 2	• 'Went to the doctors and he dismissed it as symptoms of a virus and that was it' • 'I think as I said Drs. haven't got the knowledge now […] my doctor I don't think really knew'
	Self-diagnosis	Individual Interview 1	• 'so I started checking up on Dr. Google and it came up with idiopathic pulmonary fibrosis'
		Individual Interview 2	• 'eventually – err I - I googled – erm - lung conditions […] conference in Manchester […] I hadn't been diagnosed with IPF at that time, it was just 'chesty' you know.'
		Focus Group 1	• 'and it wasn't until I went on the internet I realised how serious it was'
		Focus Group 2	• 'Still had the breathlessness […] went to see a cardiologist, I paid privately.'
Delay in Investigations		Individual Interview 1	• 'Lung biopsy […]point it was a bit long time getting the results back' • 'this is a problem in a way, you're not my local hospital […] the authorities don't talk to each other very well […] I've had to sort of try and make sure that any letters or results I've had from one is passed to the other'
		Focus Group 1	• 'Eventually they referred me to- arranged for a scan that obviously showed quite a lot of damage to the lungs' • 'one of the problems I think the NHS suffers from is a lack of communication between the authorities, I mean there's no real- real proper communication because I had to work between two authorities.'
Satisfaction once diagnosis confirmed		Individual Interview 1	• 'I came here and er you've taken over my care and - I've been very happy with the results so far'
		Focus Group 1	• 'Eventually, I saw a more imminent consultant who definitively diagnosed IPF […] from that moment on, a lot of my problems disappeared.' • 'once you're in the system and you're known, I think it works pretty well, but it's getting through this problem of the early stages of your illness.'
Incidental Diagnosis		Individual Interview 4	• 'actually went to my local hospital for – erm – pains in my back […]they did x-rays and scans and that and they picked up'
		Individual Interview 5	• 'I found out when I got double pneumonia […] did all these tests on me […] put me on these tunnels […] then he referred me to […] Dr. X.'
		Individual Interview 9	• 'I had colon cancer […]Towards the end of my chemo I was getting very breathless […]that's when he diagnosed the IPF'
		Focus Group 2	• 'I had to have two tests at the hospital for – erm – kidneys – erm – the bowel […] they'd put a little note on the CT scan that there was something at the bottom of my lungs.' • 'P4 was diagnosed unusually early because they picked up an abnormality or something suspicious […] on other tests so P4 hasn't quite got the normal symptoms that would drive you to the GP.' • 'I rushed to get to the hospital and that's when I get out of breath, they noticed it […] gave me an x-ray and that's when they picked it up'
		Focus Group 3	• It was something that was picked up because before Radley would operate on the hernia, he wanted to make sure my chest would […] take the anaesthetic.
Emotional Response	Frustration	Individual Interview 2	• [in regards to home improvement] 'which really annoys me, because I know what to do but I just can't do it.'
		Individual Interview 3	• 'nobody would listen to ya […] I've also got the back (patient had a recent back issue requiring what sounded like a brace) […] the doctor said you must wear it, and I said, "I cannot wear it, I cannot breathe!" […] he said, "you're refusing to then"'
		Focus Group 1	• 'I got a diagnosis, which wasn't clearly explained to me at the time and I didn't clearly understand, and other than saying that the disease was terminal and there was nothing they could do for me […] which left me somewhat dissatisfied at the time.' • 'it wasn't explained to me that steroids over a long period of time wasn't good.'

			• 'I mean I'm physically, there's nothing wrong with my body, it's a frustration, you know I liken myself to a car that's passed the MOT, but they haven't changed the air filter.'
		Focus Group 2	• 'the wife's in a wheelchair, I can't push her […] Things like that which frustrates me […] and I think it upsets you in a way […] that you can't do what you used to do, and it's so frustrating.'
	Acceptance	Individual Interview 2	• 'it's just you can't cure it, it would be nice if you could but-'
		Individual Interview 8	• 'I suppose the thing that he said was the most critical, "you must realise that from the date of the initial analysis of IPF the average lifespan is 3 to 5 years." Right? And that then puts it in […] one big nutshell.'
		Individual Interview 9	• 'but the chemo you're thinking well we'll beat this, but with this one you're thinking well – hopefully they'll work, but if they do work it's just gonna slow it down apparently.'
		Focus Group 1	• 'You've been good to last 10 years as well. I don't think I'll last 10 years.' • 'I don't look that I've got a terminal illness right, I get on with life!'
		Focus Group 2	• 'he said to me […] this is your quality of life is more important for you at this stage.' • 'you've got to make the best of it.' • 'I think once you've accepting the diagnosis, then you know all that you can do.' • 'There's no way back is there you've just gotta keep going.' • 'you can stick your head in the corner and scream the place down, but at the end of the day, you gotta live your life.' • 'Purely because only like I'm at a certain age, I don't expect to live much longer you know and my 79 nearly it's- I'm gonna give myself another 5 years at least, but I won't give in to that. I'll use it, but I won't give in to it.'

Table 3-17 Themes and subthemes for diagnosis of IPF found in individual and focus group sessions.

3.3.2 Management themes and subthemes

Theme	Sub-themes	Interview number	Quote
Choice of Antifibrotic – weight up of benefits and risks	Doing what you are told by the doctor	Individual Interview 2	• 'there was nintedanib […] I think CNS – sort of steered me towards […] pirfenidone […] I just went along with – erm – with-with what we were told here yeah.'
		Individual Interview 5	• 'Professor X said that I take it he doesn't like wearing a lot of clothes and he won't wear the sun cream […] so I'm not gonna put him on that one […] put him on the other one, which doesn't burn or affect him.'
		Individual Interview 9	• 'because of the- the- the bowel cancer […] she (specialist nurse) reckoned that the one that we're on (Pirfenidone) now would be more beneficial.'
	Making a decision in collaboration with medical teams	Individual Interview 1	• 'Pirfenidone […] sounded messy and inconvenient and err altogether less reliable than the – nintedanib.'
		Individual Interview 3	• 'they said oh you get sunstroke, you get this, you get sick and nausea […] it sounded so horrible […] there was this other one, this nintedanib – erm – which doesn't have all these horrible effects. […] that first one they offered (pirfenidone) was so horrible – that I said no forget it.' • 'You've either gotta have one or the other. Listen to the side effects, assess it yourself […] if you feel it's something you cannot stand […] fall for the other one.'
		Individual Interview 4	• 'because the nintedanib, one of the side effects was possible diarrhoea […] that was the reason we went with the pirfenidone.'
		Individual Interview 10	• 'pirfenidone seemed to be the one for me because the other one- you had a chance of bad diarrhoea and stuff like that. […] which […] with the condition you have you don't- you don't really want anything else.'
		Focus Group 1	• 'it was agreed that probably pirfenidone would be better for me, or rather try pirfenidone first' • 'I was given the choice of the other one nintedanib. I now know I can't have it because I got- I had an embolism on this lung.' • 'P: would the 3 capsules 3 times a day be an influence for you? Patient: Personally I'd choose the nintedanib.'
Managing side effects	Adjusting lifestyle, taking concomitant medication to aid tolerance of antifibrotic	Individual interview 1	• 'get yourself onto a plateau with it […] you got all this poo and diarrhoea […] so – it's a bit of a delicate balance' • 'I have deliberately missed it once or twice […] when I knew we were going to go out […] just so I could give myself that little bit of lee way'
		Individual Interview 2	• 'if I haven't had a large meal I get a bit of dizziness' • 'P: how about the […] sun exposure? Patient: that's my fault because I've not been using […] it's such a bind putting it on you know.'
		Individual Interview 5	• 'it was very good to start with, but then the diarrhoea sort of followed in […] and he was on some diarrhoea tablets [Loperamide]'
		Individual Interview 6	• 'I felt a little nauseous at first, but the – professor gave me some – tablets to quell that.'
	Persisting with antifibrotic despite side effects	Individual Interview 8	• 'You can lose your appetite a lot. […] but then you still gotta force yourself because you want to be on this drug that is going to slow down the rate of progression of your IPF. […] so you gotta force yourself then to eat.' • 'ah now that (experience on nintedanib) can be up and down! […] I can have another spell where it upsets my system with going to the toilet'
		Focus Group 1	• 'I got very itchy skin […] little red spots that were itchy […] but I admit I probably wasn't very good with the factor 50 all the while.' • 'it's really difficult to know how much you attribute to the drugs, or how much is your general condition […] I tend to blame everything initially on pirfenidone, but then I thought I don't really know if I'm honest.'
	Negotiating	Focus Group 2	• 'I did try the pirfenidone to start with, it didn't suit me at all, it made me feel really ill. I didn't want to get out of bed of a

	with clinical team to change antifibrotic if initial choice poorly tolerated		morning. I'd got no quality of life, I just felt ill all the time. […] I spoke to Professor X and he said, "come off it and we'll try you on something else."' • 'I find they do upset me stomach and I also don't want to eat. […] I've lost two stone in weight. I don't know whether to come off pirfenidone unless it was the other tablet.' • 'I used to feel nauseous […] he gave me that cyclizine.'
	Titration of Dose/Treatment Holiday	Individual Interview 2	• 'after a while you get- you get to manage it [pirfenidone] yourself, you know you don't have to go to your GP and ask this that and the other- you can do it yourself.'
		Individual Interview 4	• 'so you've been on the reduced dose then, to see if the skin was secondary to the tablets?'
		Individual Interview 5	• 'at the moment he's got a lot of stomach problems and his appetites gone so CNS's took him off them to give him a break.'
		Individual Interview 6	• 'CNS took me off them for about a month because I was having sun rash.'
		Individual Interview 8	• 'forgot me tablets (nintedanib) […] see what happens now that you're off them for a few days […] and I didn't have a problem – no diarrhoea, no nothing.'
		Focus Group 1	• 'as I went onto the full dose, the nausea became quite unbearable. Dropped back down to a lower dosage, for another 3-4 weeks and then stepped up to the main dose – erm – and from there on, for about two years no [problems].' • 'I wonder if you could have a mixture of both, so small tablets with some of the big ones […] juggle your medication with a bit more flexibility.'
Understanding of treatment effect	Good perception of treatment effect	Individual interview 1	• 'The decline […] has been helped by it, because it's been quite slow'
		Individual Interview 7	• 'breathing test was not too good like you see, now coming and they it's almost in the same range as last you see, so it's [helpful]'
	Poor perception of treatment effect	Individual Interview 3	• 'I mean whether it's slowing it down, whether it's stopping it, whether it's doing nothing at all I don't know'
		Focus Group 2	• 'I've been taking it [antifibrotic] for about 15-16 months and I don't know whether it's doing me any good.' • 'that's the one thing we're waiting for really, to see if it made any difference, but it doesn't seem to have done, you just don't know do you.'
Treatment regime	Tablet burden issues	Individual Interview 4	• 'it's (nintedanib) easier to take (than pirfenidone)'
		Individual Interview 9	• 'it's not so much the 3 tablets 3 times a day, it's the other 12 tablets that I gotta take with that.' • 'But we've been able to reduce it to the one tablet. It's a big help.'
		Focus Group 1	• 'The other one that I think a lot of us suffer from us is pill overkill. You know taking so many pills, and so many tablets 3 times a day.'
	Impact on lifestyle	Individual Interview 2	• 'sometimes I forget […] not often!'
		Individual Interview 8	• 'It's to do with your lifestyle – taking 3 tablets 3 times a day. That's the only thing with pirfenidone.' • 'we know people who've said – "not doing it! […] because it impinges on my lifestyle".'

Table 3-18 Themes and sub-themes on management of IPF found in qualitative individual and focus group sessions.

3.3.3 Perception of specialist service

Theme	Sub-Theme	Interview Number	Quote
Satisfaction with set up at BCC	Satisfaction once in the support system of BCC	Individual Interview 1	• 'service at the chest clinic has been very good'
		Individual Interview 2	• 'Can't fault it (service at chest clinic)'
		Individual Interview 3	• 'I find the service here and the people – the staff – excellent.'
		Individual Interview 4	• 'absolutely excellent […] all the staff are- are very good, excellent.'
		Individual Interview 5	• 'the service? Brilliant!'
		Individual Interview 6	• 'Excellent (service at the chest clinic)'
		Individual Interview 7	• 'Well it's (service at the chest clinic) alright reasonably yes.'
		Individual Interview 8	• '(with regards to service at chest clinic) Brilliant!'
		Individual Interview 9	• '(with regards to service at chest clinic) top draw'
		Individual Interview 10	• 'this hospital here? […] Outstanding!'
		Focus Group 1	• 'Very good! Once you're in the loop, you get the right attentive care.'
		Focus Group 2	• 'The chest clinic was fantastic.' • 'I've had wonderful treatment!'
	Parking Problems	Individual interview 1	• 'you can't park! I've finally given up coming in the car'
		Individual Interview 2	• 'parking used to be a problem […] we found a parking place […] but the walk from there used to bloody kill me […] now you've got the disabled parking outside. But there's only two spaces.'
		Individual Interview 6	• 'P: anything that you feel could be improved? Patient: the parking outside.'
		Individual Interview 8	• 'P: you mentioned coming on the bus […] Relative: Because of the parking.'
		Focus Group 1	• 'the only problem we have is there's – erm – only two parking spaces so we've gotta make sure that we're there.' • 'all this work that's going on in paradise circus being a nightmare. I've parked […] in that multi-storey the other side of the main drag. You know and I have to sort of walk and I'm finding it more difficult now.
Poor perception of delivery of drugs	Recent change in delivery company with current change-over period	Individual interview 1	• 'delivery systems changed […] not sure that's an improvement […] they're not so good at Boots […] I don't know if the company is new and finding their feet […] I'd prefer boots at the moment.'
		Individual interview 2	• 'we did take a break […] they didn't deliver the tablets! […] I think they hadn't been ordered […] so I had to start all over again after that first month.' • 'on the transition between one supplier and the other […] I must have fallen between the erm- the floorboards.'
		Individual Interview 4	• 'there's another company took over […] which I thought left a bit to be desired.' • 'I was due to go away and – the people never rang up to say they're sending the next order and I had to chase it up through Helen here.'
		Focus Group 1	• 'you do get slightly paranoid about […] you can see your tablets going down down down down – and – you're expecting delivery and it didn't come.'
Specialist Nurse satisfaction	Emotional Support	Individual Interview 3	• 'CNS […] she's lovely that woman is, you know you can talk to her and she understands.'
		Individual Interview 5	• 'I can feel really down […] and I come here just to talk to CNS and – brings me back up.'
	Dedication	Individual Interview 5	• 'Brilliant especially CNS […] she'll cut her right hand off for you.'

	to patients		
	Developing good rapport with patients	Individual Interview 8	• 'Helen is brilliant!'
		Focus Group 2	• 'CNS is one of her own.'
	Used by patients as gateways to support systems	Focus Group 1	• 'I think if there were specialist nurses and groups like this […] that you could just ring up and just say oh my husband's got a stiff neck is that anything to do with the medication, or my husband's really breathless today what should I do […] that would be good' • 'don't take away our specialist nurses!' • 'they (specialist nurses) are so critical to- to us.' • 'they're (specialist nurses) the lifeline to all the other support services as well.'

Table 3-19 Themes and sub-themes for the perception of specialist care specifically related to the set up at BCC found on qualitative individual and focus group sessions

3.3.4 Travel and location

Theme	Sub-Theme	Interview Number	Quote
Difficulty of Travel	Distance to travel	Individual Interview 1	• 'it's (Travel) not something I look forward to because […] it's quite a trip […] it's not a nice pleasant journey by any means'
	Difficulty with walking	Individual Interview 5	• 'oh it's hard (travel to chest clinic), very hard, we're having a nightmare with that. […] when he first went down the oxygen we used to get the bus […] getting back home he couldn't walk it- he couldn't walk it, it was impossible.'
		Individual Interview 7	• 'I'm bringing my own car […] but walking is quite – [a problem?] – because I have to park on other side of the road and then I'm gonna need to come here.'
		Individual Interview 10	• I have to get taxis I can't […] I can't walk […] if I walk on uneven ground, or on hills or things like that I get out of breath very quick.'
Travel not a deterrent	n/a	Individual interview 1	• 'No. I would still come whatever […] care about my health more than the – temporary discomfort of an afternoon'
		Individual Interview 2	• [regarding the travel] no it's an excellent service, the train service]
		Individual Interview 4	• 'P: never influenced your decision to come to an appointment? Patient: no'
		Individual Interview 5	• 'P: has that ever influenced your decision to come? Patient: oh no we always get here.'
		Individual Interview 6	• 'P: has the travel ever influenced […] decision to come to an appointment? Patient: no, no!'
		Individual Interview 7	• 'no no, I don't miss any appointments at all.' • 'It doesn't matter sometimes if any problem for driving, I tell my son and they bring it and they drop it by the door you see.'
		Individual Interview 9	• 'no not at all (travel not influenced decision to attend)'
		Individual Interview 10	• 'P: does the travel every influence your decision to come to an appointment? Patient: no! […] it's to do with my health so travel shouldn't interfere you know.'

Table 3-20 Themes and sub-themes for travel and location found in the qualitative individual and focus group sessions

3.3.5 Health service and community support

Theme	Sub-Theme	Interview Number	Quote
Negative perceptions of community support	Connotations of meeting place	Individual Interview 1	• 'the name Marie Curie puts one off because you think, whoa! That's for people who are dying'
		Individual Interview 8	• 'It's the connotation that come with the building! St. Giles' hospice! And basically we all know if you're going into a hospice, there's only one way you're gonna come out.'
	Possible lack of knowledge of services available or how to engage them	Individual interview 2	• 'I could do with […] something at home […] I'm finding it so difficult to get up the stairs that - - - I have to pee in a bottle I just can't get up the stairs in time.' • 'We get no help'
Negative perceptions of interacting with groups	n/a	Individual Interview 8	• 'The one at St. Giles (support group) seemed very very formal! […] and everybody who knew everybody sat with everybody. […] whereas the other one, you didn't care who it was, you just sat down, cup of tea, what have you got what have you got?'
		Individual Interview 10	• 'I'm not being disrespectful to anyone that has it but I deal with it my way. I don't want to sit down with a bunch of people being mard about it.'
Positive experiences with healthcare groups	Benefit from physical pulmonary rehab classes	Individual Interview 1	• 'I have my pulmonary rehab classes […] they've been very good looking after me'
		Individual Interview 8	• 'I tell you what was the better thing […] from heartlands – I went to a – physical support group – at kingstanding baths. […] I felt that was the best thing.'
		Focus Group 3	• 'have you been offered pulmonary rehab? […] and that's improved mum's fitness no end! […] It really builds up your core strength and I think you need to push that with them.'
	Group learning	Focus Group 1	• 'when people first come obviously, people are reticent. Although everybody's very welcoming and friendly it's just- once you get over the initial stages- and you can learn from one another.' • 'some of the new people […] they literally just had the diagnosis- they're still in shock quite literally' • 'yeah, I live on my own so I can go bit stir crazy […] if I don't get out.' • 'you pick up all sort of things about diet, about the medication […] insurance!'
Family and Friends	n/a	Individual Interview 1	• 'my family I think that I would say is my biggest support' • 'my dear wife here who – works very hard trying to keep me on the straight and narrow'
		Individual Interview 3	• 'I've got a good family support' • 'I'm not depressed let's put it like that'
		Individual Interview 4	• 'P: do you have a good social network at home? Patient: yeah'
		Individual Interview 5	• 'my daughter in law's very good with us. […] she (CNS) was going to get palliative care to just pop in and see us.'
		Individual Interview 6	• 'Live on my own […] but my friend is always popping in.'
		Individual Interview 7	• 'my children you know, they look after very well, no problem there.'
		Individual Interview 8	• 'well, there's just the two of us now. […] but basically, the friends we've got – Relative: they're brilliant.'
		Individual Interview 9	• 'there's a couple of members of the family that haven't been there for us, but there's a lot of members of the family that have. […] We have some very good friends.'
		Individual Interview 10	• 'I've got fantastic friends and people you know'

Table 3-21 Themes and subthemes for community support services found on qualitative and focus group sessions

3.3.6 Patient to patient advice

Theme	Interview Number	Quote
Patient Advice	Individual Interview 1	• 'if you really want to make a difference you gotta be prepared to put up with a bit of inconvenience in terms of – side effects of the- the medication'
	Individual Interview 2	• 'get on with it.'
	Individual Interview 3	• 'if you don't try it, you ain't gonna get nowhere with it.'
	Individual Interview 4	• 'persevere with it because it's erm- it's very helpful.'
	Individual Interview 5	• 'try it, you've got nothing to lose. Try it.'
	Individual Interview 6	• 'just do as you're told.'
	Individual Interview 8	• 'do it sooner rather than later […] if you're uncertain and you've got the web and everything – check it out first […] talk to people who've been on it that's very important […] and then ultimately you have to make your own mind up.'
	Individual Interview 9	• 'if you've got the will you gotta take these options otherwise – you're disrespecting everybody ain't ya. You Know, if you don't take the advice – you know – at the end of the day people are not – giving these drugs just for the fun of it.'
	Individual Interview 10	• 'Look – it's there for a reason. It's there to improve your condition. It's not there to hinder you in any way. So I would advise anybody who wants to try it – by all means take it. […] People has gotta understand it's not a cure, that's the first you gotta realise!'
	Focus Group 1	• 'not to get depressed' • 'take it and see I think is the only answer really, I mean everybody's different and I mean some people take to it really better than others. […] you just have to have faith in it I think.' • 'to get out and about and not stay at home- mix with others.' • 'still live your life'

Table 3-22 Patient advice given to other patients who are thinking about starting antifibrotics.

4 Discussion

4.1 Summary

Our results show that physiological factors (gender and gas transfer at diagnosis) increase the risk of early discontinuation at both 30 days and 90 days when compared with social factors (eg. distance to travel, socioeconomic status etc.). There is agreement with the qualitative arm of the study where patients do not feel that social factors are barriers to treatment continuation. A theme found in the qualitative arm centres around diagnostic delay, which can lead to advanced disease by the time of initial assessment at the tertiary ILD service. This, as our results show, leads to higher risk of early discontinuation.

4.2 Strengths and limitations

There were a number of limitations in our study. The first of which is the study design, which is retrospective, cross-sectional and spanned a long period of time at UHB HGS. The retrospective nature of the study meant that we were reliant on good documentation throughout the 4 years of data collection. In a number of cases, deficiencies were noted in documentation of the diagnostic pathway, which included information on initial symptoms, occupational history, exposure history and in some cases information on radiology and histology.

One possible cause for this is the complexity of IPF requiring tertiary care such as the ILD service at UHB (HGS). For example, initial investigations and management for a number of patients were performed at a different hospital trust (secondary care), prior to referral, which were not always well documented. The initial referral letter to the ILD service at UHB (HGS) was not always available and therefore information was missing, which will have impacted the results. As patients were referred from different hospitals, the information available on our electronic systems was sometimes lacking, which included contact information, and therefore there was an inability to contact patients or patients' relatives to clarify missing information.

Change in practice over the time frame of the study is also a limitation. Over the period between 2012 and 2016, there was a change in guidance for the investigation and management of IPF and thereby the number of referrals to the ILD service changed over time; specifically, specialised commissioning in 2013 and NICE guidelines throughout 2012-2015. It will have also influenced the type of patients being referred. For example, in the initial phases of introduction of antifibrotics, there would have been many patients in other hospitals, who would have been referred even though they had been diagnosed a number of years before, and then would require re-evaluation and discussion at the ILD MDT, which then prolongs diagnosis and initiation of antifibrotic therapy, which as our results show would increase the risk of early discontinuation with increasingly advanced disease.

Missing data in our population is likely to have produced an element of selection bias. For example, 86 cases did not have information around their highest level of education, which represents 50.6% of our population. The variety of reasons for missing data in this particular instance include inability to contact the patient or patient's relative due to lack of contact information available, unavailability of medical notes, limited information on our electronic system and relatives' not knowing the patient's highest level of education. Socioeconomic class also had missing data, but only for 26 cases. Unlike level of education, a thorough occupational history was performed in the majority of cases as UHB (HGS) also has a specialist occupational lung disease service (unusual for most ILD centres) and therefore an inference of the socio-economic data was made dependent on the major or longest held occupation. The inclusion of deceased patients in our population however has gone some way to try and counteract the effect of selection bias in this study.

Measurement of post antifibrotic spirometry and gas exchange is shown in the results. However, the results should be interpreted with caution. Firstly, due to the varying time frame that patients were taking antifibrotics, there is no uniform time measurement for when the post antifibrotic spirometry and gas transfer were measured. For some patients, they had been on it for a number of years and

for other patients, only a number of days, and therefore it would be difficult to make a clear assumption or analysis on the post antifibrotic spirometry values. What can be seen however is that in 32 cases of pirfenidone and 8 cases of nintedanib, post antifibrotic FVC was not available; similarly 58 cases of pirfenidone and 14 cases of nintedanib did not have gas transfer measured post antifibrotic, which could represent rapid progression of IPF and therefore difficult measurement of spirometry due to declining lung function, therefore excluding those with more severe disease.

Exact measurements of time (i.e. to the nearest day) on antifibrotic were not possible. Patients were prescribed antifibrotics on a monthly basis and it was not always clear exactly how long they actually took the medication for. There would have been patients with only one prescription that only took the antifibrotic for one week, whereas another with one prescription may well have took more than one week. As there was no way to standardise this information we were obliged to use the length of time between prescriptions. Again, using continuous data in our regression analysis was not possible due to those patients that were still continuing with antifibrotic therapy, which would skew the data. Therefore, we used the length of time between first and last prescription and grouped the data according to those who only had 30 days, and then 90 days or less, between their first and last prescription. Ideally, we would have examined time periods with more than two groups, though this was not possible with the data available, and would require a prospective study to analyse this.

It is difficult to compare the two antifibrotic medications in our study, as the time period spans the likely first prescription of pirfenidone according to NICE or NPP guidance, and includes the introduction of nintedanib prescriptions in 2015. This may be one of the reasons that accounts for the differences in numbers between those prescribed pirfenidone and those prescribed nintedanib. Similarly, experience with using antifibrotic therapy in the ILD service has increased, which may lead to better management of adverse events, including use of treatment holidays or dose reductions, which would encourage more patients to remain on the medication. Growing clinical experience of

starting patients on antifibrotics may also increase the knowledge of clinicians as to which patients are likely to benefit from antifibrotic therapy.

When conducting telephone interviews for retrospective data, there was obvious recall bias with both patients and patient relatives not able to fully recall their experience on the medication. When discussing with patients, there were situations where they had experienced a particular antifibrotic drug to begin with and not had a pleasant experience, leading to discontinuation within a short period of time, such as one week. This then led to initiation of the second antifibrotic (as the first was not agreeable) and may cause experience on the initial drug to be less memorable, causing recall bias. This was also a problem with speaking to relatives of patients who had died, where their involvement varied from attending each clinic appointment and being heavily involved with the patient's care to being minimally involved and not having much information about their experience on antifibrotic therapy. This led to recall bias where information around side effects, reason for stopping and social factors were not obtainable, explaining the high frequency of missing information.

Patient reported side effects from telephone conversations were also subject to recall bias. Both patients and patient's relatives would likely only remember the significant side effects that they felt leading to possible discontinuation. There would also be an argument that those who are continuing antifibrotic therapy would not recall side effects, even though they occurred as it was not significant enough for them to notice. Therefore, those side effects that were reported by patients are clearly important to them and need to be taken into consideration. Interestingly, as mentioned above, lethargy and fatigue were reported by healthcare professionals and during telephone conversations, thereby showing the importance of this particular adverse event. Although in the original trials, lethargy and fatigue is not always highlighted as an important adverse event, but it is clearly something that needs to be assessed for by healthcare professionals when reviewing patients taking antifibrotics.

Telephone interviews were only possible when contact information was obtainable. In a lot of cases, there was no contact information on the electronic systems for either the patient or the next of kin (in cases where the patient was bereaved). Subsequently, there were occasions where the written case notes could not be found leading to missing information; and even in situations where case notes were found, contact information was either incorrect or unavailable. It was commonly those patients that were referred from outside of the UHB HGS trust where case notes and contact information was missing, which could lead to under-representation of a group of patients in our population.

With telephone conversations, there is an argument that the quality of data differs if you are speaking to a patient when compared with a patient's relative. This is enhanced if the patient in question has been dead for longer, which would increase the risk of recall bias if the patient's relatives are not able to remember what the patient had been reporting at that time. Additionally, the next of kin that was accompanying the patient at the time of their appointments and antifibrotic experience would commonly be their partner. As IPF is a disease of advancing age, it follows logically that patients' partners are also elderly and may have died, which leaves patients' children and other family members as next of kin, who may not have accompanied the patient at the time; therefore the accuracy of data collected may be reduced.

There were also occasions where the patient or patients' relatives were not English speakers and therefore conducting English interviews over the telephone with them became difficult, if not impossible for them to understand what was being asked and what type of data was required.

4.3 Findings in context of current knowledge

4.3.1 Descriptive analysis

4.3.1.1 Demographic analysis discussion

The demographic for our population reflects what we tend to see in clinical practice and previously published reports, which is: male patients with an average age above 65 (43). The majority are

Caucasian and speak English as a first language. This means that our results are likely to be generalisable to a larger population. What does come out from our demographic is how the majority of patients are from a lower socioeconomic group (4-6), which may reflect the local population where there is predominantly urban areas, with traditionally manual work in manufacturing sectors. This also reflects in the average highest level of education for our population which was only up to school level with the majority leaving school at the age of 15.

Despite the missing data, there was not shown to be any significant difference between men and women in the different demographic variables. However, there was a difference in the total number of men and women with men being much more commonly diagnosed with IPF and started on antifibrotics than women. This is consistent with previously published studies with more men being diagnosed with IPF than women (44). Whether this suggests an environmental involvement in the development of IPF as the majority of men in our population were shown to be in manual labour jobs, especially in the West Midlands region would be a possibility. There is an apparent association with metal fume or dust, wood dust, grains, asbestos and silica with UIP fibrosis (45, 46). There has been evidence published to state that IPF mortality has risen in parallel with that of mesothelioma and therefore raises the question of the relationship of asbestos and IPF (47). However, as Barber et al. suggest, this may also highlight the diagnostic difficulties of assessing asbestos exposure and mean that many of the 'idiopathic' causes may actually be down to historic asbestos exposure. This information would be difficult to ascertain through retrospective records and for the purposes of our research, each patient who had been started on antifibrotics would have been discussed at an ILD MDT, and thereby have their diagnosis made with a conjunction of information from radiology, histology and the clinical picture. Given that there is an occupational lung disease service at UHB (HGS), patients would be subject to a full occupational history, rather than a cursory one. As of yet, there is no evidence for the threshold dose of asbestos that causes asbestosis, therefore it is possible that low level asbestos exposure causes IPF, meaning that even though patients have a full occupational history at UHB (HGS), it may not help with the diagnosis.

4.3.1.2 Investigation and lung function

An investigation summary for all patients in our population is shown in section 3.1.2 and 3.1.3. As would be expected, the majority of patients had an HRCT with only 5 cases of unclear imaging documentation. It is unclear whether they have had the imaging done at other hospitals and therefore are not available for viewing on the electronic PACS system at UHB (HGS sites), which combined with lack of documentation in the clinical letters from the ILD clinic leads to no clear evidence of an HRCT being performed. However, given that to receive antifibrotics either under the named patient program or via an NHS prescription, they would have had to have been discussed at an ILD MDT with an HRCT as per national guidelines to make a diagnosis, we have assumed that these 5 cases would have had an HRCT at some point during their diagnostic pathway.

The majority of HRCTs performed showed Usual Interstitial Pneumonitis (UIP); other radiological diagnoses were NSIP, Chronic Extrinsic Allergic Alveolitis (or Hypersensitivity Pneumonitis) and a combination of the above three. In some cases, it was difficult to state a single diagnosis, and a simple statement of presence of ILD with a possibility of three or four differentials was presented. As per the European guidelines, presence of UIP on an HRCT with no clinical features from history or examination to suggest any underlying cause can be diagnosed as IPF (1). Equally, it is not possible to make a diagnosis in many cases with consensus from solely clinical features and HRCT without further information from serology or biopsies, which may explain why other radiological impressions were different to the final outcome diagnosis of IPF.

Looking through individual cases local practice has varied somewhat, as there are cases diagnosed near the start of the study period (i.e. 2012-2013) where despite an HRCT showing UIP, there was still a BAL +/- a biopsy performed. The service has become more efficient over the time period of 4 years with more patients diagnosed at later dates having a more efficient diagnosis due to increased confidence in radiological and clinical evidence, due to the standard of care and quality standards introduced by NICE (2013 and 2015), which was adopted locally. At UHB (HGS) in 2012 the waiting list was 3-5 months for diagnosis, then after employing an ILD co-ordinator in 2014, the waiting list

has fallen to its current level of 4-6 weeks (48). More patients are also being seen within the ILD service than by general respiratory physicians and may therefore spend less time undiagnosed than previously. Earlier diagnosis may well lead to less severe disease, which as my study shows, has reduced the likelihood of discontinuation of antifibrotics.

24.7% of the cases had a bronchoalveolar lavage, with the median lymphocyte count at 5%. An average lymphocyte count of 5% does support a diagnosis of IPF. In that, if there was a higher average of lymphocyte count, it would raise concerns of an alternative diagnosis such as fibrotic hypersensitivity pneumonitis or sarcoidosis, which would reduce the confidence in the diagnostic standard we have been using. However, the data supports the idea that investigations done to rule out other causes of ILD have gone on to support the diagnosis of IPF as per previously published data (49).

Interestingly, 42 cases (24.7%) went onto have a biopsy, of which only 35 had shown UIP, in the other cases, one had NSIP, three were normal and in four cases the result of the biopsy was unknown due to lack of documentation and lack of availability of retrospective data on the electronic system. In the case where the biopsy showed NSIP, there had been difficulty making a definitive diagnosis. Initially, the patient had an incidental ILD picked up following a chest x-ray performed during an admission for a possible transient ischaemic attack. The following HRCT showed evidence of possible honeycombing shadows and traction bronchiectasis, but after discussion at the MDT, it was felt that not enough evidence was present to make a definitive diagnosis and recommended a biopsy. The patient went onto have a VATS biopsy, the report of which stated uniform mild fibrosis with no fibroblastic foci, alveolar septal widening and increased cellularity with lymphoid aggregates present. The conclusion stated NSIP as the most likely diagnosis rather than UIP, instead of making a definitive diagnosis of NSIP. The patient was then treated as such until significant progression of symptoms in 2013 showed slight progression in the HRCT with patches of honeycombing and traction bronchiectasis and the MDT re-diagnosed UIP and IPF,

following which the patient was prescribed pirfenidone (which was stopped quickly due to significant side effects). As a final step in the patient pathway, he suffered from symptoms of inflammatory arthritis and was diagnosed as having rheumatoid arthritis and put on immunosuppressant medication. However, another repeat CT a few years later showed significant progression of honeycombing and a definitive radiological diagnosis of UIP. This case demonstrates the difficulty in diagnosis of patients with ILD, which can range from initial consultation and differential diagnosis to difficulty interpreting biopsy results and correlating with radiology. There is also a possibility that the biopsy had been taken from an unaffected area of the lung. Dual pathology could also explain the possible difficulty in diagnosis in this particular case. As shown in the case above, in some cases, only over a period of time does it become evident what the patient has, which then leads to a late recognition and diagnosis and ultimately late prescription of antifibrotics and possible early discontinuation.

There were two phases of prescription for each antifibrotic – namely the named patient program, where ILD physicians could apply for funding from the manufacturer to supply antifibrotics to named patients with IPF, and then under NHS prescription (none of the patients in our population were involved with the initial clinical trials), the average FVC percentage predicted was 78.0% for the total of our population, which is less than the 80% cut off used by the NHS (the named patient program would have included patients above the 80% cut off). The average DL_{CO} percentage predicted is 43.6%, which we have shown predicts early discontinuation. Interestingly females had a significantly lower average DL_{CO} than men did by an average of 4.2% ($p = 0.019$). Given the lower number of women in our population (44 cases – 25.9%) compared to men, the lower DL_{CO} could correlate with a more progressive and severe disease in the female population. Possible explanations for this could be that due to the increased severity of disease in women, their presence in our population is reduced by selection of fitter people as stated earlier, or that IPF is underdiagnosed in females for other reasons.

When looking at DL_{CO}, 7 cases had missing data. This was due to two reasons: lack of data from different hospitals' referral letters and therefore lack of data on the ILD MDT database, or that the patients' lung function is too poor to perform adequate gas exchange. Therefore, it may be that we are overestimating the average DL_{CO} in missing cases. It would also highlight a group of patients who would be missed by our predictive model, although patients who are too unwell to perform DL_{CO} would have a very low predicted value and therefore clinically it may be apparent that they would not be suitable for antifibrotics. Similarly, lung volumes frequently had missing data with 51 cases missing for RV and 44 cases for TLC, which may be due to patients being too unwell to perform lung volumes as previously stated. Alternatively, spirometry and DL_{CO} may be considered of more value as spirometry is required for prescription of antifibrotics and DL_{CO} is important in decisions regarding surgery or transplantations. This is reflected in the post antifibrotic lung volumes, in that 131/139 cases taking pirfenidone and 30/31 cases taking nintedanib did not have either RV or TLC measure post antifibrotic, which could represent the progression of disease and therefore the inability to perform the required physiological testing or could represent the lack of clinical use for lung volumes in monitoring patients using antifibrotics.

4.3.1.3 Referral pathway

The majority of referrals to the tertiary ILD service at UHB (HGS) have originated from secondary care within the Trust itself, with a minority from secondary care at other hospitals, such as Dudley Hospital and Hereford County Hospital. This is relevant to both the referral pathway/diagnosis and the follow up care that patients would receive. For example, if they are seeing a respiratory physician or a general practitioner who has had some experience with ILD and is fully aware of the tertiary service at UHB (HGS), then actively looking for a diagnosis in patients who present with a dry cough, shortness of breath and crackles on the chest would lead to earlier diagnosis and referral, which ultimately leads to earlier initiation of antifibrotics. With respect to follow up, some hospitals such as Hereford County Hospital, have a dedicated ILD specialist nurse, which is intended to improve the follow up care of these patients, including not having to travel to Birmingham for

tertiary follow up care. We hypothesised that patients may well be put off travelling long distances for such regular follow up (monthly for the first 3 months) and therefore would have a lower threshold for early discontinuation, however a local specialist nurse may help by supporting the initiation of treatment. What we found in our results though was that there was no significant difference between those that were travelling from nearer (within 8 miles) and those travelling from further away with regards to early discontinuation of antifibrotic medication. This is reinforced by our qualitative work, which showed that people would be willing to travel long distances for follow up. For example, individual interviewee number 10, when asked about travel being a deterrent to attending follow up, they stated, 'no! […] it's to do with my health so travel shouldn't interfere you know.' We also found that there was no significant difference in discontinuation rates between patients referred from hospitals that had dedicated specialist ILD nurses and those who did not.

Following on from this however was the result of investigating for significant differences in early discontinuation between patients referred from the UHB (HGS) sites and those referred from outside the trust. We hypothesised that referral from within the trust would be earlier due to knowledge of the ILD service and availability of a dedicated ILD team at all three sites, leading to earlier initiation of antifibrotics. Referral time was not measured. However, although our results showed no significant difference between the two groups in either 30 day or 90 day analyses, the 30 day analysis did show a p value close to significance at 0.076 with a larger proportion of cases of early discontinuation occurring from outside the trust. We had hypothesised that this may be due to 1. greater intensity of nursing care in the first few weeks at UHB (HGS) than elsewhere, and 2. tertiary care would provide better adherence to the standard of care, which was also local policy at the Trust, and a benchmark for specialised commissioning status by NHS England.

4.3.1.4 Side effects

The commonest side effects suffered for each antifibrotic are shown in the results chapter. They are largely comparable to the existing literature in the RECAP and TOMORROW trials along with Galli et al.'s paper on the safety and tolerability of pirfenidone and nintedanib (30, 38, 50). However, for

pirfenidone there are a higher proportion of patients suffering with photosensitivity rash compared to non-photosensitivity rash, which is different to the original trials. Whether this is in fact a subjective measure of the side effect from a healthcare professional point of view, it is difficult to say. In that, redness of the skin in sun exposed areas would be seen as photosensitivity rash, which may be different to other healthcare professionals who would not feel that redness reaches a threshold to label it as a rash. But, we are unable to explain the difference reliably. Further difficulty lies with no standardised objective measure of presence of side effects and the reliance on patient reporting only.

Another observation is how the proportion of patients suffering with fatigue or lethargy in our population is higher than that reported in the clinical trials (27). This is also supported by our qualitative work, which showed that many people felt fatigue to be a significant contributing factor to discontinuation of antifibrotics. Of course, it may be logical to assume that the fatigue would come hand in hand with the disease process of IPF itself. But, anecdotally at UHB (HGS) many of the patients that we see will state that following discontinuation of therapy they feel much less fatigued and at that point will decide that their quality of life is more important to them than the effect of antifibrotics. Similarly recent long term open label trials have shown fatigue to be an adverse event associated with pirfenidone, such as the RECAP study, looking at the long term safety profile of pirfenidone showing an incidence of 20% for fatigue in their cohort of 1037 patients (30).

With regards to Nintedanib, the commonest side effect seen in both healthcare reported and patient reported outcomes was diarrhoea. Our results showed a rate of 79.2% of patients suffering diarrhoea in our population, which is higher than the 61.5% and 63.2% seen in INPULSIS 1 and 2 respectively (35), but comparable. Although this is an important patient reported side effect, only 10.5% of patients taking nintedanib that responded to the telephone interviews had a dose reduction or treatment break. This would imply that if warned prior to treatment, the diarrhoea experienced with nintedanib could be well controlled, especially if loperamide (anti-diarrhoeal drug)

is prescribed alongside it, which is common practice in UHB (HGS). Perhaps more careful consideration of which patients would manage side effects better would aid adherence. Indeed this may have improved through the study period due to gained healthcare experience. For example, nintedanib is unlikely to be suitable for a wheelchair-bound patient who would struggle to mobilise to the toilet quickly and frequently.

The most common reason reported by healthcare professionals for discontinuation of antifibrotic therapy was side effects, with 47% of cases discontinuing due to this reason; the next most common being death. Almost a quarter of our population was still on treatment by the end of data collection. However there was a range in starting points throughout the four years, but each patient would have been on antifibrotics for at least one year as all those starting within a year of starting data collection had been excluded. Patients should be adequately informed about the potential side effects and also the treatment strategies involved with dealing with said side effects. This could include treatment breaks, dose reductions and other medication such as anti-diarrhoeals or anti-emetics. It does however add to the enormous amount of information received by patients throughout this period which includes diagnosis of a condition that despite education is still not well understood, which highlights the role the MDT play in helping to further educate and council patients to enable them to make an informed decision.

4.3.2 Early discontinuation discussion

4.3.2.1 30 and 90 day discontinuation analysis

The 30 day analysis looked at all of those patients who would have discontinued their antifibrotic after just one prescription compared with those who would have received more than one prescription. The 90 day analysis looked at all those who would have discontinued therapy in the first 3 months and those who would have discontinued after this time frame, the rationale being that the medical literature has shown that most side effects that may precipitate discontinuation are likely to occur in the first 3 months (31). After this time, patients may have developed strategies to

cope with the side effects and extra pill burden, leading to an increased chance of continuing therapy.

Male gender was found to significantly reduce the risk of early discontinuation when compared with female gender in both univariate and multivariate analyses for both 30 and 90 day analyses. It may be that social roles differ between sexes, which may have an impact on adherence. Women may be more likely to have the burden of caring for family, reducing focus on their own health. Other possible explanations include a physiological difference such as nutritional status and muscle mass between men and women with the side effects effecting females more than males, which may increase the risk of early discontinuation in this case.

In the 30 day univariate analysis, referring hospital from within HGS sites of UHB compared with referrals from outside the Trust showed an association for reduced risk of discontinuation, but did not reach statistical significance. This association is not the case in the 90 day analysis. Logically, those patients identified within the trust as having ILD will have better access to the ILD team and MDT, which means that initial investigations and discussions could be had earlier leading to earlier diagnosis and early initiation of treatment, which as our results suggest, would lead to reduced risk of early discontinuation. Those from outside the trust, would undergo investigations at their own trust or GP, and then referred to UHB HGS, leading to delays in definitive diagnosis, increasingly severe disease and early discontinuation. Follow up and support may also be different as those hospitals where they may be a nurse with an interest in ILD such as Hereford County Hospital would not follow up patients as regularly as the ILD nurses in UHB (HGS).

Patients who suffer from IPF with a DL_{CO} of less than 40% have been shown to suffer from worse prognosis (4). In this study, in both the univariate and multivariate analysis for 30-day discontinuation, a DL_{CO} of less than 40% predicted significantly predicts an increased risk of early discontinuation. What is interesting however, is that in the 90-day analysis, a DL_{CO} of less than 40% is not significant in the multivariate analysis. Increased disease severity leading to inability to cope with

the onset of side effects and pill burden with antifibrotics could explain the reason why patients with a DL_{CO} less than 40% predicted have an increased risk of early discontinuation. However, the initial appearance of side effects within the first few weeks of treatment could highlight to patients with IPF that the benefit of antifibrotics at such a late stage of disease severity against the risk of developing side effects and an increased pill burden is not enough. Patients would therefore rather focus on their quality of life remaining, rather than trying to prolong what is left. This is demonstrated in the qualitative work as in focus group 2, when speaking about their initial experience on pirfenidone, one of the patients states, 'it made me feel really ill. I didn't want to get out of bed of a morning. I'd got no quality of life, I just felt ill all the time. […] I spoke to Professor X and he said, "come off it and we'll try you on something else.' This ties into the recommendation that all treatment options should be discussed with the patient, which includes the possibility of not using treatment to slow disease progression, but focus on symptomatic control, with strategies for coping with breathlessness, pain and poor exercise tolerance, alongside end of life psychological support. It may be that those with a DL_{CO} less than 40% predicted that do not discontinue early, do not suffer with significant side effects and thereby continue to take the medication leading to no effect, as measured in the multivariate 90-day analysis.

An FVC of between 50 and 80% predicted is used as the cut-off eligibility for antifibrotics in the UK according to NICE. Interestingly, in our study, using a cut-off for FVC of above and below 80% has not shown to significantly increase or reduce the risk of early discontinuation in either 30-day or 90-day analysis. It may be that FVC is not a sensitive measure of disease progression. For example, when patients have emphysema in addition to fibrosis, the FVC is preserved and DL_{CO} declines over time (51, 52). Therefore, patients with a combination of IPF and emphysema may not become eligible for antifibrotics until the disease has progressed significantly. A follow on from this could possibly be further studies investigating the utility of grading systems based multiple physiological measurements, such as the composite physiology index, which could be used to identify those patients that would benefit from antifibrotics.

Gastrointestinal and skin related side effects were shown to significantly influence the risk of early discontinuation in the 30-day univariate analysis, with deconditioning side effects coming close to significance. However, when included in the multivariate analysis for 30 days, only the presence of skin related side effects was shown to significantly reduce the risk of early discontinuation. Although not significant, presence of gastrointestinal side effects reduced the risk of early discontinuation too. Considering the majority of early discontinuation as shown in our results was down to side effects, it is interesting that the presence of these side effects would produce a reduced risk of early discontinuation. It is possible that those who suffer skin related side effects, which include photosensitivity, may spend more time outdoors, implying increased independence with adequate sun exposure to cause photosensitivity. Therefore, they would be less likely to discontinue early. Alongside this, there is the possibility that those suffering with skin related side effects, which may be more tolerable or manageable than others are more likely to seek medical attention and thereby receive coping strategies such as dose reductions or treatment breaks to allow them to continue antifibrotic medication.

In the 90-day analysis, the presence of deconditioning side effects significantly increased the risk of early discontinuation. Deconditioning side effects included fatigue, which as mentioned in previous chapters is not an adverse event that was commonly reported in the original trials. It has however, in our study, shown to increase the risk of early discontinuation within 90 days. This ties in with our qualitative work where fatigue and lethargy are commonly reported side effects, which as shown in the 90-day analysis could lead to early discontinuation. Patients will state that after stopping antifibrotics, the presence of lethargy or fatigue will diminish or completely disappear leaving the patient feeling better and back to their original baseline before starting antifibrotics. This improvement after stopping the drugs implies that it is a side effect of the antifibrotics, rather than a manifestation of the disease itself.

In neither the 30- or 90-day analyses did the regression model demonstrate a high correlation or predictive value. The coefficient was low, leading to a poor predictive model. From my data and with the binary logistic multivariate analyses, it is clear that physiological factors such as poor gas transfer, age, gender and manifestation of side effects will influence the risk of discontinuation, rather than the social factors which were tested. It shows that despite distance from their treating hospital, socioeconomic level, level of education and type or difficulty of travel, patients will still be willing to travel for good clinical care, and attend follow-up appointments, highlighting a need for good clinical care locally, which could be delivered in a number of models. This is reinforced by the qualitative research results with every patient stating that travel was not a deterrent for coming to an appointment. The analysis also demonstrates that the presence of side effects does not significantly reduce the risk of early discontinuation, but is still the commonest reason for discontinuation overall. It stands to reason therefore that further progressive disease with increasingly severe manifestations and physiological parameters is the most important predictor of early discontinuation, which shows the value of early recognition, referral, diagnosis and initiation of management for the best result. It is clear that this is beneficial for the patient also as the studies show a 30% increase in length of life, the effect of which is affected by the length of prognosis of the patient.

Through the 4 years that were looked at in this study, it is clear that assessment and investigation of patients with possible IPF has changed, with the introduction of the European guidelines for the diagnosis of IPF stating that UIP on radiology with no attributable cause found on history or examination is enough to make a diagnosis of IPF through an ILD MDT discussion. From this, patients are being discussed earlier through the latter part of the study period and therefore led to earlier diagnosis and initiation of antifibrotics. Local audit has shown that UHB (HGS) discusses more patients, initiates more treatments, and has shorter ILD MDT waiting times in 2017 than in 2013 when first measured (48). Knowledge about the new antifibrotics, via an invested programme of

education for secondary care, referring centres and primary care nurses also led to earlier referrals from outside of UHB (HGS) allowing for earlier assessment and initiation of antifibrotics.

4.3.3 Qualitative thematic analysis

The results of the qualitative section of the data collection provided both deductive and inductive analysis, in that there was analysis of previously hypothesised themes (deductive) but also produced new (inductive) themes for analysis. One such inductive theme that was not looked at in the original quantitative data collection was diagnostic delay. It became apparent quite quickly that diagnostic delay was a common theme through both individual and focus group interviews. A number of causes for this have been brought up in the qualitative interviews, which include a delay in referral to a specialist with expertise in ILD. Reasons for delay in referral included lack of knowledge of primary and secondary healthcare professionals, and therefore repeated healthcare visits before a referral is made. Repeated healthcare visits may have included normal investigations such as chest x-rays and spirometry, masking the disease and therefore leading the primary care physician to dismiss the patient's symptoms, as was alluded to in a few of the interview responses. Lack of healthcare professional knowledge inferred from our data would include poor knowledge of ILD in general, poor knowledge of existence of tertiary ILD service in the West Midlands and poor knowledge of indications for referral to said tertiary service. Delay in referral in patients with a progressive disease leads to delay in confirmatory diagnosis, especially if the cause is unclear and further investigations are necessary. Therefore patients will present with a lower DL_{CO} and lower FVC and therefore reduce the chances of starting antifibrotics and also tying in with the regression analysis, an increased risk of early discontinuation.

A number of patients performed their own research on their symptoms and then presented to the primary healthcare professional seeking secondary or tertiary care referral for a diagnosis, which may or may not have included ILD. However, the need for patients to self-diagnose prior to referral to a secondary or tertiary care service highlights the need for more education in the primary care centre about the existence of ILD as a possibility to facilitate earlier referral to the service and

therefore earlier initiation on antifibrotic therapy following earlier diagnosis and lower risk of early discontinuation.

The delay in referral is associated with frustration from the patient, which encompasses anger, sorrow, low mood and anxiety, especially if they are diagnosed at a point where antifibrotics are unlikely to produce a great effect. Anecdotally in clinical practice at UHB (HGS) we come across patients with delayed referral and therefore require a full work up for a confirmatory diagnosis including awaiting ILD MDT discussion and will on occasion present with an FVC below 50% and therefore are not eligible for the medication. Clearly, there will be an impact on the patient's mental wellbeing in this circumstance especially if there has been discussion from the referring physician leading them to believe they can access available treatments for their IPF.

This is also highlighted when patients will comment on the satisfaction they feel once a diagnosis has been made, which not only allows physical treatment and pathway to be initiated, but also allows them to accept their fate and start to direct their lives in a certain way from that point onwards. It is clear that once patients are diagnosed and accept their condition and prognosis they are less frustrated about the length of survival or the fact that it is a terminal disease; in fact, responses from the qualitative data suggests that patients accept it is a terminal disease and are more frustrated about the physical restraints the disease puts on their body. It may be that there is an impact on their treatment here where patients with severe disease will quickly begin to balance the risk of adverse events from the antifibrotics against the benefit, where if they have accepted the poor prognosis, they will realise that quality of life is more important than the length of life and can initiate early discontinuation from the medication. Whereas, patients with less severe IPF who have accepted the terminal aspect of the disease, but still realise that they have a reasonable quality of life and length of life will be more likely to cope with the adverse events and therefore be on the medication for longer.

This is reflected in comments from those patients where IPF has been diagnosed incidentally. One such quote from the results from Focus Group 2 stated, 'P4 was diagnosed unusually early because they picked up an abnormality or something suspicious […] on other tests so P4 hasn't quite got the normal symptoms that would drive you to the GP.' With this particular patient her diagnosis had been made early and she had not reached a point where she qualified for antifibrotic therapy. However, due to her active involvement in the support group and regular visits to BCC, when it reaches the point of eligibility, then she will have had ample time to have weighed up her options and make an informed decision regarding which antifibrotic would be most appropriate for her. She will have heard strategies from other patients and in BCC regarding adverse events and will be better prepared for dealing with these, thereby decreasing the risk of early discontinuation.

Roughly an equal number of patients chose pirfenidone and nintedanib in the qualitative sample. Commonly the side effect profile would be the reason for picking a particular antifibrotic over the other; however, other causes included healthcare professional bias or patient circumstance. One aspect of qualitative data unfortunately is that you will only get one side of the story here, therefore when the patient in individual interview 2 suggests, 'I think CNS – sort of steered me towards […] pirfenidone,' it is only the patient's perspective that we see. Studies of shared decision making in IPF might therefore be valuable in future to see to what extent this occurs, and if or how it may influence choices (53). However, importantly, if that is what they perceive happened then there may have been a miscommunication or misunderstanding. We have not been able to measure the dynamic between the healthcare professional and the patient, therefore do not know how heavily each was involved in the decision-making process, as it would have been individualised for each patient.

It is clear from qualitative data that different side effects are more important to different patients. For example, some patients would see the diarrhoea as a negative side effect, which deters them from nintedanib, whilst other patients saw the photosensitivity and inconvenience of three capsules

three times a day a deterrent from pirfenidone. Therefore, it highlights the need for a clear discussion between clinician and patient informing them of risk and benefit of both pirfenidone and nintedanib and allowing them to make an informed decision. Clearly, there will be some patients as highlighted in our data that are unable to take nintedanib for example due to existing bowel issues and therefore makes pirfenidone the obvious choice. Whereas for others, it will be based on their lifestyle, for example patients who play golf avoiding pirfenidone due to the photosensitivity.

Adverse events of antifibrotic therapy will always play a part in their continuation in our patients as shown in both the quantitative and qualitative data. What our qualitative data does highlight however are strategies that patients have adopted to help them cope with the side effects of these medications. These would include anti-emetics for nausea, SPF 50 sun creams for photosensitivity and encouraging eating for appetite loss in patients taking pirfenidone; and then loperamide for diarrhoea associated with nintedanib. It is clear from the data that these strategies allow patients to continue with their antifibrotic therapy and thereby reduce the risk of early discontinuation.

Linked to the above was titration of doses and treatment holidays, which was another theme highlighted in our qualitative data. It clearly showed that once patients understood the technique for titrating and stopping antifibrotic medication to allow a particular side effect to settle, it allowed them to re-introduce when they were more stable and perhaps remain on a lower dose, thereby lowering the risk of early discontinuation.

A major theme was a lack of education or lack of knowledge on the part of the patient about the effect of the antifibrotics. It was a clear recurrent theme that patients did not realise what the antifibrotics were designed to do. Unlike other medications, they would not typically give a clear subjective improvement in symptoms, but would objectively aim to reduce the rate of decline in FVC. It was clear therefore that patients felt a lack of effect from the medication as it did not correlate with them feeling better. However, in those patients who understood that it was designed to slow the rate of progression were more accepting of the fact that subjectively they did not feel

any different, but objectively, their FVC had not declined as much as they thought it would have, or as much as the healthcare professionals would have expected it to if they were not on medication. This understanding of objective improvement or lack of deterioration may then correlate with a decreased risk of early discontinuation.

Along the lines of medication, the number of capsules that pirfenidone added to the total number of medications that patients with IPF would be taking was also highlighted. Being a disease of patients predominantly over the age of 65, there would be an associated risk of having other co-morbidities and therefore being on further medication. The pill burden of another nine tablets on top of those the patient may already be taking would theoretically increase the risk of discontinuation or poor compliance to medication. However, it was clear that although the patients accepted that there was an increased pill burden, other than occasionally finding it difficult to fit into their daily routine and therefore having the odd missed dose, it did not deter them from taking the medication as again the understanding for the need to slow down the rate of progression highlighted the need to take it. The recent advancement of combining all three capsules into a single capsule to allow patients to take one capsule three times a day may increase compliance with pirfenidone and thereby may reduce the risk of early discontinuation.

As already alluded to above, patients included in our qualitative analysis are clearly frustrated by the delay in referral and the difficulty in obtaining a diagnosis. Linked to this is the satisfaction they receive upon having a referral to a tertiary service. All patients interviewed that attended BCC highlighted the excellence of the service provided. Many patients highlighted that once in the loop of the tertiary service and its set up, they felt much more satisfaction and felt at ease with their diagnosis. Indeed, from Focus Group 1, it is stated by an IPF patient, ‘once you’re in the system and you’re known, I think it works pretty well, but it’s getting through this problem of the early stages of your illness.’ This statement highlights the difficulties with early referral linking to the delay in confirmatory diagnosis and therefore late initiation of antifibrotics, leading to increased risk of early

discontinuation. It does show however, that the service at BCC at present, certainly for between the dates included in our study, is acceptable to patients.

Specialist nurses for ILD have been shown in both the literature and in our clinical experience at UHB (HGS) to improve the experience of patients with IPF (54). This is once again clear in the qualitative data captured in our study where appreciation of the specialist nurses in the tertiary service demonstrates the continued need for them in patients with IPF. They have been labelled as 'critical' to the patients and the service as they provide not only a point of contact, but also a 'lifeline' to other support services. The use of language in Focus Group 2 is interesting here as they are not just a link, but these patients will see the specialist nurses as a lifeline for them and use them to their advantage to enable full support in their condition, highlighting the definite necessity of specialist nurses in IPF. Being a point of contact and link to other support services may allow patients to cope with the adverse events of antifibrotics much easier, with simple advice available on short notice for handling complications. Logically it would follow that the presence of an ILD nurse would reduce the risk of early discontinuation. But interestingly, our quantitative data does not suggest that, as there was no significant difference in patients referred from hospitals with a specialist nurse presence or not.

Once patients are referred to our tertiary centre, they tend to want to make the effort to come to see the team at BCC and therefore receive the benefits of input from the tertiary care specialist nurses, which could explain why there is no significant difference in the regression analysis in those referred from hospitals with a specialist nurse compared to those referred from hospitals without. It is obvious from our qualitative interviews that parking availability at BCC is poor, which is coupled with a many patients highlighting a difficult journey travelling to BCC. Compounding the above to are when patients are increasingly breathless and frail, requiring oxygen and therefore finding it much more difficult to walk from a distance to get to the BCC. However, there is resounding evidence from our qualitative interviews that the travel and parking would never deter the patients from attending

their appointments, which also shows how much effort is willing to be put in for treatment of their IPF. This suggests that travel and distance required to come to the BCC does not increase the risk of early discontinuation in our study population.

Although the support group in our quantitative data does not suggest any impact on the risk of early discontinuation, the qualitative data may shed some light on why this is the case. The Focus Group data will be biased in this case as they are all done from patients at the IPF support group held in the West Midlands on 2 separate occasions. It is interesting from individual interviews to hear the thoughts from patients who did not regularly attend the support group regarding connotations associated with the meeting place, which is currently a hospice, and also with the formal feel of the group dynamic. Some of the patients in the individual interviews suggested that the mere fact the support group is held in a hospice deters them from attending as they have connotations associated with attending a hospice with a terminal illness. Others have commented on the structure of the group stating that is too formal which causes intimidation to newer members and reduces the chances of them attending again in the future. The contrast to this however, are those members who do find the group very useful and as mentioned previously, one of the patients who is currently too good for antifibrotics from a lung function point of view is a long term member of the support group and therefore has reaped the benefits of information around antifibrotics prior to starting them, which logically will help to reduce the risk of early discontinuation. A suggested change in structure of the support group and possibly a move to a different meeting place may increase the number of patients willing to attend and thereby increase their knowledge base around IPF in general and the antifibrotics, which will hopefully positively impact on the discontinuation rate of antifibrotics.

Pulmonary rehabilitation, which is not held in a hospice, has been highlighted by multiple patients as a very good alternative or addition to the support group as they feel it is less formal and also offers an additional physical benefit for the patients, which at the moment the support group does not.

Emotional response to a diagnosis of IPF is an important aspect of antifibrotic therapy. Patients who accept that IPF is a terminal disease, will understand that antifibrotics are not a cure for the disease, but simply something to help slow down the rate of decline and possibly give the patient more time in life. With this understanding, it may help the patient to realise that the objective evidence of a lack of decline in lung function is what they are looking for, rather than a subjective improvement in clinical symptoms, and thereby reduce the risk of early discontinuation, though for some this is a difficult concept. Conversely, it can also highlight to the patient that the antifibrotics are only designed to increase the length of life by 30%. If however, the quality of life for that 30% is poor, on balance, they may opt to focus on their quality of life, rather than lengthening their life and thereby increase the risk of discontinuation of antifibrotics.

Despite that, when asked for advice they would give to other patients who would consider starting antifibrotics most patients would advocate others giving them a chance and trialling them. Some would point out that the antifibrotics are the only option for prolonging life, but others would equally state that there has to be a balance between side effects and risk. This is the bottom line I feel with antifibrotics, which is reflected throughout the qualitative data and themes. Ultimately it is an informed patient decision where they should weigh up the benefit of antifibrotics against the risk and inconvenience of side effects whilst keeping their quality of life in mind.

This qualitative work does suggest that there is still a significant delay in finding a definitive diagnosis for IPF leading to many patients presenting to the ILD service when their lung function is too poor and does not qualify them for antifibrotic therapy. The hope that is given to these patients after discovering they have an incurable disease is then taken away once they are denied treatment. Clearly, there is still work to be done to educate the general medical and public worlds around the entity of IPF and the need for early diagnosis and referral. Currently, imaging is often delayed to allow initial trials of treatment to rule out other causes such as asthma and acid reflux for patients presenting with cough. An initial chest x-ray is then ordered followed by a non-urgent HRCT (if there

is something on the chest x-ray). If, however, chest X-ray is normal, then the patient is referred to secondary care, leading to a wait for initial assessment in respiratory clinic, further investigations in the form of non-urgent HRCT, followed by the referral to the tertiary service where there is yet another delay in assessment and discussion at the MDT. Only after all of the above has taken place does the patient then consider starting antifibrotics, by which time, there will be progression of disease and therefore delay in starting antifibrotics, leading to higher risk of early discontinuation. So, although through the 4 years included in our study, referral habits have changed for the better, there still is work to do to increase the knowledge around a positive diagnosis of IPF.

4.4 Future work

Interest in the development and validation of antifibrotics for the treatment of IPF has increased in recent years, with others in development or subject to research currently. These medications remain a significant step in the patient's pathway with further antifibrotics being developed and further work currently being performed in combination antifibrotics to target different pathways.

Specific to our work and the study that we have conducted, there are a variety of future ideas that can be explored in relation to discontinuation rates and coping with adverse events related to both pirfenidone and nintedanib, which can also be applied to the future combination studies. One such idea would include looking at the effect of nutritional factors or loss of muscle mass on the risk of discontinuation of therapy. The antifibrotic drugs in some ways can be likened to chemotherapy medications which are not started without consideration of performance status, weight and total health of the patients. Therefore, looking at nutrition state, including weight, might be worthwhile and may well be another predictive factor that can identify those that are at risk of early discontinuation. Considering that side effects of both antifibrotics consist of gastrointestinal side effects, weight loss, fatigue or lethargy, it would logically follow that weight may have a correlation of risk of discontinuation.

Currently, in the UK, NICE guidelines stipulate that antifibrotics are only available via the NHS for patients with an FVC between 50-80% of predicted value. However, FVC alone may not identify those patients that would benefit most from antifibrotics. It may be that looking at the effect of a composite scoring system such as the composite physiology index on the risk of discontinuation may be a feasible step to take, which could possibly shape further policies produced in the future.

4.5 Conclusion

In conclusion from both the quantitative and qualitative work it is clear that physiological factors such as advanced disease demonstrated by low DL_{CO} and increasing age demonstrate an increased risk of early discontinuation. The social factors, whilst having an impact on the disease process itself, do not seem to influence the risk of early discontinuation in our study population. The social factors do highlight the need for a holistic view on the management of IPF as the importance of antifibrotics in these patients seems to be initially a priority, but after a period of time becomes less important and the quality of their remaining life with a terminal disease process comes to the forefront.

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6 Appendices

6.1 Appendix A

Telephone Interview on use of antifibrotics

Opening statement

Hello, my name is Parminder Bhomra. I am a doctor working in the Interstitial Lung Disease (ILD) service at Heartlands Hospital. We are doing an evaluation of our service to patients with idiopathic pulmonary fibrosis (IPF). I would like to ask you about 15 short questions around your experience with the medication, which will last around 15 minutes in order to help improve our service to patients in the future.

I would like to speak to…… (Patient/Patient relative) about their experience with …….. (drug name).

Confirm details of who you are speaking to and gain consent for gathering information.

Name:

DOB:

Address:

Consent gained?

☐ Yes ☐ No

Demographics:

Age: Nationality: 1st Language:

What is your highest level of education?

Did you finish your GCSE's/O-Levels?

Did you finish your A-Levels?

Did you attend University?

Any other higher education?

Are you currently working?

What did you/do you do for a living (major employment/longest job held)?

Accessibility to Hospital:

Prescribing Hospital: Method of Travel:

How difficult was it travelling to Prescribing Hospital (score 0-10 with 10 being most difficult)?

Did this influence your decision to attend appointments?

Did this influence your decision on starting medication?

Taking Antifibrotics:

Were you given a choice of antifibrotic?

Which antifibrotic did you choose? (if given the choice)

Why did you choose that particular antifibrotic? (if given the choice)

How did you find taking the medication?

Did you suffer/are you suffering with any side effects?

Did you ever have to take a break or reduce the dose of the medication?

Did you have access to an IPF support group? If so did you attend?

What advice would you give to patients starting on antifibrotics?

6.2 Appendix B

Qualitative Interview on use of Antifibrotics

Hello, my name is Parminder Bhomra. I am a doctor working in the Interstitial Lung Disease (ILD) service at Heartlands Hospital. I am doing an evaluation of the service to patients with idiopathic pulmonary fibrosis (IPF). I would like to ask you a few questions on your experience with Antifibrotics and topics around the service provided and how it could potentially be improved.

Patient Number:

How did you come to be prescribed Pirfenidone or Nintedanib (Delete as appropriate)?

- Where do you live?
- Where do you receive care?
- Which tablet?
- Why did you choose that tablet?

What was/is your experience with Pirfenidone or Nintedanib?

- Were you able to tolerate the tablet?
- Did you take the medication on time?
- Did you suffer any side effects?
- Did you have to reduce the dose or take a break?

How did you find the service at your hospitals (BHH/GHH/SOH)?

Is there anything that could be improved?

- With regards to the service
- With regards to the support
- With regards to the drugs
- With regards to the pharmacy

How do you find your travel to appointments?

Have you attended one of the IPF support groups?

If so, how did you find it?

What social support do you currently have?

- Family support
- Social care
- Community care

What advice would you give to patients starting Pirfenidone or Nintedanib?

6.3 Appendix C

Qualitative interview consent form

Hello, my name is Parminder Bhomra. I am a doctor working in the Interstitial Lung Disease (ILD) service at Heartlands Hospital. I am doing an evaluation of the service to patients with idiopathic pulmonary fibrosis (IPF). I would like to ask you a few questions on your experience with Antifibrotics and topics around the service provided and how it could potentially be improved.

I would like to audio record this interview and would request if you are happy for this to be recorded then to give consent by signing below.

All recordings will be kept anonymous and no data will ever be traced back to yourselves. Once transcribed the original recordings will be destroyed and no identifiable information will be kept. The ideas used may be published for other healthcare professionals to be able to benefit from the ideas from the session, but no identifiable information will be published.

I ……. give my consent for this interview to be recorded:

Signed: ……..

Date: ……

6.4 Appendix D

Focus Group Interview

My name is Parminder Bhomra. I am a doctor working in the Idiopathic Pulmonary Fibrosis (IPF) service at the Birmingham Chest Clinic. We are conducting a service evaluation of the IPF service across the Trust. Specifically focussing on people's experience with Pirfenidone or Nintedanib, be it good or bad.

I would like to conduct an interview with a group of people suffering with IPF, which should last no longer than 45 minutes. All personal data will be anonymised and nothing will ever be traced back to yourselves. Participation is completely voluntary. I will be audio recording the interview allowing me to devote complete attention and record what was said at a later date.

If you would be happy to be interviewed today please let me know.

6.5 Appendix E

Focus Group Interview

Hello, my name is Parminder Bhomra. I am a doctor working in the Interstitial Lung Disease (ILD) service at Heartlands Hospital. I am doing an evaluation of the service to patients with idiopathic pulmonary fibrosis (IPF). I would like to ask you a few questions on your experience with Antifibrotics and topics around the service provided and how it could potentially be improved.

Group Number:

How did each of you come to be prescribed Pirfenidone or Nintedanib (Delete as appropriate)?

- Where do you live?
- Where do you receive care?
- Which tablet?
- Why did you choose that tablet?

What were/are your experiences with Pirfenidone or Nintedanib?

- Were you able to tolerate the tablet?
- Did you take the medication on time?
- Did you suffer any side effects?

How did you find the service at your respective hospitals (BHH/GHH/SOH)?

Is there anything that could be improved?

- With regards to the service
- With regards to the support
- With regards to the drugs
- With regards to the pharmacy

How do you find your travel to appointments?

How do you find the IPF support group sessions?

What advice would you give to patients starting Pirfenidone or Nintedanib?

6.6 Appendix F

Research Governance Statement

Which factors predict early discontinuation of antifibrotics in idiopathic pulmonary fibrosis?

MSc by research, Student:
Supervisors Dr. Walters and Dr. Turner

Background to the decision that this project is a Service Evaluation

The supervisor is responsible for a specialised NHS Interstitial Lung Disease (ILD) service, which is commissioned to provide nintedanib and pirfenidone for patients with idiopathic pulmonary fibrosis.

The aim of this project was to find reasons for discontinuation of treatment. The intent was to possibly better keep patients on treatment locally, if it was clearer why patients discontinued. The scope of the project was suitable in depth and length for a Masters level thesis/dissertation.

The supervisor used the HRA Tool and matrix to make a judgement about whether this project was Service Evaluation (SE) or research prior to the project commencing, as it involved NHS patients. The supervisor assessed whether the data generated would be transferable or generalisable in line with his experience of having undertaken and published SEs, but also as an experienced researcher who had submitted a number of research projects for NHS REC review previously.

The ILD service is set up differently to other services around the UK, in terms of geographical distribution of patients, the model of care between referring centres and intensity of monitoring and nursing care for patients on the drugs. For that reason, the supervisor concluded that even if eventually presented to a wider audience or not, the results would be only of general interest and not transferable to other UK services as representative of a fairly distinct regional group of patients. This judgement was reviewed on a number of occasions through discussion at supervisor meetings. In addition the supervisor confirmed that the NHS R&D department were happy, following discussion with the supervisor. The SE route was then followed for the project.

Research Governance and Integrity Assessment

The project was undertaken in line with good conduct guidelines, specifically (1) by consenting patients for focus groups, not least because the quality of information returned would be dictated by the amount of information given before the interviews, and (2) keeping a site file with all relevant forms for audit trail purposes. There were no other specific procedural pathways for SEs within the respiratory directorate at the hospital, apart from gaining initial approval to undertake the SE from the clinical director, which was done at the outset via an evidenced email exchange.

The Head of Research Governance & Integrity checked with HRA colleagues and the HRA advised the following:

'If the sponsor has used the HRA Tool, and made the decision the findings would not be generalisable, and that the project is Service Evaluation we do not expect it to be submitted for HRA Assessment. You should document this decision.'

Confirmation was received from the supervisor that the HRA Tool was used at the time of set up. A copy was not available but a comprehensive assessment was provided evidencing the decision that the results would not transferable to other UK services.

The supervisor liaised with NHS R+D colleagues who agreed to proceed with the assessment that this was a SE and the NHS Trust process for this was followed (evidence for this was provided).

The Head of Research Governance & Integrity in collaboration with the Director of Legal Services and the Pro Vice Chancellor for Research and Knowledge Transfer agreed that the research ethics and governance review should be documented and a decision was made that no further HRA assessment was needed.

Dr Birgit Whitman
Head of Research Governance
4th December 2019