Key Considerations for Conducting Clinical Trials in Idiopathic Pulmonary Fibrosis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia that is of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia. Over time, the lung tissue becomes thickened, stiff, and scarred and the damage is irreversible. IPF is a rare disease affecting 132,000-200,000 individuals in the United States, and 37,000-40,000 in the European Union; the condition has been estimated to affect as many as 5 million persons worldwide. However, these estimates vary in the literature, as a uniform diagnostic definition of the disease has only been introduced fairly recently. The prognosis is extremely poor, with an average survival of two to three years following diagnosis. The annual mortality due to IPF is estimated to be 40,000 in the United States (US). Respiratory failure is the most common cause of death. IPF affects more men than women, and occurs primarily between the ages of 50 and 70 years with a prevalence peak at 65 to 79 years.

The number of individuals diagnosed with IPF is forecast to continue to increase, due to an increase in life expectancy, an improved clinical understanding of this condition, and earlier and more accurate diagnosis. There is no cure for IPF. Limited therapeutic options are available for patients with mild-to-moderate IPF in the European Union (EU), Canada, and Asia, and there is substantial off-label use of medications. Currently, there are no therapies approved by the US Food and Drug Administration (FDA). However, many patients are able to purchase a drug online, but there is no proof that the drug is identical to that marketed in other countries, and/or that it has not been altered.

While the number of clinical trials in this area has increased in recent years, there remains an urgent and unmet need for new therapies. This article aims to identify key methodological, practical, and ethical issues involved in IPF clinical trials, focusing on country and site identification, feasibility, and study design. Approaches for mitigating these challenges will also be described.

Current Treatments and Implications for Clinical Trials

As noted, IPF is a rare but inevitably progressive and fatal lung disease, and it has a prognosis that can be worse than that for many forms of cancer. There have been several important advances in this field over the past two years, which have increased understanding of how IPF can be managed, and this has brought new hope for patients with this devastating disease. There have been a few studies investigating the effect of thalidomide in IPF patients, indicating improvement of cough and respiratory quality of life, but until recently there were no pharmacological treatments approved for IPF.

A major advance in 2011 was the European Medicines Agency (EMA) approval of the antifibrotic agent, pirfenidone (trade names Esbriet® and Pirespa®), for treatment of adults with mild to moderate IPF in all 28 European Union member countries. The approval was based on the results of two pivotal Phase III, double-blind, randomised, placebo-controlled clinical trials demonstrating the efficacy and safety of pirfenidone. These two studies were supported by two additional Japanese clinical trials. Those studies were based on the primary endpoint of disease progression, measured by the difference between pirfenidone and placebo in the change in forced vital capacity (FVC) from baseline to treatment week 72. The product is also approved for marketing in Norway and Iceland. In 2012, pirfenidone was approved for IPF in Canada; it is also approved for this indication in Japan.
South Korea, China, India, Argentina and Mexico. Pirfenidone is not approved for sale in the United States; the FDA has requested supplemental data as one of the pivotal studies failed to meet the primary endpoint. This Phase III study was recently completed, with results announced in February 2014, and demonstrated positive efficacy results.10

Pirfenidone is currently marketed in 16 countries for IPF, and its availability must be considered when selecting countries to be involved in a clinical trial. There are both advantages and disadvantages for involving countries where this drug is marketed and reimbursed. Inclusion of a positive control for Phase III studies should be considered due to the fact that if the study design allowed pirfenidone as a background therapy, the studies would be more appealing to sites and patients, and this would increase the likelihood of the trial being approved by ethics committees and regulatory authorities. There is now a growing body of evidence regarding the use of pirfenidone in clinical practice, which influences clinical decisions for disease management, including the role of earlier diagnosis, expected clinical outcomes with pirfenidone in the real-world setting, and the role of multidisciplinary teams for diagnosis and treatment of this disease. Prior to approval of this drug, there was little impetus to diagnose a patient with IPF, as there was no treatment available that demonstrated clinically relevant improvement. These advances were reflected in the fact that the 2013 European Respiratory Society (ERS) Annual Congress included a focus on IPF, along with a review of interstitial lung disease (ILD), and discussion of the ongoing revision of the guidelines for the diagnosis and management of IPF issued jointly by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/ERS/JRS/ALAT).11

The search for effective treatments for IPF has involved numerous multicentre, randomised, placebo-controlled trials investigating agents with different mechanisms of action, although many of these clinical trials failed to demonstrate a statistically significant treatment effect, as recently reported in two reviews published by Cottin12 and Antoniou et al.13. This historical lack of positive results is due to the fact that, originally, IPF was viewed as an inflammation-driven process. However, mainly due to the lack of efficacy of the anti-inflammatory treatment approach, there was a shift to the current view that IPF is an epithelial-driven and fibroblast-activated process, in which inflammation is a secondary event.

A review of protocol designs indicates how the definition of IPF, and thus clinical trial entry criteria, have become more specific. However, study design considerations still remain a challenge as there is a continued debate on what constitutes a clinically meaningful endpoint.14 While all-cause mortality and all-cause non-elective hospitalisations have been proposed as the best choices,15 measuring these outcomes could be prohibitive, requiring the...
enrolment of a large number of patients to be followed over an extensive period of time. Others have proposed that the widely adopted primary endpoint of pulmonary function, specifically FVC, is in fact clinically relevant and is an acceptable surrogate.

Some authors have proposed definite and suspected acute exacerbations of IPF as separate outcome measures or as a combined idiopathic acute worsening endpoint. The concept of IPF as a neo-proliferative disorder of the lung may help in meeting the urgent need for a better understanding of the pathogenesis of IPF by taking advantage of learnings from cancer biology. The identification of common pathogenic pathways between the two diseases may stimulate new clinical trials with cancer drugs and with different combinations or types of drugs, as has been intensively explored in cancer. Furthermore, clinical trials in IPF could take advantage of the experience of oncologists, following the cancer model of trials of new treatments by using progression-free survival as a reasonable, if not ideal, logical and clinically meaningful endpoint.

Published literature has identified a number of endpoints as predictors of survival outcome: FVC, diffusion capacity for carbon monoxide (DLCO), the 6-minute-walk test (6MWT), dyspnea, and high-resolution computed tomography (HRCT). The FVC and 6MWT are considered the best predictors of mortality and can be viewed as the best marker of chronic disease progression. Analysis of the data from the largest trial in IPF (INSPIRE; effect of interferon γ-1b on survival in patients with idiopathic pulmonary fibrosis) has confirmed the high reliability of the 6-minute-walk test (6MWT) as an endpoint in IPF clinical trials.

Although there are no FDA-qualified patient-reported outcomes (PROs) for IPF to date, and PROs were not used as a primary endpoint in therapeutic trials in IPF, there is a growing interest in PROs in IPF studies. There are limited research data that support the validity of the Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI), the University of California San Diego Shortness of Breath Questionnaire (UCSD), the St. George Respiratory Questionnaire (SGRQ), and the Medical Outcomes Study 36-Item Instrument (SF-36) for use as outcomes in IPF trials. New IPF-specific PROs in relation to disease progression, and to measure the impact of investigations aimed to improve patient quality of life, are needed. SGRQ-I, an IPF-specific variation of SGRQ, has been developed. Another published tool to assess quality of life in IPF is ATAQ-IPF: future research to validate the use of ATAQ-IPF in IPF trials is planned.

Due to the low prevalence, short duration from diagnosis to death, the high mortality rate of IPF, and the competitive nature of the clinical trial landscape, it is important to design clinical trials that are relevant and interesting to investigators and patients. Factors such as currently available therapies, country and site selection, and study design issues must be taken into account.

Ongoing Clinical Trials
As of April, 2014, there were 54 ongoing global IPF studies (with ‘ongoing’ being defined as recruiting or not yet recruiting), as outlined in Figure 1. An identical search in early 2012 identified only 40 ongoing studies at that time. Due to the low prevalence, short duration from diagnosis to death, the high mortality rate of IPF, and the competitive nature of the clinical trial landscape, it is important to design clinical trials that are relevant and interesting to investigators and patients. Factors such as currently available therapies, country and site selection, and study design issues must be taken into account.

Published statistics for IPF studies over the last five years are provided in Table 1. Although there are no FDA-qualified patient-reported outcomes (PROs) for IPF to date, and PROs were not used as a primary endpoint in therapeutic trials in IPF, there is a growing interest in PROs in IPF studies. There are limited research data that support the validity of the Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI), the University of California San Diego Shortness of Breath Questionnaire (UCSD), the St. George Respiratory Questionnaire (SGRQ), and the Medical Outcomes Study 36-Item Instrument (SF-36) for use as outcomes in IPF trials. New IPF-specific PROs in relation to disease progression, and to measure the impact of investigations aimed to improve patient quality of life, are needed. SGRQ-I, an IPF-specific variation of SGRQ, has been developed. Another published tool to assess quality of life in IPF is ATAQ-IPF: future research to validate the use of ATAQ-IPF in IPF trials is planned.

The vast majority of ongoing clinical trials for IPF are located in the US (63%). This figure is followed by the EU (39%), where most studies for this disease are being conducted. The UK is currently at capacity for such trials. Potential regions/countries to conduct IPF studies with little to no competition are Latin America, Central Eastern Europe, India, Canada, Australia, and China.

Table 1: Interventional and Observational IPF studies in 2009-14

<table>
<thead>
<tr>
<th>Year</th>
<th>Interventional</th>
<th>Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>2010</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>2011</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2013</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>2014 (1st quarter)</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

IPF patients are mainly treated with corticosteroids such as prednisone, oxygen therapy, and a variety of other...
agents, including n-acetylcysteine, azathioprine, cyclosporine, and cyclophosphamide. Based on feedback from global clinical sites, oral corticosteroids are often used for IPF treatment, in spite of the lack of evidence-based data confirming efficacy. The dose range is fairly wide, with little apparent variability between countries. No barriers are anticipated to stopping these medications prior to enrolment in a study. Additional classes of drugs routinely used for the treatment of this patient population include immunosuppressive agents and antifibrotic agents, such as pirfenidone.24,25

It is important that the study design of these trials is consistent with the ATS/ERS/JRS/ALAT guidelines and incorporates key elements from these guidelines, such as diagnostic criteria, standard of care, and assessments to monitor the progress of the disease.

**Table 2: Unique Investigators with IPF Experience**

<table>
<thead>
<tr>
<th>Unique Sites by Region</th>
<th>Pulmonary Fibrosis Specialists</th>
<th>Pulmonary Specialists</th>
<th>Other Respiratory Speciality</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>5</td>
<td>169</td>
<td>180</td>
<td>354</td>
</tr>
<tr>
<td>Europe/Middle East/Africa (EMEA)</td>
<td>152</td>
<td>1097</td>
<td>519</td>
<td>1768</td>
</tr>
<tr>
<td>Japan</td>
<td>5</td>
<td>73</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Latin America</td>
<td>55</td>
<td>240</td>
<td>44</td>
<td>339</td>
</tr>
<tr>
<td>USA/Canada</td>
<td>293</td>
<td>538</td>
<td>112</td>
<td>943</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>505</strong></td>
<td><strong>2049</strong></td>
<td><strong>928</strong></td>
<td><strong>3482</strong></td>
</tr>
</tbody>
</table>

**Methodological Considerations**

**Global Site Identification**

In the US, pulmonary specialists are largely responsible for managing IPF patients, although such patients may briefly come under the care of other specialists, such as thoracic surgeons at the time of their lung biopsy. They may also be seen by pulmonologists in private practice and at academic hospital-based centres. Outside the US, this pattern is replicated, but with variations depending on the availability of pulmonologists or other types of respiratory specialists. IPF clinical trials typically involve collaboration with major university hospitals, research clinics, and academic centres with experience in managing such patients. Table 2 outlines investigators with IPF experience by region, based on a proprietary investigator database at the authors’ company.

**IPF Study Metrics**

The following metrics come from BioPharm Clinical’s Study Advisor tool, based on 30 IPF studies (26 sponsors; 27 interventional/3 observational studies; Phase I or I/II = 6; Phase II or II/III = 12; Phase III = 6):

- **Study length**: average duration of an IPF study is 31 months, 23.3 patients per site, dosing mean of 28 days/patient
- **Enrolment**: 70 patients/study, recruitment of 21.6 months, recruitment rate (RR) of 3.25 patients/site/month (p/s/m).

The mean enrolment per site is extremely variable based on the study design and study phase. In an attempt to better quantify the enrolment per site, completed studies with metrics available were reviewed and are summarised in Table 3.

Based on the Quintiles’ investigator database, enrolment metrics for several principal investigators who participated in IPF studies are shown in Table 4. All sites are located in Latin America (Argentina, Brazil, Chile and Mexico). The mean recruitment rate was 1.04 p/s/m (range: 0.68-2.08 p/s/m). This variability was most likely due to study-specific entry criteria and required procedures.

For IPF trials, the most promising countries are North America, Latin America (Argentina, Brazil, Chile, and Mexico), Eastern and Western Europe (Belgium, Bulgaria, the Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Portugal, Russia, South Africa, Spain, and the UK), the Middle East, and possibly Asia, depending how many sites are needed and whether certain ethnic populations need to be studied for registration purposes.

**Recruitment and Retention**

An interesting strategy would be to focus initially on the ability of sites to conduct all protocol-specific procedures, with access to required equipment, and to provide tools to help sites identify and recruit suitable patients from within their own patient population. Patients who suffer from IPF are typically established within the healthcare system and well known to the sites. It is at the site level where the highest number of patients...
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Table 4: Enrolment per Site

<table>
<thead>
<tr>
<th>SSV to Site Visit Time (days)</th>
<th>Total Pts. Screened</th>
<th>Total Pts. Randomised</th>
<th>Total Pts. Discontinued</th>
<th>Enrolment Timeframe (months)</th>
<th>Recruitment Rate (pts/s/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/a</td>
<td>13</td>
<td>12</td>
<td>5</td>
<td>7.98</td>
<td>1.50</td>
</tr>
<tr>
<td>294</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>6.24</td>
<td>1.12</td>
</tr>
<tr>
<td>274</td>
<td>13</td>
<td>12</td>
<td>2</td>
<td>7.32</td>
<td>1.64</td>
</tr>
<tr>
<td>308</td>
<td>15</td>
<td>9</td>
<td>0</td>
<td>5.74</td>
<td>1.57</td>
</tr>
<tr>
<td>217</td>
<td>15</td>
<td>4</td>
<td>1</td>
<td>3.70</td>
<td>1.08</td>
</tr>
</tbody>
</table>

SSV = Site Selection Visit; SIV = Site Initiation Visit; pts/s/m = patients per site per month

Other Study Design Considerations

A placebo arm in IPF clinical trials could potentially pose ethical concerns in some countries. This is common to indications when “standard” therapies have been established, with or without an evidence base, making it appear that participants are being denied potentially beneficial treatments.\(^26,27\) This is a particular issue for seriously ill patients. One approach would be to use a trial design with a treatment-to-placebo ratio such that more participants receive the active drug (or active comparator) than placebo. An open label extension of long duration would also be advantageous both for approval and enrolment.

A second consideration for study entry criteria is the fact that clinical trials subjects are required to have an IPF diagnosis less than five years prior to randomisation (with or without a lung biopsy), according to the 2011 ATS/ERS/JRS/ALAT joint guidelines, including the 2013 revised guidelines, which suggest that a lung biopsy is not necessary for the diagnosis.\(^28\) Inclusion of newly diagnosed individuals as well as patients who have had the diagnosis for several years is also an important consideration due to the short median survival time post-diagnosis.

A third consideration is whether to mandate that the diagnosis of IPF is confirmed by central reading of high-resolution computed tomography (HRCT) and central review of lung biopsy specimens, if performed. A median of 65% of patients are diagnosed by HRCT alone, with a median of 35% of patients...
being diagnosed by HRCT plus lung biopsy. Elements to take into account include:

- If the HRCT criterion is included, a vendor should be selected with global experience and the ability to analyse data from different types of scanners, in addition to experience with providing phantoms (used for validation of the scanner) worldwide.

- A diagnostic challenge is that IPF histology shows striking variation from one region to the next, with temporal and spatial heterogeneity. It is not unusual to find areas of normal lung next to areas with severe thickening of alveolar walls. Therefore, findings from bronchoscopic or percutaneous lung biopsy are difficult to interpret. Open lung biopsy and video-assisted thoracoscopic lung biopsy are the preferred methods.

- The variability in diagnosis of IPF comes from the inter-observer variability of radiographers and pathologists for interpretation of images.

Additionally, HRCT images should already be available in digital format. The challenge may be for sites to be able to provide digital images of lung biopsies.

Other study design factors such as treatment duration will be based on study objectives, e.g., to delay or prevent exacerbations, reduce pulmonary decline, improve patient-reported outcomes, and/or improve survival time.

Finally here, blood biomarkers for IPF should be considered due to their easy accessibility and reported association with survival or pathogenesis of the disease and consideration needs to be given to the mechanism of action of the investigational product. Examples of common biomarkers included in IPF studies are as follows:

- Disease progression biomarkers: CCL-18, KL-6, SP-A, SP-D
- Fibrosis biomarkers: MMP-1, MMP-7, circulating collagen fragments
- Th2-related cytokines and associated signature: IL-4, IL-13, YKL40, Ig E, eotaxin, CCL18, YKL-40, vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1).

Concluding Comments
While there have been significant advances in the understanding of the pathophysiology of IPF over the past decade, the mechanisms underlying this disease are still relatively poorly understood. To date, only one therapeutic agent has been approved for IPF worldwide. This leaves an urgent unmet need for new treatment modalities. Based on our experience providing clinical services for more than a dozen IPF trials involving nearly 1000 patients in 20 countries worldwide, there is room for optimism that new, effective treatment options will be developed in the foreseeable future for this severe and fatal disease.

References


7. Pulmonary Fibrosis Foundation website [http://www.pulmonaryfibrosis.org/Prevalence/]


29. Source: Quintiles internal feasibility report, conducted in March 2013

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