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ACCELERATING IDIOPATHIC PULMONARY FIBROSIS CLINICAL TRIALS

Overcoming Challenges in Recruitment and Endpoints

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Respiratory diseases are among the leading causes of deaths globally. Chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis (IPF), and interstitial lung disease (ILD), affect nearly 570 million people worldwide.[1]

IPF is the most common form of pulmonary fibrosis[2], affecting over 80,000 people in the United States.[3] This rare, chronic, progressive lung disease is characterized by the replacement of the normal, spongy, and stretchy nature of the lung tissue with scarring and stiffness. The majority of IPF patients are men above sixty. Risk factors in addition to gender and age include smoking, genetics, and certain occupational exposures to dust/chemicals. These individuals often experience progressively worsening symptoms, including exertional breathlessness, cough, and other debilitating symptoms that severely impact quality of life.

Current treatment options for IPF are limited. Several drugs, including steroids and immunosuppressants, have failed to show any beneficial effects in IPF patients in the past. The current approved therapies, Nintedanib and Pirfenidone, can slow the progression of IPF but do not reverse lung fibrosis. Moreover, these drugs provide limited survival benefit at the expense of undesirable side effects and poor symptom control. The recently approved phosphodiesterase 4B inhibitor, Nerandomilast, slows FVC decline but did not demonstrate any improvement in the quality of life of the IPF patients. The median survival post diagnosis for patients with IPF despite antifibrotic treatment is between 3 – 3.75 years which drops to 2.5 years in the untreated patients.[4]

Despite the enormous unmet need, the development of new therapies in IPF is challenging due to the rare patient population, unpredictable disease progression, and variability in endpoints. Accelerating the clinical development of novel therapies, which can help halt or reverse the progression of IPF, might reduce the burden of debilitating symptoms and improve the lives of individuals with IPF.

CHALLENGES OF IPF CLINICAL TRIALS AND STRATEGIES FOR SUCCESS

To ensure the successful execution of clinical trials in IPF, partnering with a CRO that has relevant operational, regulatory, and medical expertise is crucial for mitigating risk. A seasoned but adaptable partner can provide invaluable insights gained from managing similar trials. These insights and strategies include best practices from comparable indications, trial designs, regulatory and site interactions, and endpoint protection.

Site Selection

Medpace experts can tailor site selection strategy to meet the needs of the protocol. For studies that may require antifibrotic naïve patients, we can select countries where the current antifibrotics are not reimbursed. During feasibility, Medpace will glean data across internal and external databases to enable data driven decision making on the most current information. Our country ranking evaluates key parameters such as the competitive landscape, historical experience in IPF trials, study start-up performance, epidemiology data, and country cost efficiency. Our global experience in IPF trials allows Medpace to leverage key intel from the strong site and advocacy relationships that have been established. This in conjunction with data insights creates a targeted selection of sites and enables us to select the best countries to utilize for the IPF study to support successful study execution.

Recruitment and Retention

IPF clinical trials can face recruitment and retention challenges due to the following factors:

- The clinical landscape is highly competitive.
- The availability of eligible patients is limited due to IPF being a rare disease.
- Patients with IPF often have short-life expectancy and debilitating symptoms.
- Eligibility criteria for IPF trials are often narrow.
- Studies are long in duration with frequent assessments and site visits.

To overcome these challenges, Medpace implements strategies and insights gained from managing trials in IPF and similar indications. These include targeted outreach, patient centric trial design, leveraging digital tools, and engaging with both patient advocacy networks and experienced clinical sites.

- **Strategic Partnerships –** Strong relationships with sites, investigators, and patient advocacy groups that have longstanding relationships with potential patients play a critical role in facilitating strategic site selection, start-up, and recruitment efforts translating into successful conduct of a study.
- **Targeted Patient Outreach –** Medpace's connections to rare disease communities with access to patient registries enhance the ability to identify qualified sites and reach patients quickly in a competitive environment.
- **Patient Advocacy Groups –** Working closely with patient advocacy organizations enriches trial design and boosts recruitment by increasing trust and awareness among IPF patients. Patient advocacy groups can help tailor the study protocol and communication, ensuring broader engagement across subgroups.
- **Patient-Centric Trial Design –** Optimizing the protocol to limit in-person site visits to necessary assessments, leveraging remote patient monitoring, and factoring in patient quality of life as a consideration when designing the protocol is essential to reduce burden and improve the participant experience.
- **Site Support Services –** Medpace provides site support, including assistance with phone visits during feasibility questionnaire completion and robust training via recorded eLearning for quick reference. Medpace can contract vendors that will offer study coordinator and study nurses support to the study team, which can be requested in certain countries.
- **Medpace Patient Recruitment and Retention (PRR) Team –** Medpace develops study branded educational materials for patients and sites. Additionally, experts manage a full digital outreach campaign, including developing patient-facing websites and study websites with detailed information about the study, patient eligibility criteria, and contact details. The PRR team promotes the study on social media platforms, online forums, and IPF specific discussion boards to reach wider audiences.
- **Medpace Patient Concierge Services (PCS) –** Providing global travel support to minimize patient burden, facilitate compliance with study visits, and help keep the study on track. IPF patients often face mobility challenges, so providing comfort items can help support patients—ultimately increasing patient retention.

Endpoint Protection

Forced Vital Capacity (FVC) as the Primary Endpoint

The FDA and EMA recognize FVC as a primary clinical endpoint in IPF studies. Both absolute and relative decline in FVC is directly linked to increased mortality risk and serves as a critical measure of disease progression.

Factors favoring use of FVC as a primary endpoint in IPF studies:

- Accessibility
  - Spirometry is widely available.
  - IPF patients are accustomed to performing these assessments.
  - Most sites have trained/qualified and experienced respiratory technicians.

- Reproducibility
  - Measurements can be obtained within a small margin if performed properly.
  - Reproducibility provides confidence in the measured data.
- Standardization
  - Centralized provision of standardized spirometry machines can ensure all sites are using the same machines for data collection, avoiding machine to machine variation.
  - Centralized overread and quality grading will allow only those readings that reach study defined quality thresholds to be considered 'acceptable'.
  - Reduces longitudinal variability, increasing the statistical power of trials. Any unexplained fluctuations in the data can be identified early and sites trained to ensure high quality spirometry.
- Potential for Shorter Studies
  - A 5.7% FVC change threshold at three months can potentially predict increased mortality risk with comparable accuracy to a 10% change over 12 months.[5]

Understanding 'absolute' vs 'relative' decline in percent predicted FVC (ppFVC):

- Absolute ppFVC decline can overlook disease severity variations – 10% absolute decline from 90% to 80% is equal to 11% relative decline. However, 10% absolute decline from 40% to 30% is equal to 25% relative decline.
- A 10% absolute decline in ppFVC in an IPF patient with advanced disease may be more limiting symptomatically.
- An absolute decline in FVC of greater than 5% over 1 year is recognized as a criterion for disease progression.

Challenges with FVC:

- Absence of True Placebo – Assessing the treatment effect on top of existing antifibrotic therapy leaves a narrower margin for detecting differences and increases the need for larger patient cohorts and longer trial durations. FVC can no longer solely define treatment response on top of standard of care.
- Variability – Results are influenced by patient-related and technician-related factors.
- Quality Grade – Achieving grade A in all assessments is ideal but not practical considering the target patient population.
- Limitations – There are compliance and reproducibility issues with home spirometry.

Medpace experts can suggest strategies to ensure FVC is protected. Additionally, we can suggest sites who have provided good quality spirometry data in previous studies and avoid those with quality issues. Our feasibility can ensure all relevant data pertaining to spirometry assessment is collected prior to site selection. By leveraging our relationship with respiratory service vendors, Medpace can ensure seamless collection of high-quality FVC data.

High-Resolution Computed Tomography (HRCT) as a Clinical Endpoint

The FDA has acknowledged the value of imaging biomarkers in IPF, as serial quantitative HRCT plays a vital role in measuring disease severity.

Key advantages:

- Clinical Correlation – The extent of fibrosis measured via HRCT correlates directly with patient-reported outcomes (PROs), FVC changes, and overall survival.[6]
- Overcoming FVC Limitations – In patients with co-existing emphysema, lung volumes may appear preserved, masking disease progression when measured by FVC alone. HRCT provides a direct, non-invasive assessment of lung morphology that overcomes this "masking" effect.
- Technological Advances – Modern scanners can acquire high-quality images within a single breath-hold—a critical benefit for breathless patients—while radiation dose reduction techniques significantly lower exposure without compromising image quality.

Challenges with HRCT:

- Regulatory Hurdle – Competent Authorities and Ethic Committees may have concerns with radiation dose if CT is repeated more frequently than standard of care.
- Patient Factors – CT readings may be affected by conditions such as emphysema, pneumonitis, pulmonary edema, and other pulmonary complications.
- CT Scanner Infrastructure – Not all sites may have the availability of modern scanners or have the ability to integrate assessments with study protocol.

To lead to operational success in quantitative imaging, the following aspects are required:

- Standardized acquisition parameters are required, with the same protocol followed for baseline and follow-up scans across all studies and countries with careful attention to critical acquisition factors such as breathing instructions, patient position, and use of contrast.
- Examinations must not be performed during acute exacerbations, which would jeopardize endpoint assessment.
- Allowing qualified historical CT scans to replace repeat imaging during screening. This reduces the cumulative radiation dose and the burden of activities on the participant.
- Low-dose CT protocols should be implemented where feasible.
- Centralized Overread is required by utilizing algorithms to evaluate thin, high-resolution cuts and establishing clear parameters to determine the usability of scans, particularly when evaluating historical imaging.

The Medpace Core Lab (MCL) includes a team of board-certified radiologists with experience performing blinded independent central review in IPF clinical trials and expertise in identifying UIP and probable UIP patterns. Additionally, MCL can provide quantitative measurements of lung densitometry and of fibrosis, ground glass opacity, and honeycombing using computer-aided texture analysis software to support efficacy endpoints.

Patient Reported Outcomes (PRO) as Endpoints

PROs capture patient's assessment of their health, symptoms, mental status, functionality, etc., which is essential to understand the impact of the treatment on quality of life. A fit for purpose PRO must be able to capture information meaningful to patients that other clinical outcomes do not. Competent Authorities encourage the use of PROs in IPF trials. K-BILD (King's Brief ILD) and Living with Pulmonary Fibrosis Questionnaire have been used in multiple IPF trials and have undergone rigorous validity and reliability testing.

Key challenges:

- PROs need rigorous validation.
- Frequent assessments can be burdensome to patients.
- Translations may be required across various languages.

To support the collection and analysis of ePRO data, Medpace has developed user-friendly processes and technology through an ePRO system, which interacts directly with the electronic data capture (EDC) system. Medpace has ePRO strategies in place to minimize burden and enhance quality data. For example, providing cultural and language validated translations to assessments and a standardized script for administrators ensures the process is seamless and consistent.

To further reduce burden on sites and participants, limiting ePRO assessments to the most clinically meaningful is essential. Encouraging participants to complete ePROs prior to other activities can prevent them from getting tired or bored, which can lead to inconsistent endpoints. This focused approach supports high-quality data and maintains a positive patient experience.

Endpoints Focused on Acute Deterioration

IPF trials frequently include IPF exacerbations or respiratory-related hospitalizations as endpoints. It is critical to ensure that these are classified the same way across sites, and given that there are not standard definitions, a clinical adjudication committee can ensure continuity, especially useful for large multicenter trials. The adjudication committee can retrospectively adjudicate clinical events using data from source documents, medical records, and/or imaging results. Medpace Medical Monitoring and Clinical Endpoints teams work hand-in-hand to establish the adjudication committee, develop a Charter, and ensure events are processed/adjudicated in accordance with it.

CONCLUSION

The future of IPF trials holds immense promise, driven by innovations in clinical development and the emergence of new therapies with the potential to not only halt the progression of IPF, but also reverse its impact, offering hope for patients. A critical shift toward patient-centered endpoints—focused on how the patients feel, function, and survive—is reshaping IPF research. Despite these advancements, significant unmet needs remain, highlighting the importance of partnering with an experienced CRO capable of navigating the complexities involved in conducting these trials.

Accelerate your path to approval with guidance from Medpace's global team of medical, operational, and regulatory experts with extensive experience in respiratory and rare diseases. Through a full-service, single single-vendor outsourcing strategy, Medpace helps streamline even the most complex IPF trials. Medpace Core Labs (MCL) offers a full spectrum of medical imaging services. MCL is comprised of a dedicated team of physicians, scientists, and technologists with extensive experience—including specialized expertise in HRCT as an endpoint—who provide customized support to ensure the success of the trial. Furthermore, Medpace Reference Laboratories (MRL) conducts safety testing for global Phase I – IV trials across multiple therapeutic areas, including IPF and related respiratory diseases. With a total of four wholly-owned, built-for-purpose, CAP accredited CLIA laboratories worldwide, MRL provides rapid analysis of samples while ensuring regulatory compliance (e.g., IVDR) and consistency of results by using global SOPs and methods. Additionally, novel biomarkers for the evaluation of IPF continue to be developed; our team of PhD scientists are experts in laboratory testing for clinical trials across multiple areas (safety testing, biomarkers, molecular, cell culture, and histology) and are readily available to provide advice and discuss solutions.

Together, these integrated services and extensive experience offer the flexibility, efficiency, and scientific rigor needed to overcome challenges and accelerate your IPF clinical trial. Contact our respiratory experts to learn more.

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