White paper

Rare diseases

How is clinical research evolving in IPF and other rare respiratory diseases?

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For patients living with idiopathic pulmonary fibrosis (IPF) and other rare respiratory diseases, the past decade has brought meaningful progress, but substantial unmet need remains.

Disease-modifying therapies are beginning to transform outcomes in conditions like cystic fibrosis and pulmonary arterial hypertension (PAH), and although there is still unmet need, IPF is also seeing renewed momentum in drug development.

Yet for many patients, today's treatments still primarily slow disease progression rather than halt or reverse it. And trial participation can be logistically and physically demanding.

In this *Xtalks Spotlight*, Francis Jones, PhD, executive director of project management at the PPD™ clinical research business of Thermo Fisher Scientific, described how clinical research in rare respiratory diseases is changing. He highlighted advances in therapeutic science, evolving trial designs and the role of precision medicine in easing patient burden and improving outcomes.

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> **"I think in the last 10 years, there has been significant progress made, but there's still very much a need for better medications across many of rare respiratory indications."**
>
> **— Francis Jones**

From symptom management to disease modification in rare respiratory diseases

Looking back over the past 10 years, Jones described "significant progress" across rare respiratory indications, but emphasized that the need for better medications remains.

He pointed to cystic fibrosis as a clear example of how rapidly the treatment space can shift. Two decades ago, care centered on managing symptoms and complications. That changed with Vertex's mutation-targeted therapy, culminating in the FDA approval of Trikafta in 2019, which addresses the underlying cause of disease for many patients. As Jones noted, this has had a tangible impact on prognosis: life expectancy has moved from roughly 30–40 years to more than 60 years for babies born with cystic fibrosis today.

A similar trend is emerging in pulmonary arterial hypertension (PAH). The approval of sotatercept, widely regarded as the first disease-modifying therapy in this indication, has generated a great deal of excitement in the respiratory community. While it remains to be seen whether sotatercept can sustainably reverse or halt vascular remodeling beyond two years, the data signals a meaningful step toward altering disease trajectory rather than only relieving symptoms.

IPF, however, remains especially challenging. Despite progress, it is still a progressive disease for which the approved therapies slow decline rather than stop it. Jones mentioned the recent approval of nerandomilast — the first new IPF drug in over a decade — as an important breakthrough that offers new hope. In addition, positive Phase III data from United Therapeutics' pivotal IPF trial suggests further pipeline depth and momentum. At the same time, IPF is highly heterogeneous: some patients decline slowly, while others deteriorate rapidly, making it challenging to pinpoint who will benefit most from which therapy and when to initiate treatment.

Overall, Jones sees progress across rare respiratory diseases, accompanied by a huge opportunity for continued innovation and new drug development.

IPF Today: Multidisciplinary diagnosis, disease burden and unmet need

In IPF specifically, Jones described a dramatic shift from an era with no treatments to one where patients now have antifibrotic options and an expanding pipeline of targeted agents. The next priority is clear: moving from slowing progression to halting, or even reversing, the underlying fibrotic process.

Achieving that goal starts with accurate, early diagnosis. “The role of the multidisciplinary medical teams, the pulmonologists, the radiologists and the pathologists, remains absolutely key for that accurate early diagnosis of these patients so that we can treat them prior to significant disease progression,” he said, noting that these teams are essential for confirming IPF and distinguishing it from other interstitial lung diseases.

The day-to-day burden of IPF is substantial as well. Many patients must travel long distances to reach specialist centers, which can limit both their access to routine care and their ability to participate in trials. To mitigate this, sponsors and providers are increasingly exploring remote monitoring and at-home support to supplement center-based visits.

Even with these advances, the prognosis remains sobering. As Jones explained, “But for IPF, the life expectancy remains around three to five years from diagnosis, so there is still a huge unmet need,” underscoring the urgency of more effective therapies and more accessible trial designs.

How trial design is evolving in IPF and other rare respiratory diseases

On the clinical research side, Jones noted that both the volume and sophistication of studies targeting IPF and other rare respiratory indications have grown over the past decade.

“Trial designs have become more refined. We have better endpoints, more refined eligibility criteria, but there still very much remains a regulatory expectation around the familiarity of trial designs,” he explained.

One of the most important shifts has been the integration of precision medicine into respiratory trials. Sponsors now routinely stratify patients using more sophisticated phenotyping that incorporates imaging findings and biomarkers, enabling more personalized therapy assignment and helping ensure that targeted agents are studied in the subsets most likely to benefit.

Jones also highlighted the growing emphasis on the “feel, function and survive” outcomes to guide endpoint selection.

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Historically, respiratory trials have often relied heavily on spirometry because it is objective and relatively straightforward to measure, but spirometric values alone may not fully capture what matters most to patients in daily life.

As he puts it, “I think that focus on the feel, function and survive paradigm is key to support recruitment. So often we’ve looked at spirometry as measuring what is measurable, and maybe not so much at what is meaningful to patients. Ultimately, we must keep the patients in mind when we are designing these trials to ensure that we collect the data we need, manage that trial participation burden and develop drugs that truly make a difference in these patients’ lives.”

Designing trials around how patients feel (symptoms and quality of life), how they function (exercise capacity, daily activities) and whether they survive (mortality and progression-free survival) offers a more holistic view of therapeutic impact.

The challenge is to align these patient-centered endpoints with feasibility, regulatory expectations and site burden while still capturing the robust data needed for approval.

Have trials become more patient-centric? Progress and persistent complexity

When asked whether IPF and rare respiratory disease trials have become more patient-centric, Jones’ overall answer is yes, but “there’s still very much room for improvement.”

He noted that over the past 10 years, clinical trials have become more complex. Studies typically include more endpoints and

assessments, involve more sites and require larger patient populations. Increasingly, protocols focus on specific patient subsets, driven by:

- More complex therapies, including cell and gene therapies
- Stricter regulations and evolving safety expectations
- Advanced trial designs that demand richer datasets

These forces can push teams to collect large volumes of "nice-to-have" data that may not be essential to answering the primary scientific questions. While such information can be valuable, it may also increase burden for patients and sites, potentially affecting recruitment, retention and data quality.

At the same time, there is real progress toward patient-centric participation models. Home health care is now used more often in trials, with nurses, phlebotomists and even physicians visiting patients at home to perform assessments and collect samples. This reduces travel demands and makes participation more feasible for patients with severe respiratory limitations or those living far from specialist centers.

Remote data collection technologies are also advancing quickly. Spirometry, cough monitoring and Holter monitoring can now be performed in the home, feeding data directly into study systems. AI-enabled tools are beginning to support real-time remote expert review, enabling clinicians to interpret data promptly and manage patients proactively without requiring every assessment to occur in the clinic.

Together, these approaches are moving trials closer to patients' everyday environments while maintaining clinical oversight and data quality, an essential step in making research more inclusive and sustainable over time.

Looking ahead: Precision medicine and earlier intervention

For Jones, precision medicine represents one of the most promising areas for future advancement in IPF and other rare respiratory diseases.

He returned to cystic fibrosis as a case study in how genotype-guided therapies can reshape the treatment landscape. Mutation-specific drugs not only improve outcomes for those who respond but also clarify which patients are unlikely to benefit, preventing unnecessary exposure to ineffective regimens.

Applied to IPF and other rare respiratory diseases, precision approaches could help:

- Identify individuals with early disease susceptibility before overt symptoms or rapid decline
- Discriminate which patients are at risk of progressive disease even before progression occurs
- Inform earlier intervention windows when therapies may have the greatest impact
- Guide the selection of alternative treatment regimens better suited to each patient's biology

Jones noted that such tailored strategies could be both clinically advantageous and more cost-effective by avoiding trial-and-error approaches with multiple ineffective therapies.

Working together to deliver hope

Despite the remaining challenges, Jones is optimistic about where rare respiratory research is heading. Over the past decade, he has seen the landscape "evolve significantly," fueled by "amazing doctors and scientists working on new and revolutionary therapies."

He believes there is "definitely hope for patients on the horizon," particularly if stakeholders across clinical research, including sponsors, investigators, regulators, patients and advocacy groups, continue to work together toward a shared goal: developing therapies that not only extend life but also meaningfully improve how patients live with IPF and other rare respiratory diseases.

For sponsors and research teams, the path forward will involve balancing innovation with familiarity:

- Advancing disease-modifying science while grounding designs in clear, clinically meaningful endpoints
- Embracing precision medicine and remote technologies without overwhelming sites and patients
- Leveraging multidisciplinary expertise to diagnose earlier and treat more effectively

If these pieces come together, IPF and other rare respiratory disease trials may increasingly reflect the real-world experiences of the patients they are designed to help and bring the industry closer to the cures that are so urgently needed.

To explore even more rare respiratory clinical development strategies and advancements, visit ppd.com/respiratory

This article was created in collaboration with the PPD clinical research business of Thermo Fisher Scientific and Xtalks editorial team.