SYMPOSIUM REPORT

Meaningful Endpoints for Idiopathic Pulmonary Fibrosis (IPF) Clinical Trials: Emphasis on 'Feels, Functions, Survives'

Report of a Collaborative Discussion in a Symposium with Direct Engagement from Representatives of Patients, Investigators, the National Institutes of Health, a Patient Advocacy Organization, and a Regulatory Agency

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This symposium and report of the proceedings are dedicated to patients with IPF.

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) carries significant mortality and unpredictable progression, with limited therapeutic options. Designing trials with patient-meaningful endpoints, enhancing the reliability and interpretability of results, and streamlining the regulatory approval process are of critical importance to advancing clinical care in IPF.

Methods: A landmark in-person symposium in June 2023 assembled 43 participants from the US and internationally, including patients with IPF, investigators, and regulatory representatives, to discuss the immediate future of IPF clinical trial endpoints. Patient advocates were central to discussions, which evaluated endpoints according to regulatory standards and the FDA's 'feels, functions, survives' criteria.

Results: Three themes emerged: *1*) consensus on endpoints mirroring the lived experiences of patients with IPF; *2*) consideration of replacing forced vital capacity (FVC) as the primary endpoint, potentially by composite endpoints that include 'feels, functions, survives' measures or FVC as components; *3*) support for simplified, user-friendly patient-reported outcomes (PROs) as either components of primary composite endpoints or key secondary endpoints, supplemented by functional tests as secondary endpoints and novel biomarkers as supportive measures (FDA Guidance for Industry (Multiple Endpoints in Clinical Trials) available at: https://www.fda.gov/media/162416/download).

Conclusions: This report, detailing the proceedings of this pivotal symposium, suggests a potential turning point in designing future IPF clinical trials more attuned to outcomes meaningful to patients, and documents the collective agreement across multidisciplinary stakeholders on the importance of anchoring IPF trial endpoints on real patient experiences—namely, how they feel, function, and survive. There is considerable optimism that clinical care in IPF will progress through trials focused on patient-centric insights, ultimately guiding transformative treatment strategies to enhance patients' quality of life and survival.

Keywords: idiopathic pulmonary fibrosis; meaningful outcomes as endpoints for IPF trials; patient reported outcomes for IPF trials; FVC, 6MWT, composite endpoint for IPF trials; image and circulatory biomarkers for IPF trials

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Background

Endpoint selection is critically important in the design and execution of clinical trials enrolling patients with idiopathic pulmonary fibrosis (IPF). The choice of endpoints will not only have considerable influence on the regulatory approval process but also impact funding decisions by agencies, donors, sponsors, and industry collaborators. Furthermore, it forms the bedrock of clinical decision-making for providers, and most critically, endpoint selection is of central importance to developing reliable insights needed to improve clinical care for patients living with IPF.

The substantial symptom burden, risk of progression, and shortened survival of patients living with IPF drive the urgency for more effective treatment options. On June 19th and 20th, 2023, experts in IPF from international academic and clinical centers joined FDA representatives, patients with IPF, and representatives from patient advocacy organizations for an intensive one-and-a-half-day symposium with the National Institutes of Health (NIH) officials attending in an observational capacity. This symposium focused on discussing study endpoints that most reliably capture whether interventions provide meaningful benefit to patients with IPF, in the context of current and anticipated landscape of clinical management that has evolved based on evidence to date.

Central to the discussions of the symposium was re-evaluating IPF clinical trial endpoints in the context of regulatory approval, and exploring outcomes that are

more meaningful to patients. This shift to more patient-centered regulatory prerequisites has the potential to meaningfully enhance drug development and improve clinical care, reflecting a turning point for the future IPF clinical trials. Of note, grounded in a decade's worth of evidence specific to IPF, the decision was made to focus the symposium on IPF exclusively and defer discussions of merging patients with IPF and other progressive fibrotic interstitial lung diseases (ILDs) (i.e., progressive pulmonary fibrosis) (1) to a standalone future session.

This report reflects the captured views of authors who participated in the closed symposium held on June 19th–20th, 2023. It should be noted that the views and opinions expressed in specific sections of this report are those of the authors and should not be construed to represent the FDA's views or policies.

IPF Definition, Current Clinical Landscape, and the Urgent Need to Improve Outcomes That Are Meaningful to Patients

To understand the impact of endpoint selection, it is helpful to frame IPF in its clinical context. IPF is a unique disease entity belonging to the broad and heterogeneous category of chronic interstitial lung diseases (ILD), occurring exclusively in adults and manifesting solely within the lungs. While it typically presents without systemic disease or external symptoms, there are potential extrapulmonary manifestations (1, 2). IPF disease behavior is characterized by various slopes of irreversible lung function decline, ranging from rapid to gradual deterioration. These varying trajectories, accompanied by worsening respiratory symptoms and fatigue, significantly shorten survival, often due to disease progression with respiratory failure or associated comorbidities, with a median survival of ~3–5 years (1). While genetic predisposition factors identified in a subgroup of patients and familial pulmonary fibrosis are increasingly recognized, the cause of IPF remains unknown. The disease is characterized by well-defined imaging and/or a histopathological pattern of usual interstitial pneumonia (UIP) (1–4). Although usual interstitial pneumonia (UIP) is a defined pattern, it is not specific to IPF and may occur in several clinical conditions including connective tissue diseases, environmental exposures, hypersensitivity pneumonitis and genetic disorders that lead to pulmonary fibrosis (5).

This specific case definition enabled recruitment of relatively homogenous cohorts of patients with IPF for clinical trials, revealing key insights into the disease's behavior and natural course (6) and leading to the discovery of two antifibrotic drugs, with demonstrated efficacy (7, 8). Amid these advancements, an ongoing debate continues about the grouping of progressive fibrotic lung diseases for antifibrotic interventions in future IPF trials (2). Current trial data indicate that the average annual decline in forced vital capacity (FVC) among patients with mild or moderate lung function impairment is 150 to 200 ml per year (Figure 1A) (6), which can be slowed in patients treated with pirfenidone or nintedanib (7, 8). However, the clinical course of IPF is variable, and the rate of progression in individual patients is difficult to predict (Figure 1B).

Despite antifibrotic agents and best supportive care, patients living with IPF suffer from persistent respiratory symptoms, fatigue, and diminished quality of life. Although currently approved antifibrotics slow the rate of decline of FVC, they have not been shown to improve symptoms or quality of life, nor do they reliably halt disease progression. In fact, even with antifibrotics (or several months to years of stability without them), IPF may progress rapidly and unexpectedly. Whether gradual or rapid, progression causes symptomatic worsening and impairs patients' sense of well-being. Thus, there is an urgent need to identify more effective therapies to prevent worsening and ultimately improve how patients feel and function.

Materials and Methods

Symposium Design and Participants

Forty-three participants from the United States, Europe, and Latin America attended the day-and-a-half symposium near the FDA's Washington, DC headquarters. Co-chaired by GR and FJM alongside the FDA, attendees were selected for their expertise, spanning FDA regulatory representatives, IPF clinical and academic experts, methodologists, and biostatisticians with expertise in IPF, IPF patient advocacy organization representatives, IPF patients, and observational participants from the National Institutes of Health (NIH).

Individual sessions were led by nine core discussants with expertise in IPF endpoints or regulatory and methodological issues. These presentations sparked comprehensive discussions among participants, including three in-person patient advocates with IPF (DG, RB, DI), a recorded patient testimony (RN), ten FDA representatives, and 16 other IPF experts (full list in Table 7). The conversations revolved around endpoints for IPF clinical trials and their real-world impacts, which were contextualized by the patient advocates. The FDA provided regulatory considerations for each session. In collaboration with the core discussants and GR, MG synthesized the symposium's proceedings into a cohesive presentation and translated the discussions into a consolidated manuscript. This report of the symposium proceedings reflects the collaborative effort of all participants.
Funding for this symposium was generously provided in part by GR and FJM, and donations (*see* Acknowledgments).

Focused Sessions

The symposium included the following focused sessions, led by one or more core discussant(s):

1. An overview of key endpoints used in IPF clinical trials to ensure foundational understanding of the current standards and key knowledge gaps.
2. Statistical prerequisites that distinguish a patient-level correlate from a surrogate and application of the 'feels, functions, survives' criteria in endpoint selection.
3. An overview of FDA considerations for establishing substantial evidence of effectiveness.
4. Comprehensive synopsis of key IPF trial endpoints: FVC, composite endpoints, patient-reported outcome (PRO) measures, physical activity and walk test variables, and imaging and circulating biomarkers.

Regulatory Considerations

The presentations prepared by the core discussants were shared with the FDA for their review a month before the symposium. At the end of each focused session, FDA representatives discussed respective regulatory considerations, and the need to address these to bridge the gap between the

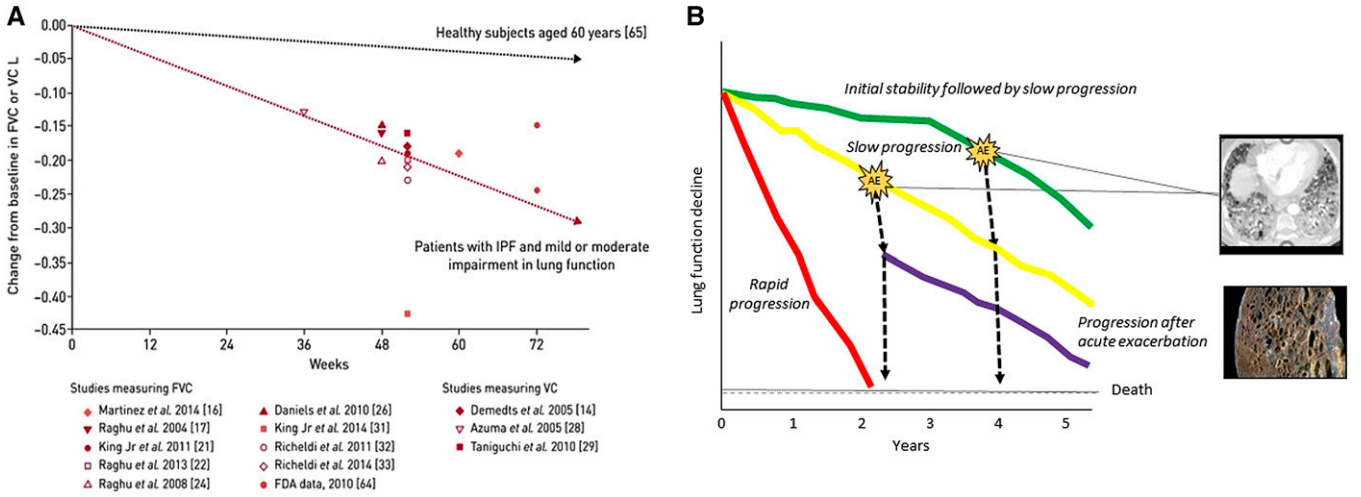

Figure 1. (*A*) Natural course of lung function decline in patients with IPF based on data from placebo arms of clinical trials. Reproduced from Raghu *et al.*, 2017 (6) with permission from the *European Respiratory Journal*. (*B*) Patients with ascertained diagnosis of IPF generally follow one of three courses: *1*) most patients follow the pathway of slow decline over 3–5 years since the diagnosis ("slow progression"); *2*) some patients experience a more rapid decline in lung function over several months ("rapid progression"); and *3*) others remain stable over several years before progressing. Acute exacerbations (AE) can occur at any time and may lead to accelerated loss of lung function or death. Progression of disease is manifested by decline in forced vital capacity and distortion of the lung by extension of honeycomb cysts from subpleural areas in lower lobes to more proximal areas in all portions of lung as seen macroscopically in HRCT scans of the chest over several years and at autopsy. Adapted from Podolanczuk *et al.*, 2023 (1) with permission from the *European Respiratory Journal*. HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis.

theoretical discourse and potential pathways for regulatory approval.

Active Engagement of Patient Advocates

Patients and advocates were actively engaged during the discussions and served as active contributors across the entirety of the symposium, underscoring the symposium's commitment to ensuring the dialogue centered around the patient experience.

Reporting of Symposium Findings

The symposium was designed to stimulate a comprehensive and liberal scientific discussion around the design and execution of future IPF clinical trials with a focus on optimizing endpoint selection. Symposium leaders and core discussants developed an initial draft of this manuscript that then was reviewed by regulatory colleagues and other symposium participants. Their input was incorporated into the final document that was approved by the authors for submission.

Patient Perspectives

The development of this symposium report was not just shaped by clinical, methodological, biostatistical, and regulatory experts; rather, it was fundamentally shaped by the lived experiences and insights of patients confronted with IPF. Contributions from patient representatives were at the center of our discussions, as they advocated for the future of IPF trials to better align our scientific objectives with the realities and needs of patients. A testament of this need is illustrated in this testimony from a patient (RN) (Box 1).

Selecting Endpoints That Assess How Patients Feel, Function, and Survive

With the goal of optimizing IPF clinical trial endpoint selection, this symposium highlighted the key characteristics of primary endpoints in Phase 3 trials: *1*) consistently and readily measurable in clinical practice; *2*) sensitive to intervention mechanisms; *3*) well-defined and reliable; and *4*) a direct measure of how a patient 'feels, functions, or survives' or a properly validated surrogate for such measures. The symposium extensively explored how current IPF clinical trial endpoints align with these characteristics, including regulatory and methodological considerations for biomarkers to accelerate drug development through trial enrichment, monitoring, or as surrogate endpoints.

Endpoints as a Window to Disease

PROs, such as disease-related symptoms and functional impacts, provide direct assessments of how patients 'feel' by capturing their lived experiences directly from them. Similarly, assessments such as the 6-Minute Walk Test (6MWT) directly measure how patients' 'function'. Biomarkers, if properly validated as a surrogate endpoint, also hold promise as replacement primary endpoints or integration into primary composite endpoints in IPF trials, and they have the potential to reduce the size and duration of clinical trials. They provide useful insights about effects of interventions on biological pathways related to the IPF disease process. As specified in the 2010 Institute of Medicine report on "Evaluation of Biomarkers and Surrogate Endpoints", "*Biomarkers are measurements of biological processes. Biomarkers include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images*" (9). Examples of biomarkers in IPF would be lung function testing (FVC, D_{LCO}), metabolic or circulatory measures, or image patterns (HRCT or PET).

However, reliance solely on biomarkers may be misleading. Patient-level correlations between biomarkers and clinical outcomes

Box 1: *"I am presently approaching 69 years old. I was first diagnosed with IPF at age 63 and was given the impression that I had only two or three years to live. It was made clear to me at the time that there were presently no medications to improve my quality of life, much less increased survival. My doctoral work was primarily in statistical analysis, and as a result, I was predisposed to quantify my decline. Through my participation in a clinical trial, and subsequent follow-ups, it became clear to me that the curves representing my quantifiable decline, and that of the actual quality of my daily life were dramatically different. About four weeks ago, my FVC dropped to 48% and my D_{LCO} to 29% of predicted values. Over the years since first diagnosis, I've experienced a modest decline in lung function, but nothing approaching the dramatic decrease, as evidenced by PFTs. I have never been this age before and didn't know quite what to expect. Although more challenged than I expected to be, I still engage in most of the recreational activities I've enjoyed over the years.*

Through this experience, it has become apparent that spirometry was measuring what is measurable, not necessarily what was meaningful to me. Living longer and enjoying life with my wife is what is most meaningful to me. Improvement in how we feel and function in our daily lives, and extending our lives is what is most meaningful to us as patients."

—Mr. RN, IPF Patient

do not confirm causality, and intervention effects on biomarkers do not ensure impact on how patients 'feel, function, and survive'. Thus, comprehensive validation as a surrogate endpoint, both clinical and statistical, is essential before adopting biomarkers as replacement endpoints.

Biomarker Limitations: Correlates Are Not Surrogates

Though biomarkers may detect effects of interventions on important biological pathways of the disease process, they might not reliably reflect treatment impact on how patients 'feel, function and survive'. A frequent approach in attempts to justify the use of biomarkers as replacement endpoints in registrational trials is to *1*) identify a biomarker that has a strong patient-level correlation with one or more direct measures for how the patient 'feels, functions, or survives'; *2*) establish the intervention's effect on that biomarker; and *3*) make the leap that it should follow that the intervention has clinically meaningful effects on how patients 'feel, function, or survive' (i.e., "*post hoc, ergo propter hoc*"). However, patient-level correlations do not establish causality. For instance, while IPF patients with improved lung function after treatment might have prolonged survival, this patient-level correlation does not confirm that enhancing lung function directly increases survival. In this example, causality might be in the reverse direction where having a slower progressing form of the disease is the reason both for longer survival and a better response to treatment, so treatment simply identifies those who would have naturally lived longer.

Our evaluation of each endpoint during the symposium centered on surrogate validity, and we considered the following four primary factors (*see* Figure 2) that explain why a patient-level correlation between a biomarker and measures of how patient's 'feels, functions, or survives' do not necessarily indicate validity (10):

1. Not being a causal pathway: A disease may causally influence the level of a biomarker as well as 'feels, functions, survives' measures, thus leading such measures to be correlated with the biomarker. However, if the biomarker is not directly within a pathophysiological pathway through which the disease process influences a 'feels, functions, survives' measure, an effect by the intervention on the biomarker may not predict its net effect on the clinical endpoint.
2. Multiple causal pathways: Diseases can affect 'feels, functions, survives' measures through various pathways, and only one of these may be mediated through the biomarker. This could lead to false negative results when relying on effects on the biomarker. For example, in oncology, while immuno-oncology agents may have better effects than chemotherapy on overall survival (OS) due to effects on long-term tumor burden, traditional measures sensitive to effects on short-term tumor burden like 'objective response rate' or 'progression-free survival' may not fully capture these benefits (11). Conversely, these multiple causal pathways could lead to false positive results when relying on biomarkers, as illustrated when comparing the SmithKline Beecham (SKB) and Aventis-Pasteur (AP) acellular pertussis vaccines (12). While the SKB vaccine was superior to the AP vaccine for effects on filamentous hemagglutinin (FHA) and pertussis toxin (PT) antibodies, it was relatively less effective on the clinical endpoint of pertussis. This was because the more effective AP vaccine impacted additional antibodies and possibly had longer-lasting biological effects, illustrating a risk of false positives.
3. Durability of effect: The durability of the intervention's effect matters. Even if an intervention has an effect on the principal causal pathway through which effects of the disease process on the clinical endpoints are mediated, often the timing, magnitude and duration of

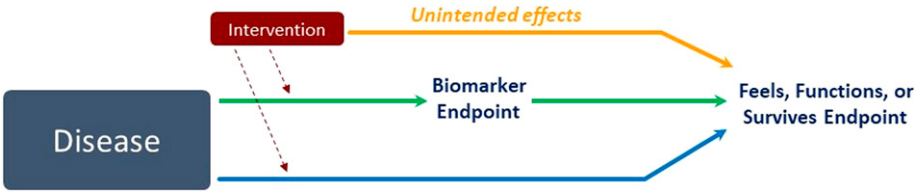

Figure 2. Multiple pathways of the disease process and an intervention's multiple mechanisms of action (10, 13).

that effect that is needed to meaningfully impact the clinical endpoint is not known.
4. Unintended Effects: An intervention that is sufficiently potent to have the intended effects on the biomarker may have unintended effects on the 'feels, functions, survives' measures that are not captured by the biomarker (13).

Regulatory Considerations: Establishing Substantial Evidence of Effectiveness

Biomarker Validation

To establish biomarkers as replacement endpoints that meet regulatory benchmarks of scientific validity in IPF clinical trials, substantial clinical and statistical insights are required, particularly a comprehensive understanding of the disease's causal pathways beyond those mediated through the biomarker. Statistically, an overview of trials for interventions, ideally in the class of the experimental intervention, is needed to determine whether there is a trial-level correlation between the intervention's net effect on the biomarker and its net effect on the measure for how patients 'feel, function, and survive'. Trial-level correlations are vital because unintended intervention effects often go undetected by the biomarker and frequently are not clinically anticipated.

For instance, the FDA's trial-level overview using the pirfenidone and nintedanib trials illustrated the surrogacy of FVC for overall survival (OS) in the IPF setting (14). However, the potential of 3-month FVC as a surrogate for OS in IPF presents a cautionary tale. Although Kahn *et al.* (15) established 3-month FVC to be a patient-level correlate for OS, GLPG1960's positive effects on 3-month FVC were misleading, as the 1,300 patient Phase 3 trial established that this agent did not have favorable effects on 12- to 18-month FVC and had adverse effects on OS.

Context-of-Use

The Institute of Medicine (9) emphasized the importance of context-of-use in determining the suitability of a biomarker as a surrogate endpoint, noting that no single biomarker can universally serve as a generic surrogate endpoint for all treatment interventions in a disease setting. This perspective was recognized by the FDA and the Cardio-Renal Drugs Advisory Committee in 2006 (16), where the validity of blood pressure as a replacement endpoint for 'feels, functions, survives' outcomes was acknowledged to potentially vary meaningfully across different classes of anti-hypertensive treatments, in part because unintended effects on the 'feels, functions, survives' measures that are not captured by the biomarker could vary across these classes. Hence, evidence to support validity of blood pressure as a potential replacement endpoint for 'feels, functions, survives' outcomes was evaluated overall, as well as by class of anti-hypertensive treatments.

Utility of Biomarkers and Cautionary Issues

Biomarkers, even if only established to be patient-level correlates, are useful for assessments of disease diagnosis and prognosis. As direct measures of biological activity, biomarkers are useful as primary endpoints in proof-of-concept trials or as supportive endpoints in registrational trials. However, their greatest utility would be as replacement endpoints in registrational trials (and yet a correlate does not a surrogate make) and in enrichment (and yet a prognostic factor does not an effect modifier make).

Relying on biomarkers as replacement endpoints often yields less reliable insights into not only the efficacy but also the safety of marketed products. If post-marketing experience reveals safety issues, such as with natalizumab when multiple sclerosis patients experienced progressive multifocal leukoencephalopathy, doubts more readily arise about whether the evidence about efficacy is sufficiently strong to justify a positive benefit-to-risk assessment.

Enhancing IPF Endpoint Selection through Composite Endpoints

The FDA supported the use of composite endpoints to improve the efficiency of trial designs without reliance on biomarkers as replacement endpoints, given the burdens of achieving their statistical and clinical validation (FDA Guidance for Industry available at: https://www.fda.gov/media/162416/download). For illustration, at the fourth World Symposium on Pulmonary Hypertension (PH) held in Dana Point, California in February 2008 (17), the composite 'time to clinical worsening' was endorsed as an alternative to the 6MWT. This included multiple components: death, lung transplantation, PH hospitalization, and a combination of an increase in functional class with a 15% reduction in 6MWD (6-Minute Walk Distance). By analogy, in IPF, the composite of death and IPF-hospitalization was advocated in 2012 by Raghu *et al.* (18). Additional components could be considered, such as the simultaneous occurrence of a 10% decline in FVC and a 50-m decline in 6MWD, however, with the recognition that 'a chain is as strong as its weakest link'.

The discussions from this symposium highlighted the advantages of composite endpoints, highlighting their efficacy in trial design as alternatives to biomarkers for replacement endpoints. An integrated approach that incorporates PROs, other direct 'feels, functions, survives' measures, and potentially validated biomarkers, can enable more meaningful evaluation of IPF treatment strategies. The following sections of this report summarize the discussions around each endpoint.

Key Biomarkers as Meaningful Endpoints for IPF Clinical Trials

Forced Vital Capacity (FVC)

The correlation between treatment effects on FVC and on mortality in patients with IPF has been consistently demonstrated, resulting in the FDA adopting FVC as an endpoint in registrational trials. As such, FVC monitoring has become a staple in clinical practice guidelines for disease management (2) and drug discovery, with the primary focus being on markers of disease progression (14). In particular, literature has stated that a categorical decline (relative or absolute) in FVC of 10% or more, as well as marginal declines between 5% to 10% within a six-month period, have been associated with an increased risk of death and should therefore be considered as clinically relevant changes (2).

FVC measurement is widely accessible, reproducible and can be centralized in clinical trials to reduce variability of measures over time, increasing the statistical power of trials. FVC also has known, yet largely addressable, methodological pitfalls, which should be carefully considered in study protocols. Consequently, FVC has become the preferred primary efficacy

endpoint in IPF treatment trials, particularly in those with positive results as illustrated in Table 1, and commensurately used in over 100 such trials. As evidence of this, over 60% of IPF randomized controlled trials (RCTs) used the change in percent predicted FVC and/or the change in absolute value of FVC as the primary efficacy endpoint (Figure 3); this proportion is similar when considering only phase 3 RCTs.

Pharmaceutical studies frequently assess FVC change as either a continuous variable or by predefined "clinically meaningful" thresholds. Continuous change analysis offers increased sensitivity, but setting FVC decline thresholds has multiple advantages. For certain patients, IPF progresses in a stepwise fashion, which might escape continuous FVC assessments. Distinguishing a "clinically meaningful" FVC decline allows those marking "treatment failure" to exit trials or enter "rescue" management. Additionally, monitoring time until decline can incorporate mortality data into progression-free survival evaluations. But there is a downside: absolute FVC change thresholds overlook disease severity variations. A 10% absolute change can suggest a minor decline in mild cases or in IPF with concurrent emphysema. Conversely, the same 10% change could mark significant progression in advanced IPF cases—a drop in FVC from 40 to 30% equates to a 25% baseline value decrease. A change threshold with varying clinical implications based on disease severity poses challenges.

One of the challenges currently faced in IPF RCTs is the allocation of patients receiving a true placebo when approved treatments are available. After 2014, the publication year of the pivotal studies for the approved treatments nintedanib (8) and pirfenidone (7), about 60% of RCTs included patients on anti-fibrotic background therapies. This poses a further dilemma in evaluating the efficacy and safety of new treatments via functional tests. However, assessing the treatment effect on top of anti-fibrotic therapy leaves narrower margins for detecting differences and necessitates larger patient cohorts and longer trial durations. A challenging, but highly desirable scenario, more likely to become real by shifting the trial population to patients with early disease, is identifying newer treatments which have the potential to increase FVC values over time, not only reduce their decline.

Recently, the validity of short (three months) change in FVC as a marker of efficacy in IPF clinical trials was evaluated (15). In nearly 2,000 patients with IPF, the study found that a 2.5% decline in FVC at three months corresponded to a 15% increased mortality risk and 30% greater likelihood of disease progression. A 5.7% FVC change threshold at three months emerged as a potent predictor of increased mortality risk, displaying accuracy comparable to a 10% change over 12 months.

However, utilizing a three-month FVC decline as the primary efficacy endpoint would require roughly double the patient sample compared with traditional 12-month trials. While a shorter trial might attract more participants, intensified recruitment challenges arise. Recent phase 2 trials, however, have laid the groundwork for larger phase 3 studies (19). Additionally, while home spirometry devices for tracking FVC change are now used in IPF RCTs (20), they come with consistent challenges, including its limited reproducibility (20). Increased assessments may discourage patient compliance, negating the benefits of regular evaluations.

With nintedanib and pirfenidone as standard IPF treatments known to decrease FVC decline over 12 months, the original 10% FVC reduction benchmark no longer solely defines treatment response on top of standard of care. It is essential to pair lung function assessments with other clinically relevant outcomes. Given the limited data on non-FVC endpoints in clinical trials for patients with IPF with severe lung function impairment, an innovative strategy is required, urging the scientific community to broaden trial efficiency by evaluating benefits beyond just pulmonary function.

Regulatory considerations for FVC. The FDA emphasized FVC's role as an established clinical endpoint with regulatory precedence, due to biological plausibility and emerging evidence, as well as its limitations, including challenges with the time course for treatment effect (FVC maturity) and interpretability. The need to look at endpoints beyond FVC was stressed by the group and supported by the FDA, placing importance on endpoints with a sustained therapeutic response. They cautioned against shorter trials and the use of 3-month FVC with an analysis, citing the INPULSIS-1 trial, a 12-month treatment study, lasting a total of 847 days looking at an approximate 100 mL FVC change in 515 patients. By comparison, they presented a hypothetical 12-week trial scenario, assuming the same power and standard deviations, but a smaller 50 ml change in FVC, which would require almost four times the sample size (∼1,980 patients) and twice the total time at around 1,800 days. The inability for an earlier FVC to expedite trial completion, coupled with concerns on durability of effect supported their advocacy for trials longer than three months, as they often yield richer datasets, thus enhancing drug development. Concerns were also raised about home spirometry assessments for FVC, particularly issues with device reliability and the compromise between quality and frequency.

Composite Endpoints

Composite endpoints, which aggregate multiple outcomes into a single endpoint (21–23) (FDA Guidance for Industry available at: https://www.fda.gov/media/162416/download), present an alternative to standalone endpoints like FVC, as previously discussed, and OS. The latter has been felt to be challenging due to its potential infrequency in a typical clinical trial (24). Potential advantages to composite endpoints include: *1*) providing a primary outcome when a clear first choice is lacking (21); *2*) enhanced statistical efficiency in time to event analyses due to higher event rates and possibly smaller sample sizes (21); and, *3*) potentially bypassing competing risks during outcome assessment (25). These composites can manifest as a total score or index, an event rate over a set duration, or time to the first event, with the latter commonly seen in oncology trials as relapse-free or progression-free survival (26).

Ensuring that each component is valid, reliable (26), and clinically meaningful to patients (25) could optimize study design and interpretation. A large gradient of importance of the individual components may negatively impact the overall value of the endpoint. The larger the discrepancy in frequency of the most and least important components can risk the clinical relevance of the composite (25). Lastly, it is ideal if the components are biologically linked to the intervention, with similar magnitudes of relative risk reduction and narrow confidence intervals to facilitate interpretation (25).

A relevant example, as illustrated earlier in this report, is seen in phase 3 PH therapeutic development, which was significantly facilitated by the introduction of

Table 1. IPF Clinical Trials with FVC as Primary Endpoint and Positive Results

Report	Patient Population				Respiratory Physiology					
Reference	Study Phase	Age (years)	FVC (%predicted)	D_{LCO} (%predicted)	FVC (%)	FVC (ml)	FVC Decline (Drug *vs* Placebo)	Central Review	AF Add-On Therapy	Time Frame (weeks)
Richeldi *et al.*, 2011 (108)	II	65.1 ± 8.6	80.2	3.6 mmol/min/kPa		X	130.0	X		52
Richeldi *et al.*, 2014 (8) INPULSIS I	III	66.9 ± 8.4 (nintedanib) 66.9 ± 8.2 (placebo)	79.5 ± 17.0 (nintedanib) 80.5 ± 17.3 (placebo)	47.8 ± 12.3 (nintedanib) 47.5 ± 11.7 (placebo)		X	125.3	X		52
Richeldi *et al.*, 2014 (8) INPULSIS II	III	66.4 ± 7.9 (nintedanib) 67.1 ± 7.5 (placebo)	80.0 ± 18.1 (nintedanib) 78.1 ± 19.0 (placebo)	47.0 ± 14.5 (nintedanib) 46.4 ± 14.8 (placebo)		X	93.7	X		52
Noble *et al.*, 2011 (109) Study 004	II	68.0 (±7.6) (pirfenidone 1,197 mg/day) 65.7 (±8.2) (pirfenidone 2,403 mg/day) 66.3 (±7.5) (placebo)	76.4 (±14.4) (pirfenidone 1,197 mg/day) 74.5 (±14.5) (pirfenidone 2,403 mg/day) 76.2 (±15.5) (placebo)	47.2 (±8.2) (pirfenidone 1,197 mg/day) 46.4 (±9.5) (pirfenidone 2,403 mg/day) 46.1 (±10.2) (placebo)	X		4.4 (vs pirfenidone 2,403 mg/day)			72
Noble *et al.*, 2011 (109) Study 006	II	66.8 (±7.9) (pirfenidone) 67.0 (±7.8) (placebo)	74.9 (±13.2) (pirfenidone) 73.1 (±14.2) (placebo)	47.8 (±9.8) (pirfenidone) 47.4 (±9.2) (placebo)	X		0.6*			72
King *et al.*, 2014 (7)	III	68.4 (±6.7) (pirfenidone) 67.8 (±7.3) (placebo)	67.8 (±11.2) (pirfenidone) 68.6 (±10.9) (placebo)	43.7 (±10.5) (pirfenidone) 44.2 (±12.5) (placebo)		X	116.0	X		52
Raghu *et al.*, 2018 (110)	II	69.0 (±6.3) (pentraxin) 67.6 (±7.1) (placebo)	67.7 (±10.9) (pentraxin) 67.4 (±11.4) (placebo)	40.1 (9.14) (pentraxin) 43.2 (10.5) (placebo)	X		2.3	X	X	28
Richeldi *et al.*, 2019 (86)	II	68.3 (7.1)	73.8 (11.5%)	53.4 (13.7%)		X	200.0	X		48
Richeldi *et al.*, 2022 (19)	II	69.9 ± 8.3 (BI 1,015,550) 71.8 ± 9.3 (placebo) 69.3 ± 6.6 (nerandomilast + AF) 67.5 ± 10.7 (placebo)	80.4 ± 16.0 (BI 1,015,550) 82.1 ± 17.7 (placebo) 75.8 ± 17.9 (nerandomilast + AF) 71.7 ± 12.3 (placebo)	52.0 ± 16.7 (BI 1,015,550) 48.3 ± 12.1 (placebo) 49.0 ± 18.3 (nerandomilast + AF) 47.2 ± 14.8 (placebo)		X	88.4 (Without AF) 62.4 (With AF)	X	X	12
Palmer *et al.*, 2018 (111)	II	69 (45-87)	68 (48-106)	41 (11-97)		X	93	X		26

Definition of abbreviations: AF = antifibrotics; FVC = forced vital capacity; D_{LCO} = diffusing capacity for carbon monoxide.
*$P = \cdot 501$.

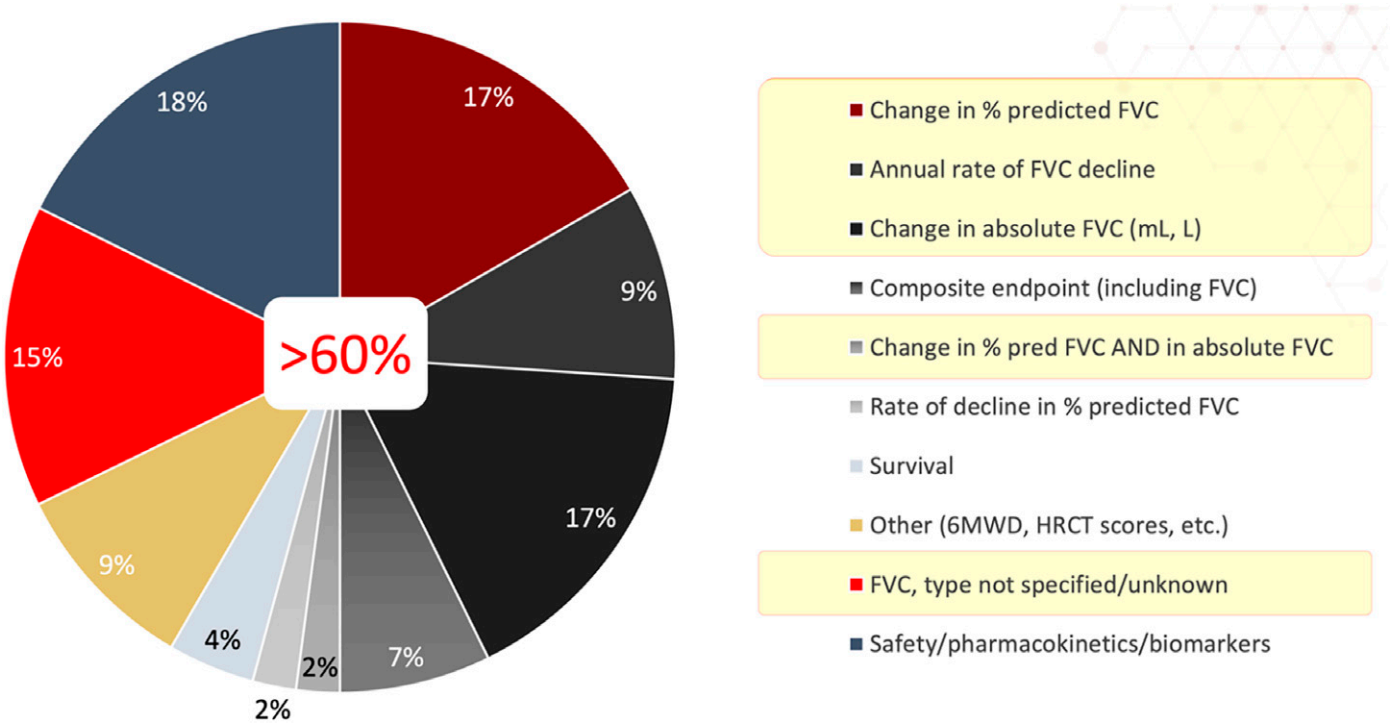

Figure 3. IPF trials with FVC as the primary efficacy endpoint.

6MWD as an endpoint (27, 28). However, with combination therapy, the predictive value and responsiveness of 6MWT lessened (29). This prompted investigators to modify their approach, leveraging time to clinical worsening, which incorporated changes in functional class, 6MWT, and biological markers (28).

Early therapeutic development in IPF utilized composite endpoints with a wide range of physiological criteria of different potential clinical significance, death, and various acute clinical events; the distribution of events was roughly associated with baseline measures of disease severity (30–32) (*see* Table 2). A key milestone resulted from an analysis of three IPF Network clinical trials (33). Change in FVC ⩾ 10% (HR 4.68, 95% CI 1.83–11.99) was confirmed as a predictor of subsequent mortality as was non-elective respiratory hospitalization (HR 5.97, 95% CI 1.81–19.74). Non-elective, non-respiratory hospitalization was not associated with subsequent mortality (HR 1.16, 95% CI 0.15–8.92). Of patients without an early decline in FVC, 30/510 experienced a respiratory hospitalization. The combination of FVC decline and respiratory related hospitalization was associated with a numerically greater risk of mortality (HR 5.65, 95% CI 2.19–14.56) (33).

This timing of clinical events before physiological deterioration has been supported by others (34, 35). Analyses of clinical trials that used FVC decline as a primary endpoint confirmed therapeutic responsiveness to antifibrotic therapy using progression free survival incorporating physiological decline (FVC or 6MWT) and death; the former variables predominated in number (36). Subsequent clinical trials have operationalized composite clinical endpoints incorporating physiological deterioration (6MWT [37]) and clinical endpoints such as OS (37–39), non-elective respiratory hospitalization (37–39), or lung transplantation (39) as the primary endpoint (*see* Table 2). This was facilitated by the development of robust criteria to adjudicate the nature of clinical events in IPF trials (40, 41). Data are limited on patients with IPF regarding the ranking of importance of various endpoints, which could be potential components of a composite. The focus has primarily been on mortality, change in lung function, imaging, and dyspnea (42). Composite clinical endpoints that are easily measurable and/or adjudicated reflect a feasible construct for the conduct of future clinical trials in IPF.

Regulatory considerations for composite endpoints. The FDA generally supported the use of composite endpoints to augment the efficiency of trial designs, though several complexities must be addressed. These include challenges in interpreting results, potential overlap of components, component equivalence, and feasibility of ranking components based on their clinical importance. Therefore, while the implementation of composite endpoints in IPF trials offers promising benefits, the associated regulatory considerations around interpretability, equivalence, and redundancy must be meticulously navigated.

Patient-reported Outcomes (PROs)

Lung function measures, such as FVC, only weakly correlate with patient reported symptom measures (43, 44), suggesting they do not fully capture a patient's experience of symptoms, functional limitations, or treatment effects. However, individuals living with IPF seek treatments that will improve their overall health-related quality of life (HRQOL), reduce symptom burden, and support daily functioning (45, 46). Despite IPF therapeutic advances in disease modification, there is little evidence that current treatments significantly influence these high-priority patient-centered outcomes (47, 48).

A PRO, as defined by the FDA's 2009 Guidance for Industry (49, 50) is a

Table 2. Different Composite Endpoints and Their Wide Range of Physiological Criteria Used in Early IPF Clinical Trials

		Clinical Components				Respiratory Physiology			Functional Measures	
Report	**Patient Population**	**Mortality***	**Hospitalization***	**AE IPF***	**Lung Txp**	**FVC***	**D_{LCO}**	**Resting Oxygenation**	**6MWT***	**PRO Parameters**
Primary analysis										
Raghu *et al.* (30)	Age ~63.5 FVC ~64.0 D_{LCO} ~37.0	X				X		X		
King *et al.* (31)	Age ~63.6 FVC ~74.3% D_{LCO} ~47.8%	X								
Noth *et al.* (32)	Age ~67 FVC ~58.8% D_{LCO} ~33.7%	X 61%	X† 91%			X				
Raghu *et al.* (112)	Age ~68.1 FVC ~61.9% D_{LCO} ~37.8%	X 3.8%				X 96.2%				
Wilson *et al.* (39)	Age ~71.3 FVC ~55.7% D_{LCO} ~43.9%	X 25.6%	X‡ 73.2%		X 0.01%					
Martinez *et al.* (38)	Age ~71.6 FVC ~70.0% D_{LCO} ~38.9%	X 31%	X§ 69%							
Behr *et al.* (37)	Age ~69.5 FVC ~68.6% D_{LCO} ~25.6%	X 20%	X§ 40%						X 51%	
Secondary, other, or *post hoc* analyses										
King *et al.* (113)	Age ~65.2 FVC ~67.7% D_{LCO} ~41.9%	X 2.7%		X 4.7%		X 31.4%	X	X		
Noble *et al.* (36)	Age ~67.8 FVC ~70.7 D_{LCO} ~43.1%	X 5.1%				X 17.7%			X 19.5%	
Maher *et al*	Age ~69.9 FVC ~78.0% D_{LCO} ~54.7%		X§			X				X‖

Definition of abbreviations: 6MWT = 6-min walk test; AE IPF = acute exacerbation of idiopathic pulmonary fibrosis; Lung txp = lung transplantation; PRO = patient reported outcomes.

*Percent reflect proportion meeting component when available – percentages may not add up to 100% based on available data or multiple components achieved.

†Non-bleeding, non-elective.

‡Non-elective.

§Non-elective respiratory related.

‖St. George's Respiratory Questionnaire (SGRQ)

measurement based on a report obtained directly from the patient regarding their health condition, unaltered and uninterpreted by a clinician or anyone else. A PRO can be measured by either self-report or interview, with the requirement that only the patient's response is recorded (22). As such, PROs can contextualize trial results within a framework of relevance and meaningfulness to patients.

FDA guidance, alongside expert opinions, have established benchmarks (51–54) that aid in determining if a PRO is "fit for purpose" (49, 55). For example, items on a PRO should be derived directly from patient feedback, thus ensuring relevance to the target population (56, 57).

The ideal fit-for-purpose instrument in IPF would be patient-informed, relevant, comprehensive (i.e., capture all relevant aspects of the concepts of interest), comprehensible, and easy to complete (58, 59). It should strike a balance between respondent burden and information capture.

A fit-for-purpose PRO has scores that meet psychometric criteria for reliability, validity, and responsiveness (60). The selection of PRO(s) for a trial depends on several factors, including but not limited to, the specific target population, the design and duration of the trial, the intervention's mechanism of action and its expected effects. Before selecting PRO measures for IPF trials, investigators should first conduct a comprehensive literature review to gather preliminary evidence regarding their content validity and psychometric properties. Following this initial step, it is crucial to engage in discussions with the FDA to determine the necessity for additional qualitative and quantitative research to further establish and confirm the content validity and psychometric properties.

Numerous PROs have been used in therapeutic trials in IPF (7, 8, 61, 62). Each PRO instrument has different characteristics that may fit better for certain intended uses than others. Notably, K-BILD and Living with Pulmonary Fibrosis Questionnaire were both developed with input from patients living with IPF and have undergone rigorous validity and reliability testing. The evaluation of validity is a process, not a threshold phenomenon; as such, the more a PRO is used in the target population—in different trial settings—the more we learn about what its scores tell us about patients and interventions under study.

The interest, desire, and need to assess the effects of interventions on things that matter to patients suggest PRO scores should be high-tier endpoints in IPF trials. PROs that are appropriately developed and validated as fit-for-purpose may be able to capture information meaningful to patients that other clinical outcomes do not. In the trial planning phase, investigators should consult with PRO experts to help ensure the most well-suited PRO(s) are included. Comprehensive guidelines outline how to structure sections of study protocols covering PROs and how to report PRO results. Incorporating adequately validated, fit-for-purpose PROs into clinical trials, potentially as co-primary endpoints, previously not done in IPF trials, could fuse the analytical strength of objective endpoints with patient-centric perspectives for a more holistic evaluation of treatment effectiveness.

Regulatory considerations for PROs. The FDA encouraged the use of PROs in IPF trials. In IPF, PROs can assess symptoms such as dyspnea, cough, anxiety, depression, or fatigue, providing valuable insight on treatment efficacy and patients' quality of life. The FDA emphasized the importance of using simple fit-for-purpose PROs that are developed with patient's in put and less burdening for patients in evaluating how patients 'feel' and/or 'function' for the context of use (49).

Physical Activity and Walk Test Variables

Previous sections of this symposium report delved into the challenges posed by FVC as a primary endpoint in IPF trials, such as overlooking the vascular component of the disease's pathophysiological consequences, as well as its impairment on patients' HRQOL and curtailment of their physical activity (63). Although the D_{LCO} might offer insights into both pulmonary circulation and gas exchange, its variability often hampers its utility (64). Since lung function measurements often only loosely translate in how a patient feels and functions, physical activity tests can provide more direct measures.

There are several tests of physical activity available, which differ in their characteristics and practicability (64). The formal cardiopulmonary exercise test (CPET) is relatively complex and expensive in terms of resources and time, difficult to standardize across centers and provides complex results which are difficult to interpret. Relatively less complex and easy to perform are the 6MWT and the incremental or endurance shuttle walk tests (ISWT or ESWT). ISWT and ESWT are maximal exercise tests, aiming to stop when the patient is completely exhausted. In contrast, the 6MWT is a submaximal exercise test, where the patient is asked to perform a vigorous but individually still tolerable activity, which is generally more convenient for the patients (63, 64). For patients with chronic bronchopulmonary diseases like IPF and COPD, the 6MWDhas been found to be significantly related to peak oxygen uptake, a crucial measure obtained from CPET (65). Moreover, changes in 6MWD in serial measurements at 6 and 12 months are closely related to changes in Saint Georges Respiratory Questionnaire total score (SGRQ, TS) and FVC (66). Even more important, the 6MWD at baseline has also been shown to be statistically significant linked to mortality or transplantation-free survival (67). Finally, a decline in 6MWD is significantly related to mortality or lung transplantation with a clinically minimal important difference of about 30–40 m (67, 68). Table 3 depicts the application of these functional measures in IPF randomized controlled clinical trials.

The 6MWT has been used as a clinically relevant primary endpoint in many PH trials (69). It was successfully applied as a secondary endpoint in the ASCEND trial testing oral pirfenidone in IPF and as a primary endpoint in the INCREASE trial testing inhaled Treprostinil in pulmonary fibrosis and PH (7, 70). Initial findings support the safety of the 6MWT for patients suffering from moderate to severe chronic lung diseases (71, 72). When applying the 6MWT in the setting of clinical trials, rigorous standardization across all participating centers is crucial. This includes familiarization tests to correct for learning effects, and standardized handling of oxygen supplementation, assistive devices including wheelchair use, and stopping rules with desaturation.

The 6MWT, under a standardized protocol, not only demonstrates reliability, practicality, and safety for the targeted IPF population (Figure 4), it also provides a clinically meaningful measure reflecting how patients feel and function (in contrast to FVC or D_{LCO}) with a significant correlation to mortality. Its selection as a primary

Table 3. 6-min Walk Test (6MWT) as Outcome Parameter in IPF Randomized Controlled Clinical Trials

Study	Patient Population	Characteristics	Intervention	Functional Measures		
				6MWT - Distance	6MWT - Change in Minimal Sp_{O2}	6MWT - Steady State Exercise Test
Primary analysis						
King *et al.*, 2008	IPF	*N* = 158 Age ~65 yrs. FVC ~67 pp D_{LCO} ~42 pp	Oral bosentan	−18 m n.s.	—	—
Zisman *et al.*, 2010 (114)	IPF	*N* = 180 Age ~69 yrs. FVC ~56 pp D_{LCO} ~26 pp	Oral sildenafil	+16.7 m *P* = 0.11 (n.s.)	—	—
Waxman *et al.*, 2021 (70)	Fibrotic ILD – IPF most prevalent	*N* = 326 Age ~66 yrs. FVC ~63 pp D_{LCO} ~29 pp	Inhaled treprostinil	+31.12 m *P* < 0.001	—	—
Azuma *et al.*, 2005	IPF	*N* = 64 Age 64 yrs. FVC ~80 pp D_{LCO} ~58 pp	Oral pirfenidone	—	—	Change in minimal Sp_{O2}; n.s.
Secondary, *post hoc*, other analyses,						
Noble *et al.*, 2011	IPF Capacity 1	*N* = 435 FVC ~75 pp D_{LCO} ~47 pp	Oral pirfenidone	+16.4 m n.s.	n.s.	—
Noble *et al.*, 2011	IPF Capacity 2	*N* = 344 FVC ~75 pp D_{LCO} ~47 pp	Oral pirfenidone	+31.8 m *P* = 0.0009	n.s.	—
King *et al.*, 2014 (24)	IPF Ascend	*N* = 55 Age ~68 yrs. FVC ~68 pp D_{LCO} ~54 pp	Oral pirfenidone	+26.7 *P* = 0.036	—	—
Behr et al, 2016 (115)	IPF	*N* = 122 Age ~67 yrs. FVC ~69 pp D_{LCO} ~42 pp	Oral N-acetylcysteine versus placebo plus pirfenidone background therapy	+7.4 m *P* = 0.541 (n.s.)	—	—
Behr *et al.*, 2021 (37)	PPF	*N* = 126 Age = 63 yrs. FVC ~62 pp D_{LCO} ~38 pp	Oral pirfenidone	+28.0 n.s.	—	—

Definition of abbreviations: 6MWT = six-minute walk test; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; m = miles; N = number of patients; n.s. = not significant; pp = percent predicted; PPF = progressive pulmonary fibrosis; Sp_{O2} = peripheral oxygen saturation.

Figure 4. Summary of the features of the 6-minute walk test (6MWT) in IPF patients.

endpoint in RCTs for IPF necessitates careful consideration of the study's population and the investigational drug's potential effects.

Regulatory considerations for physical activity and walk test variables. Echoing the regulatory considerations for PROs, the FDA emphasized consistent standards for measures of how patients' 'function', encouraging the use of fit-for-purpose performance outcome (PerfO) measures. While the discussions highlighted the important dimensions captured by functional assessments, it also highlighted the crucial need to explore additional measures that capture the holistic impact of IPF.

Imaging Biomarkers

Computed tomography (CT) is routinely used for diagnosis and monitoring of fibrotic lung disease. CT provides a direct and noninvasive assessment of lung morphology, and the CT datasets are readily amenable to being evaluated with quantitative techniques including artificial intelligence. With advances in CT technology, multidetector helical CT scanners image the lungs within seconds, enabling high resolution reproducible imaging in a single breath-hold, even for patients who are breathless. Importantly, radiation dose reduction techniques have significantly reduced radiation exposure, while maintaining image quality (73–75), crucial for patients living with IPF who may undergo multiple CT examinations over their lifetime.

Multiple quantitative CT (QCT) tools have been applied to CT images to identify and quantify imaging features of fibrosis (76). These methods, developed following visual evaluation by panels of expert radiologists, have been further enhanced by recent advances including the use of adaptive denoising and machine learning (Table 4) (77–80). The value of these quantitative imaging biomarkers is evident from their use as key endpoints in many retrospective observational cohort studies, as well as a few prospective clinical trials of antifibrotic treatment (Table 4). The baseline fibrosis extent in a patient with IPF correlates with severity of pulmonary function impairment and SGRQ and is an independent predictor of FVC decline (79, 81–85). Additionally, change in fibrosis extent on serial CT examinations correlates with FVC decline (81, 83, 86–88). Two observational studies have shown that change in fibrosis extent at 6 months may predict change in FVC at 12 months (89, 90). Furthermore, serial change in fibrosis extent predicts survival (91), and in cohort studies fibrosis extent was found to be a predictor of mortality across disease subtypes (92), even in patients with preserved FVC (79). QCT may help overcome some limitations of FVC. For example, emphysema may occur in 8-67% of patients living with IPF (93), resulting in relatively preserved lung volume and attenuated FVC decline, masking disease progression by FVC. Additionally, use of QCT may lead to discovery of novel biomarkers; for example, quantitative assessment of vessel-related structures in the lung or pulmonary vessel volume has been shown to be an independent predictor of mortality in IPF (94).

Despite their promise, QCT biomarkers are associated with several limitations. Radiation dose from CT remains a concern. Most of the evidence supporting utility of QCT derives primarily from observational or retrospective analyses of cohort or clinical trial studies, raising concern for possible selection bias and quality of evidence (Table 4). Evidence on the short-term reproducibility of QCT is limited (95). QCT techniques are sensitive to variation in CT acquisition and reconstruction parameters, and to variation in inspired lung volume. QCT metrics may be affected by complications such as exacerbation of pneumonitis, emphysema, and pulmonary edema. For quantitative imaging to be successful in clinical trials, acquisition parameters must be standardized, with the same protocol followed on baseline and follow-up scans. The Quantitative Imaging Biomarkers Alliance of the Radiologic Society of North America has provided a detailed protocol for acquiring QCT examinations in other disease/applications (96), which should be used as a model in future clinical trials. Careful attention to critical acquisition factors such as breathing instructions, patient position, and use of contrast are essential for providing reproducible QCT metrics. CT examinations should not be performed during acute exacerbation of symptoms.

The evidence summarized in Table 4 supports the utility of QCT fibrosis extent as a metric for disease severity in IPF, correlating with PROs, baseline and longitudinal pulmonary function, and

Table 4. Major CT Biomarkers for Extent of Lung Fibrosis in IPF: Correlations with Patient Reported Outcome Functions at Baseline and Varying Follow Up Intervals and Survival

	Clinical Utility and Correlations			
QCT Application and Primary Fibrosis Metric*	**Patient Reported Outcomes**	**Function**	**Changes in Function and Progression-Free Survival**	**Survival**
AMFM (Adaptive Multiple Features Method) Fibrosis metric: Groundglass reticular extent (GGR)			Baseline fibrosis independently associated with disease progression. Change in fibrosis associated with change in FVC (116).	
CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) Fibrosis metric: Fibrosis extent (reticular and/or honeycombing)		Fibrosis correlates with multiple physiologic indices (82, 88, 95, 117).	Change in fibrosis is associated with FVC decline (88, 118).	Fibrosis predicts survival (119–121). Change in fibrosis predicts survival (91).
QLF/QILD (Quantitative Lung Fibrosis/Quantitative Interstitial Lung Fibrosis) Fibrosis metric: QLF	Fibrosis change > 2% at 6 mo correlates with change in SGRQ- (83).	Fibrosis correlates with multiple physiologic indices (83, 122).	Fibrosis change is associated with lung function decline (83, 86, 87, 89, 122). Fibrosis change at 6 mo predicts change in FVC at week 48 (89, 90).	
DTA (Data-driven Textural Analysis) Fibrosis metric: QLF	Baseline fibrosis correlates with SGRQ (81). On serial evaluation, MCID for change in SGRQ is 5.35% (81).	Baseline fibrosis correlates with multiple physiologic indices (77, 79, 81).	Baseline fibrosis predicts more rapid FVC decline and shorter progression free survival. Increase in fibrosis on serial CT is associated with decreased pulmonary function MCID for changes in FVC, DLco and 6MWD are 3.40%, 5.09%, and 5.28 m respectively (81).	Fibrosis independently predicts mortality in all morphologic subtypes of UIP (92). Fibrosis predicts mortality even in patients with preserved FVC (79).
CORELINE AVIEW Fibrosis metric: Fibrotic lung volume (CT-Fib%)		Baseline fibrosis correlates with multiple physiologic indices (84).	Baseline fibrosis independently predicts decline in FVC (85).	Fibrosis and interval change in fibrosis predict survival (84, 123).

Definition of abbreviations: 6MWD = 6 min walk distance; AMFM = Adaptive Multiple Features Method; CALIPER = Computer-Aided Lung Informatics for Pathology Evaluation and Rating; CT = computed tomography; CT-Fib% = CT-fibrotic percentage; D_{LCO} = diffusion capacity for carbon monoxide; DTA = Data-driven Textural Analysis; FVC = forced vital capacity; GGR = groundglass reticular extent; m = meters; MCID = minimal clinically important difference; QCT = quantitative computed tomography; QILD = quantitative interstitial lung disease; QLF = quantitative lung fibrosis; SGRQ = St. George's Respiratory Questionnaire; UIP = usual interstitial pneumonia.
*Clinicaltrials.gov identifiers for prospective clinical trials in which quantitative CT fibrosis metrics have been or are being used: CALIPER: NCT04552899; QLF: NCT01979952, NCT01890265, NCT05373914, NCT01766817, NCT04419558, NCT03955146, NCT02688647, NCT06003426; DTA: NCT01371305, NCT01769196, NCT02808871, NCT02597933, NCT03538301, NCT02510937, NCT03142191, NCT05285982, NCT04093024.

survival. Integrating QCT fibrosis extent as a central, standardized outcome in a clinical trial may support enrichment decisions in phase 2 studies and could complement primary outcomes measured by FVC and composite endpoints. While QCT endpoints are not sufficiently characterized to be used as primary endpoints in registrational trials, the use of QCT as an exploratory or secondary endpoint in numerous studies signifies its growing importance as a trial outcome and clinical practice in the future. However, a prospective trial(s) primarily designed to assess QCT fibrosis extent is necessary to determine comparative performance with other endpoints, such as FVC.

Regulatory considerations for imaging biomarkers. The FDA acknowledged the utility for imaging biomarkers in screening, diagnosing and enrichment of IPF clinical trials. Such imaging tools should fundamentally be capable of identifying the requisite findings for each UIP radiological pattern, such as ground glass reticular extent

(GGR), traction bronchiectasis, and honeycombing. Reproducibility to allow differentiation between commonly encountered findings such as emphysema with requisite features such as honeycombing must be ensured. Additionally, it is imperative that the HRCT input is of a sufficient quality to resolve these requisite findings, considering aspects such as slice thickness, noise pattern, resolution, and low contrast detectability.

Key considerations in developing and validating these imaging tools include appropriate establishment of ground truth, suitability of radiological dataset, and ensuring the images are technically and clinically acceptable for use. The context of use for any radiological biomarker is important to define risk and tolerance for uncertainty. Performance transparency for users is necessary to optimize utility of a biomarker particularly given the increased prevalence of black box outputs with unproven correlation with physiological findings. Imaging biomarkers are currently utilized as supplemental or exploratory in clinical trials, but they have not been demonstrated to be superior or non-inferior to FVC and survival.

A consistent predictive relationship between imaging biomarkers and clinical outcomes in IPF is difficult to ascertain due to variability in patient-image acquisition systems and technique (e.g. scanner technological characteristics, acquisition parameters, filters, reconstruction, post-processing), data analysis systems (e.g., level of automation, algorithm design, software version), and interpretation (Figure 5), in addition to patient sources of variability (e.g., exacerbation, progression, non-IPF findings, variations in patient anatomy or pathology). Note that data-driven algorithm performance is generally more sensitive to variations in input when compared with other more traditional image processing techniques. The type and extent of evidence needed to validate the biomarker should be informed in part by the tool's design and its impact on uncertainty and reliability within the imaging biomarker's context of use. Robust, multi-center validation studies to confirm the utility and operating characteristics of imaging biomarkers as endpoints are necessary. As such, imaging biomarkers at present are not ready for use as registrational endpoints, although there is utility to imaging providing additional visual information in assessing fibrosis (e.g., providing a real-time visual assessment).

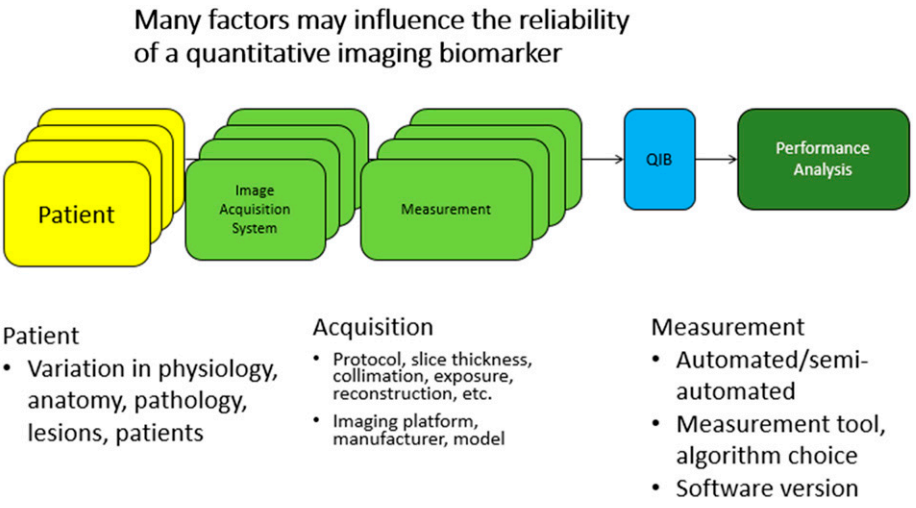

Figure 5. Factors that may influence the reliability of an imaging biomarker. QIB = quantitative imaging biomarker.

Circulating Biomarkers

Biomarkers are objective indicators of biological, pathogenic, or therapeutic processes in response to therapeutic interventions (97). In IPF, there remains an unmet need for biomarkers that are not only predictive of disease progression and treatment response but also reflect how patients feel, function, and survive. For instance, glycosylated hemoglobin in diabetes not only signals potential treatment responses; it also has the potential to reliably prognosticate or indirectly inform the impact of the intervention on patients' lives.

IPF is characterized by marked changes in levels of circulating proteins when compared with healthy age matched controls (98, 99). Many of these biomarkers (e.g. Matrix metalloproteinase 7 (MMP7), CA-125, C-reactive protein degraded by MMP (CRPM), pro-collagens (Pro-C)-3 and -6 and CYFRA 21-1) have been shown to identify newly-diagnosed IPF patients susceptible to accelerated disease progression, as shown in Table 5 (100–104). These observations are not limited to IPF; an unbiased proteomic screen has identified a panel of proteins that predict progressive fibrosis in individuals with a range of non-IPF fibrotic lung diseases (105). In individuals with IPF, three-month change in the levels of several biomarkers maps with disease progression and provides prognostic information over and above baseline levels (101, 103). Anti-fibrotic therapy with nintedanib has been shown to significantly reduce circulating levels of CA-125, C3M (collagen 3 degraded by MMP) and soluble intercellular adhesion molecule-1 (sICAM-1) (106). Whether these reductions predict longer-term survival remains to be demonstrated.

Such findings suggest that circulating biomarkers could be used in IPF and PPF trials for several purposes, including enrichment, stratification, and key efficacy endpoints. However, before this can happen, several considerations must be addressed (13). Many proposed biomarkers require high quality, reproducible assays with defined short- and long-term handling characteristics. Additional longitudinal studies are required to demonstrate that circulating biomarkers really are measures for survival and that treatment-induced changes correspond to prolonged survival benefit. Blood biomarkers should ideally provide additional insights beyond what is already offered by FVC by measuring the therapeutic effect on how patients feel, function, and survive. Blood biomarkers could potentially fill that need of measuring individual treatment response, potentially reshaping future IPF trials, mirroring treatment failure trials seen in oncology.

Regulatory considerations for circulating biomarkers. Although exploratory circulating biomarkers are often measured in early phase IPF trials, to date, none are adequately validated as surrogate endpoints for registrational trials. Over the past decade,

Table 5. Circulating Biomarkers That Have Been Shown to Change in Concentration Following Therapeutic Intervention with Antifibrotic or Putative Antifibrotic Drugs

Potential Theragnostic Biomarkers for IPF Trials				
Therapeutic Agent	**Biomarkers**	**Study Size**	**Study Duration**	**Supporting Literature**
Nintedanib	C3M CA125 KL-6 sICAM-1 SP-D	347 subjects	12 mo	Maher TM *et al.* 2019
Omipalisib	Pro-C3 Pro-C6	17 subjects	10 d	Lukey P *et al.* 2019
TD139 (Galectin 3 inhibitor)	YKL-40 PAI-1	24 subjects	14 d	Hirani N *et al.* 2021
BI1015550 (PDE4B inhibitor)	MMP-7 SP-D KL-6	147 subjects	3 mo	Richeldi *et al.* 2022 (19) and Maher TM *et al.* 2022 (124)

Definition of abbreviations: CA125 = Cancer Antigen 125; C3M = Collagen Type III Metabolite; KL-6 = Krebs von den Lungen-6; MMP-7 = Matrix Metalloproteinase-7; PAI-1 = Plasminogen Activator Inhibitor-1; PDE4B inhibitor = Phosphodiesterase 4B inhibitor; Pro-C3 = N-terminal Propeptide of Collagen Type III; Pro-C6 = N-terminal Propeptide of Collagen Type VI; sICAM-1 = Soluble Intercellular Adhesion Molecule-1; SP-D = Surfactant Protein D; TD139 = Galectin-3 Inhibitor; YKL-40 = Chitinase-3-like protein 1 (CHI3L1).

understanding of potential circulating biomarkers and their relationship to disease progression and therapeutic response has matured. Recent phase 3 studies have incorporated biomarker measurement, offering insights on future investigations of the relationship between changes in biomarker levels and survival (107). Many necessary assays are at or near clinic readiness, but uncertainties persist that limit their use as surrogate endpoints. With appropriate justification, however, use of circulating biomarkers for enrichment of an IPF trial population may be reasonable to accelerate drug development.

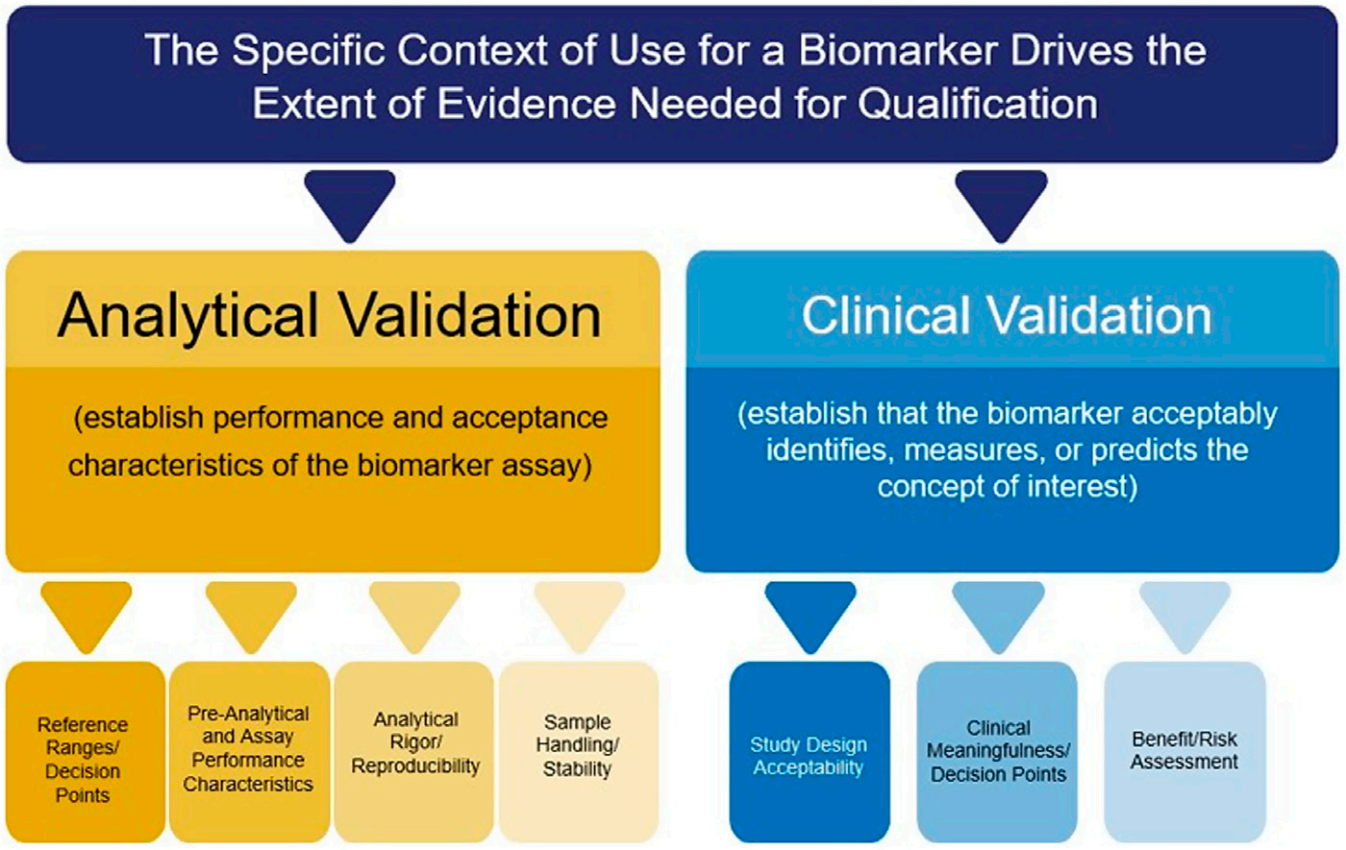

Figure 6. Process of biomarker qualification driven by specific context-of-use.

Table 6. Key IPF Clinical Trial Endpoints and Their Alignment with How Patients Feel, Function, and Survive

Endpoint*	Merits	Challenges and Opportunities	"Feels, Functions, and Survives" Alignment
FVC‡	Widely accepted primary endpoint for IPF trials; offers consistent, reproducible, feasible, standardized, validated, and objective lung function measurement; correlates with disease progression and survival.	Limited in capturing quality of life, functional ability, and overall health; insensitive to early disease progression and minimal clinically important differences. Accessible to standardization across centers and central reading.	Accepted clinical endpoint; not directly related to how patients feel or function.
Composite Endpoints	Combines meaningful outcomes: all cause-mortality, hospitalization, lung transplantation, acute exacerbation, functional assessments; enhances event rates, reduces sample size for more comprehensive insights on disease course and treatment effects.	Choice of endpoints for combining is crucial. May require adjudication of individual components; can mask important information if components yield mixed results; challenging to interpret composite scores.	Aligns with "functions" and "survives" criteria.§
PROs	Captures patients' assessments of their health, symptoms, and well-being; essential for improved understanding of the real-world impact of treatment.	Measures need rigorous validation; questionnaires can be burdensome; influenced by factors like mood or cognitive function. Frequency of questionnaire administration can bias results and requires optimization. Need standardization across multi-center/multinational settings. Blinding important.	Directly captures "feels"; may capture "functions" and "survive".
Physical Activity and Walk Test	Provides measures of functional status, daily activities, and exercise tolerance; relevant to quality of life and daily activities.	Needs standardization and feasibility across multi-center/ multinational settings. Influenced by non-pulmonary factors like musculoskeletal problems, cardiovascular disease, PH, fitness, patient motivation, and managing oxygen needs throughout a study. Not suitable for all patients. Blinding important.	Aligns with "functions" and "feels".
Quantitative Imaging Biomarkers	Identifies and measures extent of abnormality and features of fibrotic lung disease (such as ground glass and reticulation), and disease progression on high resolution CT images of the lungs.	Challenges include: i) standardization (e.g., CT acquisition parameters and reconstruction kernels; consistent inspiratory breath-holding); ii) variability in interpreting semi-quantitative visual interpretations due to co-existing conditions; iii) quantitative measures are not non-inferior to FVC; iv) lack of evaluation in diverse cohorts with primary focus on imaging biomarkers or thorough endpoint validation.	Insufficient evidence: studies needed to correlate with clinical outcomes, symptoms, functional status, and survival.
Circulating Biomarkers	Offers objective measures in easily collected peripheral blood samples; has the potential to detect early disease changes or predict treatment response.	Lack of validated and reliable biomarkers; may not directly correlate with clinical outcomes; influenced by factors such as age, sex, and comorbidities.	Insufficient evidence: studies needed to correlate with clinical outcomes.

Definition of abbreviations: FVC = forced vital capacity; PH = pulmonary hypertension; PROs = patient-reported outcomes.
*All endpoints represent changes from baseline.
‡FVC refers to change in FVC from baseline over 12 to 18 mo.
§Composite endpoints align with "feels, functions, and survives" criteria, but degree of alignment is modulated by the individual components in the composite.

Table 7. List of Participants*, Their Expertise, and Their Role

Name	Expertise	Affiliation(s)
Co-Chairs		
Ganesh Raghu, MD (also, Moderator)	Pulmonologist; ILD-IPF expert and investigator	University of Washington
Fernando J. Martinez, MD, MS (also, Moderator)	Pulmonologist; ILD-IPF expert and investigator	Weill Cornell Medicine
US FDA Lead Representative		
Banu Karimi-Shah, MD (also, US FDA Representative)	Pulmonologist; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Evidence Synthesis Lead		
Marya Ghazipura, PhD, MS, MPhil	Methodologist; expert in study design and appraisal	ZS Associates; New York University Langone Health
Core Discussants		
Thomas R. Fleming, PhD	Biostatistician; expert in clinical trials	University of Washington
Kerri Aronson, MD, MS	Pulmonologist; ILD-IPF expert and investigator	Weill Cornell Medicine
Jürgen Behr, MD	Pulmonologist; ILD-IPF expert and investigator	Ludwig Maximilian University Hospital
Kevin K. Brown, MD (also, Moderator)	Pulmonologist; ILD-IPF expert and investigator	National Jewish Health
Kevin R. Flaherty, MD, MS (also, Moderator)	Pulmonologist; ILD-IPF expert and investigator	University of Michigan Health System
Ella A. Kazerooni, MD, MS	Radiologist; expert in ILD-IPF imaging and investigator	University of Michigan Health System
Toby M. Maher, MD, PhD	Pulmonologist; ILD-IPF expert and investigator	University of Southern California Keck School of Medicine
Luca Richeldi, MD, PhD	Pulmonologist; ILD-IPF expert and investigator	Gemelli University Hospital IRCCS
Moderators		
Joseph A. Lasky, MD	Pulmonologist; ILD-IPF expert and investigator	Tulane University; Pulmonary Fibrosis Foundation
Jeff Swigris, DO, MS	Pulmonologist; ILD-IPF expert and investigator	National Jewish Health
US Food and Drug Administration (US FDA) Representatives		
Robert Busch, MD	Pulmonologist; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Lili Garrard, PhD	Biostatistician; FDA clinical outcome assessment expert	United States Food and Drug Administration (US FDA)
Dong Hyun-Ahn, PhD	Biostatistician; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Ji Li, PhD	Reviewer; FDA clinical outcome assessment expert	United States Food and Drug Administration (US FDA)
Khalid Puthawala, MD	Pulmonologist; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Gabriela Rodal, MS	Reviewer; FDA radiological imaging expert	United States Food and Drug Administration (US FDA)
Sally Seymour, MD	Pulmonologist; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Nargues Weir, MD	Pulmonologist; FDA regulatory expert	United States Food and Drug Administration (US FDA)
Mary Thanh Hai, MD	FDA regulatory expert	United States Food and Drug administration (US FDA)
Group Discussants		
Sonye K. Danoff, MD, PhD	Pulmonologist; ILD-IPF expert and investigator	Johns Hopkins University
Neil Ettinger, MD	Pulmonologist; site principal investigator of several IPF clinical trials	St. Luke's Hospital
Jonathan Goldin, MD	Radiologist; expert in ILD-IPF imaging and investigator	University of California, Los Angeles
Marilyn Glassberg, MD	Pulmonologist; ILD-IPF expert and investigator	Loyola University
Leticia Kawano, MD	Pulmonologist; ILD-IPF expert and investigator	Research Institute - Hospital do Coracao
Nasreen Khalil, MD	Pulmonologist; ILD-IPF expert and investigator	University of British Columbia

(*Continued*)

Table 7. (*Continued*)

Name	Expertise	Affiliation(s)
Lisa Lancaster, MD	Pulmonologist; ILD-IPF expert and investigator	Vanderbilt University
David Lynch, MD	Radiologist; expert in ILD-IPF imaging and investigator	National Jewish Health
Yolanda Mageto, MD	Pulmonologist; ILD-IPF expert and investigator	Baylor University
Imre Noth, MD	Pulmonologist; ILD-IPF expert and investigator	University of Virginia
Jessica Shore, PhD	Pulmonary Fibrosis Foundation Vice President	Pulmonary Fibrosis Foundation
Marlies Wijsenbeek, MD	Pulmonologist; ILD-IPF expert and investigator	Erasmus MC University Medical Centre
IPF Patients as Patient Advocates		
Robert Brown, MD	IPF patient advocate; general internist	Patient Advocate
Daniel Grogan	IPF patient advocate	Patient Advocate
Dorothy Ivey	IPF patient advocate	Patient Advocate
Administrative Manager		
Patrycja Golinska, MS	Administrative Manager	Weill Cornell Medicine
Observers		
Gus Matute-Bello, MD	Pulmonologist; NHLBI/NIH regulatory expert	National Heart, Lung, & Blood Institute/National Institutes of Health
Matt Craig, PhD	NHLBI/NIH Lung Biology and Disease Branch Chief	National Heart, Lung, & Blood Institute/National Institutes of Health
Sumita Khatri, MD	Pulmonologist; NHLBI/NIH regulatory expert	National Heart, Lung, & Blood Institute/National Institutes of Health
Laurie Burke, MPH	Patient-reported outcomes expert for clinical trials	LORA Group

Definition of abbreviations: FDA = US Food and Drug Administration; ILD = interstitial lung disease; NHLBI/NIH = National Heart, Lung, & Blood Institute/National Institutes of Health; PPF = progressive pulmonary fibrosis.
*Group photograph in supplement.

Regulatory acceptance of blood biomarkers as a surrogate endpoint for phase 3 trials demands ongoing collaborative academic and industry efforts. Statistical and clinical validation, understanding associated risks (e.g., reliability, tolerance, uncertainty), comparing them to known reference standards, and accounting for variability in measurement tools, all informed by the specific context-of-use for a selected biomarker are needed. Importantly, while these biomarkers serve as surrogates, potentially substituting for direct measures of patient survival, function, or well-being, they do not themselves measure the clinical benefit of primary interest. Instead, they are anticipated to predict clinical benefit or harm, grounded in robust epidemiologic, therapeutic, pathophysiologic, or other scientific evidence (Figure 6).

Conclusion

This meeting was a collaborative effort, uniting patients with IPF, FDA representatives, academic investigators, and clinical and quantitative experts in a dialogue about the future of IPF clinical trials. The consensus was clear: trial endpoints should resonate more closely with the tangible experiences of patients, reflecting how they feel, function, and survive. Table 6 summarizes the key IPF clinical trial endpoints in relation to these patient-centric criteria.

A key takeaway from our discussions was that it is time to consider endpoints beyond FVC to assess treatment effect and safety. There was an encouraging discussion on the potential of composite endpoints, anchored with FVC, to serve as primary trial endpoints, requiring rigorous validation and evaluation of each component to accurately depict treatment impacts. There was discussion that integrating adequately validated, fit-for-purpose PROs as key endpoints in clinical trials, a strategy unexplored in IPF clinical trials to date, will be an important step in capturing how a patient feels, functions, and survives. While PROs and functional assessments serve as direct measures of how patients feel and function, differentiating them from endpoints like FVC, use of PROs still requires further validation prior to use as key trial endpoints. The 6MWT, provided it is anchored with rigorous standardization and careful consideration of the target IPF population, may be positioned as a potential key clinical endpoint. Further, simplifying PROs with patient input and other functional assessments to be more user-friendly and less burdensome to patients could solidify their role as secondary endpoints. In contrast, imaging biomarkers are currently not at a stage of development allowing for their use as key endpoints in IPF clinical trials. Their promising role in longitudinal studies, because of their ability to visualize progression of fibrosis, is noteworthy, but inherent limitations, such as scan inconsistencies and co-existing conditions, must be addressed. Likewise, circulating biomarkers, which have been gaining traction in early-phase IPF trials, lack validation and there is currently insufficient evidence to support their use as key endpoints in IPF clinical trials. Our hope is that these insights can guide investigators and sponsors toward designing transformative IPF clinical trials that are fundamentally aligned with the complex needs, unique realities, and rich tapestry of lived experiences of patients with IPF.

Participants

The 43 symposium participants with academic, clinical, and regulatory expertise are listed in Table 7. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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