



A new era in idiopathic pulmonary fibrosis: considerations for future clinical trials

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ABSTRACT The past decade has seen substantial progress in understanding the pathobiology, natural history, and clinical significance of idiopathic pulmonary fibrosis (IPF), culminating in the establishment of two effective medical therapies. Now seems an important time to reconsider the design and conduct of future IPF clinical trials. Building on lessons learned over the past decade, we use this perspective to lay out four key considerations for moving forward effectively and efficiently with the next generation of clinical trials in IPF. These are: development of a coordinated IPF clinical trials network; establishment of expectations for early phase proof of concept studies; adaptation of late-phase efficacy trial designs to the emergence of approved therapies, and; agreement on primary end-points for late phase clinical trials. Continued progress in the field of IPF will require creativity and collaboration on the part of all stakeholders. We believe that addressing these four considerations will encourage and enable investment in this new era of drug development in IPF, and will lead to more rapid development of effective therapies.



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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease characterised by the presence of the histopathological pattern of usual interstitial pneumonia (UIP) [1]. It is a disease of older adults, limited to the lungs, and of unknown cause. Patients with IPF suffer from progressive dyspnoea and functional impairment, and have a median survival from time of diagnosis of approximately 3 years [2].

The past decade has seen tremendous progress in our understanding of the pathobiology, natural history, and clinical significance of IPF. This historic era culminated in the recent publication of two successful phase III clinical trial programmes and the establishment of two therapeutic options for IPF patients [3, 4]. This is a remarkable accomplishment that will better the lives of patients with IPF, and is a tribute to the thousands of patients who have participated in IPF clinical trials. Despite these new therapies, however, patients will continue to experience disease progression and die from IPF; there remains no cure. Better therapies, in particular more effective drugs and combinations of drugs, remain an urgent need [5].

We anticipate that the next few years will witness substantial changes in the design and conduct of IPF clinical trials, driven by our increasingly sophisticated knowledge of clinical trial design. This new era will require creativity, flexibility and collaboration on the part of all stakeholders (patients, clinicians, academics, professional respiratory societies, industry and government sponsors, and advocacy groups) [6]. Clinical trials will need to adjust to the presence of effective therapies and an ever-increasing number of potential targets and stakeholder priorities.

This article presents four key considerations that the authors view as central to future progress in IPF clinical trials (table 1). As these considerations are not unique to IPF, we believe they are generalisable to other conditions that are making the transition to a more complex and sophisticated clinical trial landscape. These considerations represent the views of the authors, who were chosen by the lead authors (H.R. Collard and K.K. Brown) for their interest and expertise in the field, as well as their diverse opinions and constituencies, and do not reflect the views of any particular organisation. We believe that successfully addressing these four considerations will promote a broadly representative, organisational infrastructure for clinical trial conduct in IPF and establish standard practices and protocols for both early and late phase clinical trials that will maximise efficiency and each research subject’s contribution.

TABLE 1 Key considerations

Consideration	Rationale
Development of a centralised IPF clinical trials network	A fragmented approach to study site identification and engagement is costly, time consuming, and inefficient Procedural differences across trial sites introduce significant risk of confounding and make cross-study comparisons challenging A global effort to develop a coordinated clinical trials network (or group of networks) with pre-identified patient populations and standardised methods would greatly improve trial efficiency and should be a top priority
Establishment of expectations for early phase proof of concept studies	Initial early phase clinical trials in IPF have generally been too large, too long, and too dependent on clinical efficacy end-points Early phase end-points should, whenever possible, be biological and mechanistic Early phase trials should utilise cohort enrichment strategies and more efficient study designs to be cheaper, smaller, and faster
Adaptation of late-phase efficacy trial designs to the emergence of approved therapies	There are now two therapies for IPF that slow progression of disease and will be widely used by patients Enrolling subjects with mild to moderate physiological impairment has resulted in low event rates and statistical power Future late phase efficacy trials should include available therapies (e.g. head to head or add-on studies) Cohort enrichment strategies to identify patients at greater risk for the trial end-point or greater likelihood of response to therapy should be incorporated into trial designs
Agreement on primary end-points for late phase clinical trials	Lack of consensus around acceptable primary end-points is a source of confusion to clinical trialists, sponsors and other stakeholders There is strong regulatory precedent for change in FVC as a primary end-point; change in FVC should be an acceptable primary end-point for late phase clinical trials End-point choice should depend on the patient population being studied and the therapeutic target

IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity.

Development of a coordinated IPF clinical trials network

A coordinated IPF clinical trials network composed of investigators and centres experienced with the conduct of IPF clinical trials, developed and administered by a broad coalition of stakeholders (patients, providers, scientists, professional societies, advocacy organisations, industry and governmental agencies), would provide a stable and strong foundation for future drug development in IPF [7–9]. Active engagement of these constituent groups would assure that their priorities are incorporated into this next phase of clinical trials research in IPF. The clinical trials network concept has been successful in other rare diseases (*e.g.* cystic fibrosis) and has recently been endorsed by the National Cancer Institute (NCI) through the development of an institute-wide clinical research network [10].

A global effort to develop and fund a coordinated IPF clinical trials network (or group of networks) could provide many important benefits. Perhaps most valuably, it would enable the development of an easily accessible, well-characterised cohort of study subjects interested in clinical trial participation, greatly improving the speed and efficiency of trial recruitment. Such a cohort, through an associated registry, could also provide valuable data on the natural history, clinical impact and cost-effectiveness of specific therapeutic approaches, particularly with respect to patient adherence, resource utilisation and safety. In addition, the collection of biological samples linked to comprehensive clinical phenotyping at selected network centres could have broad scientific impact by facilitating the testing and validation of tissue and blood biomarkers.

A coordinated clinical trials network could also facilitate standardisation of trial design and conduct. Currently, centres participating in multiple clinical trials have to navigate a variety of trial-specific protocols that include differing methodology and timing of research procedures (*e.g.* spirometry and 6-min walk test). This variability in study design and conduct is often arbitrary and unnecessary, and has made cross-study comparisons difficult. A clinical trials network could establish core protocols and study design templates for use as a basic frameworks for future trial designs, similar to the recently launched Lung Cancer Master Protocol (Lung MAP) developed as a public-private partnership between the NCI, private foundations and five pharmaceutical companies [11].

The development and implementation of best practices across a coordinated clinical trials network would reduce the risk of variation in routine clinical care across centres (*e.g.* more frequent pulmonary rehabilitation or use of supplemental oxygen) that could introduce meaningful effect modification and complicate interpretation of clinical trials. Even minor effect modification or unmeasured confounding are relevant in IPF, where the expected impact of most single-drug therapies is modest.

Clinical trial administration (*e.g.* contracting, ethics approvals, site activation and monitoring) is a major logistical and financial burden on study sponsors. A collaborative clinical trials network could establish centralised review processes and streamlined study site administration, as demonstrated by the NCI's National Clinical Trials Network [10]. It may be that a coalition of national networks is the most feasible approach given international differences in trial administration, regulatory requirements, funding and priorities.

Finally, a coordinated clinical trials network could engage the broader IPF community in future trial design, development and conduct. This would reduce the risk of sponsors investing considerable resources in clinical trials of compounds with limited interest in the patient community, questionable biological plausibility, and challenging or inefficient study designs. As competition for patients grows and required sample sizes increase, a coordinated clinical trials network could provide invaluable input and guidance to sponsors looking to develop high-quality, high-impact trials.

Establishment of expectations for early phase proof of concept studies

Sustained investment in basic science research studying the biology of pulmonary fibrosis has led to the identification of compounds with promising preclinical profiles. Nonetheless, moving these compounds into patients imparts substantial risk: both clinical risk for participating subjects and financial risk for sponsors. This risk is pronounced because reliable preclinical models of IPF that could be used to “de-risk” the potential drug compounds do not yet exist. While ongoing investment in preclinical models (in particular, human tissue-based models) is essential, we believe a rational and efficient approach to early phase proof of concept (or proof of mechanism) trials will allow for cheaper, smaller, faster and smarter early phase trials that provide drug developers with actionable information regarding a compound's potential for clinical efficacy.

Many aspects of early phase proof of concept trial design are driven by the specifics of the compound of interest and its proposed target, but we suggest all sponsors incorporate the following basic principles into their study designs when possible.

First, early phase proof of concept end-points should inform biological activity and mechanism of action. This will require that preclinical development go beyond animal models to include the use of human tissue-based investigations that identify biomarkers (*e.g.* blood, bronchoalveolar lavage and imaging) that may

serve as readouts of a compound's biological effect in patients. Clinical efficacy end-points (*e.g.* change in forced vital capacity (FVC) or 6-min walk distance, all-cause or respiratory hospitalisation, acute exacerbation) should be no more than exploratory in early phase studies. This approach will require sponsors to make decisions about moving from early to later phase development based primarily on an understanding of the compound's mechanism of action and on evidence of an expected biological effect in patients.

Secondly, early phase proof of concept study designs should maximise efficiency by increasing the likelihood of a positive signal. The identification of subgroups of patients more likely to respond to a compound's mechanism of action (so called "predictive" cohort enrichment) may allow for the detection of significant differences in biological end-points in relatively small sample sizes [12–14]. Additional study design approaches that enhance trial efficiency such as crossover groups, trials with multiple periods of comparison, and analytical methods that use average rank scores considering multiple end-points can also greatly enhance study power [15–18].

Finally, the testing of repurposed drugs (*i.e.* drugs developed for other indications) should proceed only when there is compelling preclinical data supporting their use in IPF. Testing repurposed drugs risks the off-label use of these compounds prior to any meaningful clinical trial results demonstrating benefit, and in some cases may cause harm [19–22].

Adaptation of late phase efficacy trial designs to the emergence of effective therapies

The global IPF community now has access to two effective therapies, nintedanib and pirfenidone, for the treatment of IPF. This has dramatically altered the management of patients with this disease [4]. The emergence of effective therapies has substantial implications for the design of future late phase clinical trials.

First, enrolling late phase clinical trials involving groups receiving no therapy at all will prove impractical, at least in the population of IPF patients that have been the focus of most clinical trials to date. While some patients may choose not to take, may not have access to, or may stop taking nintedanib or pirfenidone due to intolerance or continued disease progression, we believe this group may be challenging to identify and unrepresentative of the general IPF population. If this is true, future late phase clinical trials will need to incorporate available therapies, either by designing head-to-head or add-on protocols.

Secondly, the background use of effective therapies by patients enrolled in clinical trials is likely to slow disease progression, alter measures of disease activity, reduce event rates, and increase dropout rates due to increased adverse effects. These factors will increase sample size and/or trial duration requirements in order to maintain adequate statistical power. Sponsors will need to adjust their study design considerations accordingly, maximising feasibility while preserving clinical interpretability and meaningfulness. We believe the most efficient approach to this is cohort enrichment.

Cohort enrichment strategies use patient characteristics to prospectively select a study population in which the detection of a compound's effect will be enhanced [12]. Cohort enrichment increases trial efficiency in two ways: first, by including those patients with a greater likelihood of having an outcome (end-point) of interest; and secondly, by including those patients with a greater likelihood of responding to the compound. Cohort enrichment has been used with increasing success in cancer and other diseases (where it has been incorporated into the concept of precision medicine) [23, 24]; however, it has not yet been established in IPF.

The use of prediction models to identify patients at increased risk for outcomes of interest (*e.g.* disease progression, acute exacerbation or death) provides an opportunity for "prognostic" cohort enrichment [12, 25–30]. An example of prognostic enrichment in IPF would be the recruitment of patients with severe physiological impairment for a trial powered for hospitalisation and mortality, since these patients have been shown to experience these outcomes at an increased rate [31]. Enrolment might be limited to this population, or the trial might use this cohort as a pre-specified target subgroup for which there is stratified randomisation [32]. As described for early phase proof of concept studies, cohort enrichment may also provide an opportunity for "predictive" cohort enrichment in later phase clinical trials by identifying subgroups of patients more likely to respond to a given drug [33, 34]. This could be useful for treatments targeting specific sub-phenotypes of IPF, such as those with concomitant emphysema (so-called combined pulmonary fibrosis and emphysema) or pulmonary hypertension. Whenever possible, the use of cohort enrichment strategies in late phase clinical trial design is strongly encouraged.

Agreement on primary end-points for late phase clinical trials

Late phase clinical trials in IPF have been inconsistent in their choice of, and analytical approach to, primary end-points. The most common primary end-point to date has been change in FVC over time. There are many reasons for this, including the importance of FVC for patient management, its association with mortality, its ease of measurement and its favourable performance characteristics (resulting in smaller

sample sizes and shorter study durations). The primary limitation of change in FVC as a primary end-point has been uncertainty about its clinical meaningfulness, and its vulnerability to missing data. While there remains a lack of consensus regarding the relative strengths and limitations of FVC [35–37], there is now strong regulatory precedent for the use of change in FVC; we believe that change in FVC is an acceptable end-point for late phase clinical trials in IPF. There should be standardisation of analytical methodology (e.g. handling of missing data, choice of statistical test and presentation of magnitude of effect) so that future trials can be more easily contextualised.

There is broad agreement on the pros and cons of commonly mentioned candidate primary end-points such as FVC, symptom burden and mortality. Composites of these and other end-points can be used to more broadly define change in disease burden or progression, and can improve sensitivity to drug effect and trial efficiency [38–40]. Methodology ranking multiple end-points (e.g. mortality, acute exacerbation or disease progression) through a hierarchy that accounts for their relative clinical importance may also allow for improved efficiency [41, 42].

We provide a starting point for discussion of the relative merits of selected primary end-points in table 2. Importantly, we believe several potential primary end-points (e.g. quantitative measures of symptoms/disease burden, blood biomarkers and radiology) require further development before they are ready for use and are not included. The choice of primary end-point in late phase clinical trials will depend upon the hypothesis being tested (e.g. disease modification *versus* symptom management) and the patient population being enrolled (e.g. IPF patients with pulmonary hypertension or concomitant emphysema). Clinical trialists should incorporate the impact of issues such as cohort enrichment strategies (e.g. mild *versus* severe physiological impairment) and proposed mechanism of action (e.g. antifibrotic *versus* symptom relief) into their decision-making around end-points, and solicit input from all relevant stakeholders (e.g. patients, providers, scientists, advocates, industry and governmental agencies).

Summary

There remains a large unmet medical need for patients with IPF. Four key considerations are described that we believe will lead to more effective and efficient clinical trials in IPF in the future. We hope that the development of a coordinated IPF clinical trials network, the establishment of expectations for early phase proof of concept studies, the adaptation of late phase efficacy trial designs to the emergence of effective

TABLE 2 Selected potential primary end-points

End-point	Advantages	Disadvantages
Forced vital capacity	Regulatory precedent Easy to perform Efficient Measure of disease progression Reproducible	Surrogate for clinical events (disease progression, death) May miss important treatment effects Prone to missing data
6-min walk distance	Measure of exercise capacity Efficient	Technically challenging in a multi-centred study Performance affected by non-IPF morbidity Training effect May miss important treatment effects Prone to missing data
Hospitalisation (all-cause or respiratory)	Common clinical event Clinically relevant	Variation in clinical criteria for hospitalisation across sites, healthcare systems and countries
Mortality (all cause or IPF-related)	Clinically relevant Easy to measure	Inefficient (<i>i.e.</i> low event rate) May miss important treatment effect (e.g. improved function or symptoms)
Composite end-points[#]	Capture multiple dimensions of efficacy Can be composed of events that are of direct clinical relevance	Challenging interpretability Outcome generally dominated by single component

IPF: idiopathic pulmonary fibrosis. [#]: examples of composite end-points are: progression-free survival (categorical decline in forced vital capacity, 6-min walk test, respiratory hospitalisation or death); and hospitalisation-free survival (all-cause hospitalisation or death). We do not believe that patient reported outcomes (e.g. symptom scores, quality of life and functional status measures), chest imaging metrics or tissue-based biomarkers are adequately validated at this time to serve as primary end-points for definitive late phase clinical trials.

therapies, and an agreement on primary end-points for late phase clinical trials will encourage all stakeholders to invest in this new era of drug development in IPF.

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