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Study Design Implications of Death and Hospitalization as End Points in Idiopathic Pulmonary Fibrosis

Harold R. Collard, MD, FCCP; Kevin K. Brown, MD, FCCP; Fernando J. Martinez, MD; Ganesh Raghu, MD, FCCP; Rhonda S. Roberts, MSPH; and Kevin J. Anstrom, PhD; for the IPFnet Investigators

BACKGROUND: The feasibility of an interventional clinical trial in idiopathic pulmonary fibrosis (IPF) using death and hospitalization as primary end points is an area of uncertainty. Using data from a large well-characterized clinical trial population, this article aims to illustrate the impact of cohort enrichment and study duration on sample size requirements for IPF clinical trials in which death alone or death plus hospitalization serve as the primary end point.

METHODS: Event rate estimates for death and hospitalization were determined from patients enrolled in National Institutes of Health-sponsored IPF Clinical Research Network clinical trials. Standard equations were applied to estimate the total sample size required for varying gender, age, and pulmonary function (GAP) stage-based cohorts.

RESULTS: Risk estimates for death and hospitalization in the clinical trial cohort were substantially lower than those published. An IPF trial with death as its primary end point enrolling subjects designated as GAP stage 1 and 2 over 1 year with a minimum follow-up of 1 year would require an estimated 7,986 subjects to achieve 90% power for a hazard ratio of 0.70. Alternatively, an IPF trial with death plus hospitalization as its primary end point enrolling subjects with GAP stage 2 and 3 over 2 years with a minimum follow-up of 1 year would require an estimated 794 subjects for the same power and hazard ratio.

CONCLUSIONS: Study design decisions, in particular cohort enrichment strategies, have a substantial impact on sample size requirements for IPF clinical trials using time-to-event primary end points such as death and death plus hospitalization. CHEST 2014; 146(5):1256-1262

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ABBREVIATIONS: ACE-IPF = Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis; GAP = gender, age, pulmonary function; IPF = idiopathic pulmonary fibrosis; IPFnet = Idiopathic Pulmonary Fibrosis Clinical Research Network; PANTHER-IPF = Prednisone, Azathioprine, and N-acetylcysteine: a Study That Evaluates Response in Idiopathic Pulmonary Fibrosis

AFFILIATIONS: From the Department of Medicine (Dr Collard), University of California San Francisco, San Francisco, CA; Department of Medicine (Dr Brown), National Jewish Health, Denver, CO; Department of Medicine (Dr Martinez), University of Michigan, Ann Arbor, MI; Department of Medicine (Dr Raghu), University of Washington, Seattle, WA; and Duke Clinical Research Institute (Ms Roberts and Dr Anstrom), Durham, NC.

Dr Martinez is currently at Weill Cornell Medical Center (New York, NY).

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CORRESPONDENCE TO: Harold R. Collard, MD, FCCP, Department of Medicine, University of California San Francisco, 505 Parnassus Ave, Box 0111, San Francisco, CA 94143; e-mail: hal.collard@ucsf.edu

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and ultimately fatal disease.[1] Because of this, there has been an increasing number of clinical trials testing potential therapies and an increasing focus on the choice of end points used to assess efficacy.[2-4] One of the central areas of uncertainty in IPF clinical trial design is the feasibility of using mortality and hospitalization as primary end points, in particular, the number of subjects required for adequate statistical power.[5]

The impact of cohort selection on the incidence of death and other clinical events, such as hospitalization, in clinical trial populations is an important, undercharacterized issue in IPF clinical trial design. Median survival in patients with IPF enrolled in longitudinal cohorts has been largely reported as 3 years from the time of diagnosis,[6-8] but clinical trials of patients with IPF have demonstrated substantially lower numbers of deaths than this estimate would predict.[9-13]

Data from tertiary care cohorts provide a framework for cohort selection in IPF based on risk of death.[14] Patients can be classified into three stages (gender, age, and pulmonary function [GAP] stages) with varying risks of death over time using the baseline clinical variables GAP (FVC and diffusing capacity of lung for carbon monoxide). This article uses the GAP construct to provide model-based estimates of sample size requirements for IPF clinical trials in which time to death and time to death plus hospitalization are the primary end points, with event rates for death and hospitalization determined from a large, well-defined cohort of patients with IPF enrolled in IPF Clinical Research Network (IPFnet) clinical trials.

TABLE 1] Cohort Characteristics

Characteristic	Value
No. patients	517
Age, y	68 ± 8.5
Female sex	104 (20)
Former or current smoker	327 (63)
BMI, kg/m^2	29.3 (26.7-32.8)
Comorbidities	
CAD	58 (11)
Emphysema/chronic bronchitis	23 (4)
Diabetes	56 (11)
GERD	149 (29)
Baseline physiology	
FVC, %	65.3 ± 16.8
FEV_1, %	75.3 ± 14.1
FEV_1/FVC ratio	0.77 ± 0.02
Dlco, %	37.2 ± 13.5
Baseline 6-min walk distance, m	322 ± 128
Baseline oxygen use	96 (18.6)
Surgical lung biopsy	275 (53)
GAP stage	
1	136 (26.3)
2	227 (43.9)
3	154 (29.8)

Data are presented as mean ± SD, No. (%), and median (range). CAD = coronary artery disease; Dlco = diffusing capacity of lung for carbon monoxide; GAP = gender, age, pulmonary function; GERD = gastroesophageal reflux disease.

Materials and Methods

Cohort Description and Enrichment Strategies

The study cohort comprised patients enrolled in the following IPFnet clinical trials: STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis), ACE-IPF (Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis), and PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine: a Study That Evaluates Response in Idiopathic Pulmonary Fibrosis).[15-17] Patients randomized to warfarin in ACE-IPF or the three-drug regimen (prednisone, azathioprine, acetylcysteine) in PANTHER-IPF were excluded due to harm from these therapies. All patients were given a diagnosis of IPF according to consensus criteria at the time the studies were conducted.[18] All patients provided informed consent for research participation. The research described in this article was exempt from institutional review board review because of its use of existing anonymous clinical data.

Patients were stratified into three groups using the GAP model.[14] Briefly, points were assigned to each patient for sex (female = 0, male = 1), age at enrollment (≤ 60 years = 0, 61-65 years = 1, > 65 years = 2), enrollment FVC % predicted (> 75% = 0, 50%-75% = 1, < 50% = 2), and enrollment diffusing capacity of lung for carbon monoxide % predicted

TABLE 2] Estimated Rates of Death and Death or Hospitalization by GAP Stage

	Event Rates, %	
Cohort/End Point	6 Mo	12 Mo
GAP stage 1		
Death	0.0	0.0
Death or hospitalization	1.5	7.3
GAP stage 2		
Death	3.3	4.8
Death or hospitalization	12.4	18.5
GAP stage 3		
Death	10.4	20.3
Death or hospitalization	34.4	41.9

Data represent Kaplan-Meier event rates. See Table 1 legend for expansion of abbreviation.