Evaluating Whether Oxygen Treatment Helps People with Pulmonary Fibrosis Breathe Easier

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A. ABSTRACT

**Background:** Pulmonary fibrosis (PF) is a life-shortening condition marked by progressive shortness of breath, fatigue, and ever-declining quality of life.\(^1\) For many patients with PF, supplemental oxygen (O\(_2\)) is prescribed to maintain normoxia and stave off complications of hypoxemia, in the hopes of improving symptoms and maintaining day-to-day physical functioning. Very little is known about O\(_2\) in patients with PF—whether and how patients benefit by using it and how they perceive its benefits and hardships.\(^3\)

**Objectives:** To enhance understanding of O\(_2\) and its utility in and adoption by PF patients, by examining how they perceive it and by comparing how perceptions and a range of outcomes change from before to after daily O\(_2\) use was initiated.

**Methods:** We partnered with PF patients and other relevant stakeholders to conduct a mixed methods research program. We collected quantitative data at 4-time points (enrollment [T0], the week prior to O\(_2\) [T1], 1 month after O\(_2\) [T2], and 9-12 months later [T3]) in a nationwide, pre–post longitudinal study, and we collected qualitative data via semi-structured telephone interviews with the aim to enrich findings resulting from the quantitative data.

**Results:** Of 300 subjects enrolled, 43 were started on O\(_2\) by their treating practitioners. Most were white men who had idiopathic pulmonary fibrosis. On average, O\(_2\) did not improve dyspnea ratings from immediately before the start of supplemental oxygen to 1 month later (primary endpoint). However, on secondary analyses, nearly one-third of subjects’ dyspnea ratings improved by an amount greater than the questionnaire’s minimum important difference. The mean 7 months from T0 to T1 showed a trend toward increasing fatigue (slope for Fatigue Severity Scale score 0.41 ± 0.32 points per month; \(p = 0.2\)) that improved significantly by 1 month after O\(_2\) (slope –2.5 ± 1.2; \(p = 0.03\)) but was not sustained to 9 to 12 months later. Physical functioning declined significantly among subjects whose need for O\(_2\) increased (from exertion only to continuous) from T2 to T3, but not among subjects whose O\(_2\) need remained stable (exertion only) during that time.

In the qualitative work, patients and loved ones experienced benefits and hardships from O\(_2\) and described ways to make the process of using O\(_2\) better. Caregivers described how
O₂ helped their patient loved ones (PLOs). They also explained how it created several mental and physical challenges for them and their PLOs, stating it forced them to take on more of the physical work around the home; constrained their social participation; and, for many, created strain on their relationship with their PLO.

**Conclusions:** Supplemental oxygen may improve certain outcomes in PF patients, but significant hardships are associated with its use. Additional research should identify ways to make the process of obtaining and using O₂ easier for these patients and their loved ones.

**Limitations and subpopulation considerations:** The primary limitation of the longitudinal study was small numbers. We needed 83 subjects to have 80% power to detect a 5-point difference in dyspnea score from T1 to T2. We had only 25% power to detect this difference. We were not equipped to determine if O₂ was prescribed as we believe best or if subjects used it as prescribed. Because the study lacked a control group, results should be interpreted with caution.
B. BACKGROUND

**General.** Pulmonary fibrosis (PF) is a progressive, irreversible disease. While shortening patients’ survival, PF insinuates itself into their lives, leaving them breathless and unable to perform physical activities. Although nearly every PF patient will be prescribed supplemental oxygen (O₂), current knowledge of its effects on patients is almost nil. Limited data, collected from only a handful of PF subjects, reveal that O₂ induces immediate improvements in laboratory-based tests of exercise capacity. The paucity of data has left an expansive gap in evidence for patients and practitioners who need to make informed decisions about O₂: No studies have been conducted to examine what patients and prescribers expect PF patients to gain by using O₂; to determine whether O₂ use creates durable, meaningful improvements in PF patients’ daily lives; or to discern whether such putative improvements outweigh patients’ perceptions of being “tied to [their] hoses [oxygen cannulas].” Because thousands of PF patients are prescribed O₂ despite a globally insufficient understanding of whether or how it affects them, there is a vital need to conduct studies that aim to discern whether O₂ improves symptoms and enhances well-being, to find out whether O₂ is—as a patient in 1 of our recently conducted focus groups stated—a “tether” or a “lifeline.” Our overall objective was to enhance understanding of O₂—its utility in and adoption by PF patients—by examining how patients perceive it and by comparing how perceptions and outcomes change from before to after daily-use O₂ is initiated.

**Impact of PF on the health of individuals and populations.** Although understanding of the pathogenesis of PF remains murky, what is clear is that increasing age is a risk factor for PF. Because the US population is aging, PF will be an expanding health problem for the foreseeable future. Given its estimated US prevalence of about 50 per 100 000 persons, PF may not be a rampant burden on the US health care system right now, but it absolutely and unrelentingly weighs down patients. Patients with PF suffer. They have poor quality of life, and as the disease progresses (and in nearly every case, it will) their ability to perform physical activities dwindles. Many are forced to stop working, and 50% of PF patients face death within 3 years of diagnosis.

**Innovation and potential for improvement through research.** Two drugs are approved by the Federal Drug Administration for a certain type of PF called idiopathic
pulmonary fibrosis (IPF). These drugs slow the disease’s progression but do not improve how IPF patients feel or function. To date, no therapy has been indisputably proved to benefit PF patients. Nonetheless, a search of websites from US centers with expertise in caring for patients with PF shows that O2 is a recommended treatment for patients whose peripheral oxygen saturation falls below 89%. Studies to support this recommendation, or studies that systematically examine the effects of supplemental oxygen on outcomes meaningful to patients with PF, such as those proposed above, do not exist. As a result, prescribers are severely limited in their ability to confidently inform patients about how O2 will change their lives. In clinics where patients with PF receive treatment, discussions about supplemental oxygen occur daily. In those discussions, prescribers are forced to draw from the chronic obstructive pulmonary disease (COPD) literature—a cache of data that is controversial and limited, and contains dubious applicability to PF patients. Perhaps because of the limited information available, most patients with PF rate themselves as “uninformed” on managing supplemental oxygen—they do not know what to expect while using it, and there is a paucity of data to substantiate the benefits prescribers (the principal investigator [PI] included) hope their PF patients will realize from using O2.

We proposed partnering with patients to define a new standard of knowledge about O2’s effects on patients with PF. The interstitial lung disease (ILD) field should not be satisfied with depending entirely on the COPD literature or with making clinical decisions about O2 in PF patients based on assumptions that have been formulated on extrapolations of limited data from patients with a different disease. In this study, we aimed to systematically collect and analyze data from PF patients across the country, to more fully elucidate the effects of O2 on patients’ lives. We hoped these data would reveal the benefits of—or call attention to misconceptions about—supplemental oxygen therapy for PF patients. Consequently, we expected the ILD field to gain confidence that current conceptions about and prescribing practices for O2 were correct or that conceptions and practices needed to be substantially modified to improve patients’ lives. For example, we hypothesized that O2 would improve activity space (i.e., expand patients’ worlds by allowing them to do more and go more
places), but we allowed that finding the opposite could be true: Because of the burdens it imposes (delivery devices are heavy and do not allow patients to stray too far from home), \( O_2 \) could shrink patients’ worlds even more. Either way, we believed conducting a mixed methods project would generate useful data for PF patients and the practitioners who care for them.

**Relevance to patients.** Through qualitative research, 10 years of caring for patients with PF, and working closely with the patients and other stakeholders who formed the research team for the current proposal, we have learned that, by far, the 2 greatest factors impairing quality of life among patients with PF are dyspnea-induced limits on functioning and the burdens of \( O_2 \).\(^4\,7-9,20\) The questions this proposal sought to address are patient centered and apply directly to each of the 4 key questions mentioned in PCORI’s definition of patient-centered outcomes research.

- **“Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?”** The proposed research aimed to better understand PF patients’ views and preferences about \( O_2 \) and to learn whether and how supplemental oxygen affects how they feel and function day to day. This type of study is critically important because it aimed to equip patients and prescribers with evidence needed to answer patients when they ask the important question, “What can I expect if I go on supplemental oxygen?”

- **“What are my options and what are the potential benefits and harms of those options?”** Comprehensive data to inform the answer to this question in patients with PF do not exist. Currently, supplemental oxygen is prescribed to patients with PF if oxygen saturation falls below 89%, but patients can (and some do) refuse to use it at all—or as prescribed. As a patient in a focus group mentioned, “It’s a constant tug-o-war [between the burdens and benefits of \( O_2 \)].” In this study, we aimed to learn more about each of the 2 sides of this tug-o-war.

- **“What can I do to improve the outcomes that are most important to me?”** Above all, patients with PF wish for better functioning: They want to be able to take walks with
their partners, play with their children or grandchildren, walk to the mailbox, and even exercise. They want to do these things without having to stop multiple times to catch their breath or feeling like they’ve just run a marathon. We hypothesized that using O2 would allow them to complete everyday activities without feeling breathless.

- “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?” Patients and prescribers will make decisions together based on data and perceptions, and they can make the best decision about O2 if armed with appropriate evidence. This study aimed to generate this evidence.

Central hypothesis and specific aims.

The central hypothesis of this proposal, synthesized by our team of stakeholders, was that O2 use improves outcomes meaningful to patients with PF. Without this research, prescribers and patients will linger uninformed about the effects of this universally prescribed therapy, and when PF patients and their practitioners set out to make critical decisions about O2 together, they will remain hamstrung by the absence of data to inform their choices. We used mixed methods to pursue 3 aims and achieve our objective: (1) Launch P4f (Patient Participation Program for Pulmonary Fibrosis) from which to recruit subjects for this project; (2) determine the effects of O2 on a full range of outcomes meaningful to PF patients; and (3) identify primary supporters’ and prescribers’ expectations and perceptions of O2, and for patients, their expectations and perceptions of O2 before and after it was prescribed. This research embraces PCORI’s mission to involve key stakeholders, targets PCORI’s interest in addressing care for patients with rare conditions and aligns with PCORI’s emphasis on studies conducted in “typical clinical populations” and “considering the full range of patient-centered outcomes.” Our research will at long last create a foundation of information that can be used to improve patient/prescriber communication and decision making about O2.
C. PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS IN DESIGN, CONDUCT, AND DISSEMINATION

Patients are the foremost key stakeholders for the research we conducted. They live with PF. They suffer with PF. When $O_2$ enters the home, it can affect the relationships PF patients have with their primary supporter and the dynamics of family life. Thus, PF patients’ primary supporters are key stakeholders. Other stakeholders include practitioners who prescribe $O_2$ to PF patients, nurses, and other health care team members who work with patients over the course of their disease; PF patient advocacy groups like the Pulmonary Fibrosis Foundation and the Coalition for Pulmonary Fibrosis, which have a keen interest in educating and disseminating information about a host of disease-related topics; PF support group leaders, who have the advantage of reaching patients in person; $O_2$ supply companies; and Medicare, whose $O_2$ prescribing criteria are followed by all US health care payers.

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Table A: Patient Partner Involvement

Patient and Stakeholder Engagement Plan. Patients and other key stakeholders (primary supporters, patient advocacy group representatives, support group leaders, physicians, and a nurse with expertise in caring for PF patients) were meaningfully involved since this project’s conception (see Table A).

The end-users of our research will most certainly include PF patients, their caretakers, PF patient advocacy groups, PF support group leaders, $O_2$ supply companies, and Medicare and other national health care representatives.

Stakeholder recruitment. The key stakeholders on our research team were identified and
recruited in the following manner: (1) In an attempt to include a broad array of PF patients, we recruited patient partners from the National Jewish Health (NJH) Interstitial Lung Disease clinic, the Joe Walsh Memorial PF Support Group at NJH, and the Wheat Ridge PF Support Group; (2) Dr. Swigris leveraged his membership on the Pulmonary Fibrosis Foundation’s Medical Advisory Board and a strong working relationship with Ms. Kervitsky and the PFF’s president and CEO, Dr. Dan Rose, to secure the PFF’s involvement; (3) we reached out to the National Home Oxygen Patients Association (NHOPA) for information and guidance, and by teaming with NHOPA we ensured that our study will reach the greatest number of patients possible; and (4) we recruited Ms. Brenda Crowe, a local PF support group leader.

**Stakeholder engagement in study design.** During support group meetings, O₂ is by far the topic that raises the most interest—and questions. Identifying the research question flowed naturally from support group interactions. We used a portion of support group and research-specific meetings to construct the research question and objectives, shape the study design, define the essential characteristics of study participants, and select the specific outcome measures. We selected the PROs we used by reviewing candidate questionnaires for item relevance, missing themes, length, and available response options. The instruments used in this project were selected by consensus and approved by all members of the research team.

**Stakeholder monitoring of study conduct.** Each month, the research team met in person at NJH to discuss progress, review enrollment, and decide what, if anything, needed to change. Stakeholders participated in 6-months of conference calls to PCORI. One example of how our team worked together was, because we were slow to recruit participants, we created a plan to tweak our recruitment strategy. Initially, we had described the study as an investigation of O₂, which is true. However, we found out that PF patients who were not on O₂ (the ones we were trying to recruit) did not think they were eligible. So, we changed our advertising and recruitment picked up considerably, allowing us to reach our goal.
Stakeholder involvement in dissemination of results. We have already published 2 methods papers and some of the data from our study. Patient partners are (and perform the requisite work to be placed) on the author line for our manuscripts. We have presented data at international meetings of the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP). The greatest example of PCORI’s influence on our research program occurred when our patient partners presented posters at the ATS and ACCP meetings. After deliberation, the ATS and ACCP determined how our patient partners could register for the meetings. Meeting attendees were surprised to discover our presenters were patients. It gave our patient partners a better appreciation for how these meetings work, and it gave meeting attendees a look into PCORI and patient-centered/patient-active research. There is more dissemination work to do (e.g., website posting, grand rounds), and patients will remain actively involved in these efforts.

D. METHODS

Overview of funded research and study design. We used a mixed methods approach to pursue our aims: We collected quantitative data via questionnaires and other sources, and we collected qualitative data via semi-structured telephone interviews and used those data to enrich findings resulting from the quantitative data. First, we launched P4f (the name changed to P3f) and our study website (www.PFresearch.org) and used the site’s database to recruit subjects for the studies. We used a pre–post design and longitudinal study methodology to determine how O₂ affected outcomes meaningful to PF patients. We conducted individual, in-depth phone interviews with PF patients, their primary supporters, and their physicians to learn from each of them their perceptions of O₂. We conducted multiple interviews with patients to learn how their perceptions of O₂ changed over time. For the longitudinal, pre–post study, we enrolled patients with PF of any cause who had not yet been prescribed O₂ for daily use (see Figure A).

We collected primary data at 4-time points: (1) at enrollment; (2) just before supplemental
oxygen was prescribed by subjects’ treating physician; (3) after 1 month (± 1 week); and (4) after 9 to 12 months of daily O2 use.

**Forming the cohort.** Participants for the longitudinal study were recruited from across the United States via the P4f and internet advertisements for the study on the PF website and its social media outlets, advertisements in ILD clinics across the country, and letters to pulmonary physicians, as well as by posting the study on www.clinicaltrials.gov. Our goal was to recruit a sample representative of the general PF population; this included people of both genders, from several ethnic/racial groups, and across the range of socioeconomic status. Potential subjects obtained consent forms either from the P4f website or via US mail. Research coordinators conversed with potential subjects via telephone. Potential subjects signed an authorization form that allowed the research team to contact their physician’s office to acquire records, including results of pulmonary function tests and imaging studies. We discussed with each patient’s physician the methods for the study; specifically, the plan to collect data at the second-time point (just before oxygen is started). The physician consented to delaying the patient’s start of O2 for 1 week after it is prescribed. This allowed us to collect data for the second-time point. The patients we aimed to enroll were those whose PF progressed to the point at which their peripheral oxygen saturation was acceptable at rest (e.g., > 88%) but fell with activity—and a decision had been made for them to begin daily O2 use. We did not recruit PF patients who were prescribed oxygen for an acute illness. Inclusion criteria included subjects’ self-report diagnosis of PF (that was confirmed by the study team via review of chest imaging and medical records), those who were not prescribed O2 for use during the day, those who were able to complete English-language questionnaires, and those with forced vital capacity < 75% and diffusing capacity < 65% of predicted values. We excluded subjects if their physician did not allow them to wait 1 week before starting O2.

**Study setting.** We conducted the study in subjects’ home environments. Subjects were recruited from across the United States, and data collection occurred via email and by data capture devices. Devices were mailed to participants at data collection time points, and participants returned them via prepaid delivery envelopes. **Interventions.** There were no study
interventions. Decisions about whether and when to start O₂ were made by subjects’ treating physicians. Patients prescribed O₂ were instructed to follow the directions of the prescribing practitioner. Study personnel gave no directions on how O₂ was to be used.

**Follow-up.** Remote data collection occurred via email at 4-time points: (1) at enrollment; (2) just before O₂ was started; (3) after 1 month (± 1 week); and (4) after 9 to 12 months of daily O₂ use. Questionnaires were emailed to subjects, and wearable devices were mailed to subjects via a shipping service at each time point.

**Outcomes.** The primary endpoint was change in dyspnea (as measured by the University of California San Diego Shortness of Breath Questionnaire [UCSD]²¹) from baseline (pre-O₂) to after 1 month of daily O₂ use. Secondary endpoints included change in quality of life (QOL), fatigue, cough, day-to-day functioning (as measured by an accelerometer), and activity space (as measured by a portable global positioning system, or GPS) from baseline to 1 month, and change from the start of O₂ to 9 to 12 months later for all of these outcomes.

**Data collection and sources.** Outcome measures included the following:

- The UCSD is a 24-item dyspnea questionnaire that asks respondents to rate themselves from 0 (“Not at all”) to 5 (“Maximally or unable to do because of breathlessness”) in 2 areas: (1) how short of breath they are while performing various activities (21 items); and (2) how much shortness of breath itself, fear of hurting themselves by overexerting, and fear of shortness of breath limit them in their daily lives (3 items). Scores range from 0 to 120, with higher scores indicating greater dyspnea.²¹ The PI has published a paper on the UCSD that includes data for the following: (1) the validity of the UCSD as an instrument capable of assessing dyspnea over time in patients with PF; and (2) an estimate for the change in UCSD score that constitutes a minimum clinically important difference (MCID) in patients with PF: range 5 to 11.²⁰ The UCSD takes 5 minutes to complete.

- The Short-form 36-item Instrument (SF-36) is a generic health-related QOL (HRQL) questionnaire with 8 domains that comprise 2 component summaries (physical and mental).²² Each domain and component is scored from 0 to 100, with higher scores
connoting greater HRQL. The PI has used the SF-36 extensively and published a paper that includes MCID estimates for the SF-36 and data to support the validity of the SF-36 as an instrument capable of assessing HRQL over time in patients with PF.23 The SF-36 is the most popular HRQL instrument ever used and takes 15 minutes to complete.

- The Fatigue Severity Scale (FSS) is a 9-item questionnaire, scored from 9 to 63; higher scores indicate more severe fatigue. The FSS takes less than 5 minutes to complete.

- The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that taps the physical, psychological, and social aspects of cough.24 Scores range from 7 to 63; higher scores indicate better cough-related QOL. The LCQ takes 5 minutes to complete.

- The accelerometer we used is the Actigraph GT3X+ Tri-Axis Actigraphy Monitor. It is a small, lightweight (19 grams), plastic device (about the size of a matchbox) affixed to an elastic band and comfortably worn around the wrist or waist. The device continuously records step count data that can be downloaded onto a computer via a USB cable.

- The lightweight GPS unit we used is the iGotU GT-600 GPS data logger from MobileAction Technologies (http://www.i-gotu.com/). These small units are easily worn on a lanyard around the participant’s neck. They have good reliability and spatial accuracy, even in urban settings.25 The GPS data loggers tracked the movement patterns of participants during a typical week and develop measures of “activity space.” Activity space is often defined as the local areas within which people move or travel while completing their daily activities26 and can be used to examine whether people’s mobility changes during medical treatment. Recent research suggests that collecting GPS data on people’s movements is more accurate than using travel diaries or semistructured interviews that ask participants to recall their activities and movements throughout the study period.27,28 We imported data from the GPS loggers into ArcGIS mapping software and used them to create secondary outcome measures.
that examined the extent of a participant’s activity space and how it changed over time.\textsuperscript{29-31} We generated 2 measures of activity space from GPS data: a standard deviational ellipse (SDE) and a road network buffer (RNB). The SDE is the area within which a subject spent 68\% of his or her recorded time. The RNB is the space within which a subject traveled during the day, with larger values indicating greater distance traveled away from the home.

**Analytical and statistical approaches.** For the longitudinal study, we generated summary statistics for baseline characteristics. We used paired \( t \) tests to compare outcomes from just prior to starting \( O_2 \) (baseline for the primary endpoint) to 1 month later and from 1 month on \( O_2 \) to 9 to 12 months later (secondary analysis). For GPS, accelerometer, and questionnaire outcomes over time, secondary analyses included the development of linear mixed models using visit, forced vital capacity (FVC), age, and gender as key predictors. To account for repeated measures, we included for subjects a random intercept (which induces a compound symmetric covariance structure on repeated measures). We considered a spatial power structure to account for the unequally spaced measures among subjects, but it did not improve the model fit, so we retained the random intercept model. Because FVC measurements were not necessarily collected on the same day as the outcome variables, we matched outcome and FVC values based on nearness of dates of measurement. Models yielded point estimates at the 4 study time points as well as slopes over time.

In ongoing work, we are examining regression calibration to predict FVC for exact dates on which other outcomes were measured. In these models, predicted FVC values are used in place of measured FVC values in the outcome models. We used gender, race, height, weight, age (time varying), and smoking status to predict FVC. We are still refining the predictors, including possibly adding time as a class variable, in addition to age.

For all qualitative analyses, we used grounded theory and a team analytic approach to identify themes, code text, and generate conceptual frameworks for answers to questions posed.

**Conduct of the study.** The final protocol is found in appendix A. Originally, we had planned to enroll only subjects with FVC < 75\% and DLCO < 65\% of predicted values, but we amended
our approach to include any patient with diffuse pulmonary fibrosis, for a number of reasons: (1) Recruitment was slow; (2) some patients with combined pulmonary fibrosis and emphysema would be excluded under the initial criteria; and (3) PF is unpredictable and can progress at any time or rate, and we did not want to miss the opportunity to recruit those subjects. The work for this project was approved by the National Jewish Health IRB (HS-2789 and HS-2790).

E. RESULTS

Results are organized to align with our 3 specific aims as displayed in Figure F: Aim 1—Launch P4f from which to recruit subjects for this project; Aim 2—Determine the effects of O2 on a range of outcomes meaningful to PF patients; and Aim 3—Identify perceptions of O2 before and after it is prescribed.

Results for Aim 1—launch the P4f from which to recruit subjects to participate in this project. Our study website (www.PFresearch.org) became the face of our research program, replete with a physician blog, a patient/caregiver forum, and a conduit for enrollment.
Figure 1. Overview of the Various Facets of the Research Program

Any U.S. Patient with Pulmonary Fibrosis

Note: FSS = Fatigue Severity Scale; GPS = global positioning system; LCQ = Leicester Cough Questionnaire; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire.
Results for Aim 2—determine the effects of O₂ on outcomes meaningful to PF patients.

Three hundred subjects consented to participate. The CONSORT diagram shows subject flow throughout the study. Forty-three subjects were prescribed O₂ by their physician a median 7 months after enrollment. Of those 43 subjects, 30 contributed data at T1 (the week prior to starting O₂); 5 died or were lost to follow-up; and an additional 13 (who contributed baseline but not T1 data) contributed data at T2. Twenty-five subjects contributed data at both T1 and T2. The 25 subjects who contributed T3 data also contributed data at T2.

**Figure 2.** CONSORT Flow Diagram for the Longitudinal Study

- 300 subjects enrolled
- 43 subjects prescribed O₂ at some point during follow-up
- 30 contributed data for some outcomes assessed 1 week before starting O₂
- 38 contributed data for some outcomes assessed 1 month after starting O₂
- 25 contributed data for some outcomes assessed 9-12 months after starting O₂
- 2 confirmed death before T2
- 4 missing T1 PRO data
- 6 missing T2 PRO data
- 2 died
- 2 transplant
- 9 lost f/U

Note: T0 = enrollment; T1 = 1 week prior to starting O₂; T2 = 1 month (± 1 month) after starting O₂; T3 = 9 to 12 months after starting O₂.

The cohort. The cohort prescribed O₂ was predominantly white, and idiopathic pulmonary fibrosis was the most common diagnosis (Table 1).
Table 1. Baseline Characteristics of Subjects Prescribed O₂ for Use During the Day

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<td>cHP</td>
<td>2</td>
</tr>
<tr>
<td>FPF</td>
<td>4</td>
</tr>
<tr>
<td>IPF</td>
<td>24</td>
</tr>
<tr>
<td>RAPF</td>
<td>1</td>
</tr>
<tr>
<td>SScPF</td>
<td>1</td>
</tr>
<tr>
<td>Other PF</td>
<td>11</td>
</tr>
</tbody>
</table>

**Note:** O₂ = supplemental oxygen; cHP = chronic hypersensitivity pneumonitis; FPF = familial pulmonary fibrosis; IPF = idiopathic pulmonary fibrosis; RAPF = rheumatoid arthritis-related pulmonary fibrosis; SScPF = systemic sclerosis-related pulmonary fibrosis; PF = pulmonary fibrosis.

**Primary outcome.** There was no difference in the primary outcome of UCSD score (range 0-120) from just prior to O₂ to 1 month later (difference 0.9 ± 8.7; *p* = 0.6). Responder analyses revealed that of the 19 subjects with UCSD scores available at T1 and T2, 6 improved by greater than 5 points (the minimum important difference for the UCSD).

**Secondary outcomes.** There were trends toward significant improvements in fatigue (difference 4.4 ± 11.9; *p* = 0.1) and the vitality domain of the SF-36 (Table 2). Among subjects with non-IPF diagnoses, O₂ improved fatigue and the role emotional domain of the SF-36. Results for other secondary analyses are presented in Tables 3 and 4.
**Table 2.** Differences in Outcomes From Pre-O₂ to Post-O₂

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Entire Cohort T1 Minus T2, N = 25</th>
<th>IPF Only T1 Minus T2, N = 13</th>
<th>Non-IPF T1 Minus T2, N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD</td>
<td>0.9 ± 8.7, p = 0.60*</td>
<td>0.9 ± 10.5, p = 0.70**</td>
<td>0.9 ± 6.4, p = 0.60***</td>
</tr>
<tr>
<td>FSS</td>
<td>4.4 ± 11.9, p = 0.10*</td>
<td>0.9 ± 12.9, p = 0.80**</td>
<td>9.3 ± 8.9, p = 0.02***</td>
</tr>
<tr>
<td>LCQ</td>
<td>0.6 ± 2.3, p = 0.20*</td>
<td>−0.3 ± 2.2, p = 0.70**</td>
<td>−1.2 ± 2.5, p = 0.20***</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>−0.4 ± 5.5, p = 0.70*</td>
<td>0.2 ± 4.9, p = 0.80**</td>
<td>−1.3 ± 6.3, p = 0.50***</td>
</tr>
<tr>
<td>RP</td>
<td>−0.7 ± 11.0, p = 0.70*</td>
<td>1.9 ± 8.4, p = 0.40**</td>
<td>−4.4 ± 13.6, p = 0.30***</td>
</tr>
<tr>
<td>BP</td>
<td>1.7 ± 6.8, p = 0.20*</td>
<td>3.7 ± 6.8, p = 0.10**</td>
<td>−1.1 ± 5.9, p = 0.60***</td>
</tr>
<tr>
<td>GH</td>
<td>−1.5 ± 5.8, p = 0.20*</td>
<td>−1.4 ± 4.8, p = 0.30**</td>
<td>−1.6 ± 7.3, p = 0.50***</td>
</tr>
<tr>
<td>SF</td>
<td>0.6 ± 8.1, p = 0.70*</td>
<td>−1.5 ± 6.0, p = 0.40**</td>
<td>3.4 ± 10.0, p = 0.30***</td>
</tr>
<tr>
<td>VT</td>
<td>−2.0 ± 5.5, p = 0.10*</td>
<td>−2.2 ± 6.3, p = 0.20**</td>
<td>−1.8 ± 4.7, p = 0.30***</td>
</tr>
<tr>
<td>RE</td>
<td>−3.3 ± 13.2, p = 0.20*</td>
<td>0.0 ± 14.9, p = 1.00**</td>
<td>−7.9 ± 9.3, p = 0.04***</td>
</tr>
<tr>
<td>MH</td>
<td>0.06 ± 5.2, p = 0.90*</td>
<td>−0.6 ± 4.5, p = 0.60**</td>
<td>0.9 ± 6.3, p = 0.60***</td>
</tr>
<tr>
<td>Steps/day</td>
<td>391.4 ± 2012.0, p = 0.30</td>
<td>19.2 ± 2077.3, p = 0.90</td>
<td>794.5 ± 1945.2, p = 0.10</td>
</tr>
<tr>
<td>RNB</td>
<td>47.9 ± 216.9, p = 0.30</td>
<td>4.3 ± 1717.1, p = 0.90</td>
<td>92.8 ± 90.3, p = 0.30</td>
</tr>
<tr>
<td>SDE</td>
<td>8633.1 ± 41797.0, p = 0.30</td>
<td>6.7 ± 92.9, p = 0.80</td>
<td>18830.8 ± 61671.5, p = 0.30</td>
</tr>
</tbody>
</table>

**Note:** Values are mean ± standard deviation. *N = 19; **N = 11; ***N = 8; O₂ = supplemental oxygen; BP = bodily pain; FSS = Fatigue Severity Scale; GH = general health; LCQ = Leicester Cough Questionnaire; MH = mental health; PF = physical functioning; RE = role emotional; RNB = road network buffer; RP = role physical; SDE = standard deviational ellipse; SF = social functioning; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire; VT = vitality.
### Table 2a. Differences in Outcomes From Pre-O₂ to Post-O₂ Between Men and Women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men T2 Minus T1</th>
<th>Women T2 Minus T1</th>
<th>Difference Women Minus Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD</td>
<td>−1.0 ± 7.4</td>
<td>−0.6 ± 12.1</td>
<td>0.4 ± 9.0, <em>p</em> = 0.900</td>
</tr>
<tr>
<td>FSS</td>
<td>0.5 ± 9.9</td>
<td>−15.1 ± 8.7</td>
<td>−15.6 ± 9.6, <em>p</em> = 0.004</td>
</tr>
<tr>
<td>LCQ</td>
<td>0.6 ± 2.8</td>
<td>0.7 ± 1.2</td>
<td>0.1 ± 2.4, <em>p</em> = 0.900</td>
</tr>
<tr>
<td>SF-36 PF</td>
<td>−1.0 ± 5.3</td>
<td>3.5 ± 4.7</td>
<td>4.5 ± 5.2, <em>p</em> = 0.090</td>
</tr>
<tr>
<td>SF-36 RP</td>
<td>−1.1 ± 11.1</td>
<td>4.7 ± 10.6</td>
<td>5.8 ± 11.0, <em>p</em> = 0.300</td>
</tr>
<tr>
<td>SF-36 BP</td>
<td>−2.3 ± 4.4</td>
<td>−0.4 ± 10.8</td>
<td>1.9 ± 6.9, <em>p</em> = 0.600</td>
</tr>
<tr>
<td>SF-36 GH</td>
<td>0.5 ± 6.4</td>
<td>3.5 ± 4.1</td>
<td>3.0 ± 5.8, <em>p</em> = 0.300</td>
</tr>
<tr>
<td>SF-36 SF</td>
<td>0.0 ± 6.3</td>
<td>−1.8 ± 11.7</td>
<td>−1.8 ± 8.3, <em>p</em> = 0.700</td>
</tr>
<tr>
<td>SF-36 VT</td>
<td>2.0 ± 5.9</td>
<td>2.0 ± 5.3</td>
<td>−0.03 ± 11.1, <em>p</em> = 0.900</td>
</tr>
<tr>
<td>SF-36 RE</td>
<td>−0.8 ± 11.7</td>
<td>12.3 ± 12.3</td>
<td>13.1 ± 11.9, <em>p</em> = 0.030</td>
</tr>
<tr>
<td>SF-36 MH</td>
<td>−2.0 ± 4.5</td>
<td>4.2 ± 4.4</td>
<td>6.2 ± 4.7, <em>p</em> = 0.010</td>
</tr>
<tr>
<td>Steps/day</td>
<td>−119.7 ± 1715.0</td>
<td>−874.3 ± 2493.9</td>
<td>−754.5 ± 2020.3, <em>p</em> = 0.400</td>
</tr>
<tr>
<td>RNB</td>
<td>−15.0 ± 83.5</td>
<td>−109.5 ± 356.8</td>
<td>−94.5 ± 217.0, <em>p</em> = 0.300</td>
</tr>
<tr>
<td>SDE</td>
<td>−200.4 ± 1621.5</td>
<td>−25498.6 ± 72435.3</td>
<td>−25298.2 ± 40881.0, <em>p</em> = 0.200</td>
</tr>
</tbody>
</table>

**Note:** Values are mean ± standard deviation. O₂ = supplemental oxygen; BP = bodily pain; FSS = Fatigue Severity Scale; GH = general health; LCQ = Leicester Cough Questionnaire; MH = mental health; PF = physical functioning; RE = role emotional; RNB = road network buffer; RP = role physical; SDE = standard deviational ellipse; SF = social functioning; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire; VT = vitality.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Younger Than 65 T2 Minus T1</th>
<th>Older Than 65 T2 Minus T1</th>
<th>Difference Younger Minus Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UCSD</strong></td>
<td>–3.8 ± 9.5</td>
<td>1.7 ± 7.7</td>
<td><strong>–5.5 ± 8.6, p = 0.100</strong></td>
</tr>
<tr>
<td><strong>FSS</strong></td>
<td>–6.4 ± 9.7</td>
<td>–2.6 ± 13.9</td>
<td><strong>–3.8 ± 12.1, p = 0.500</strong></td>
</tr>
<tr>
<td><strong>LCQ</strong></td>
<td>0.9 ± 2.3</td>
<td>0.4 ± 2.4</td>
<td><strong>0.4 ± 2.4, p = 0.600</strong></td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>0.5 ± 4.9</td>
<td>0.4 ± 6.2</td>
<td><strong>0.1 ± 5.6, p = 0.900</strong></td>
</tr>
<tr>
<td>RP</td>
<td>4.7 ± 10.6</td>
<td>–2.8 ± 10.6</td>
<td><strong>7.5 ± 10.6, p = 0.100</strong></td>
</tr>
<tr>
<td>BP</td>
<td>0.3 ± 7.7</td>
<td>–3.4 ± 5.7</td>
<td><strong>3.7 ± 6.7, p = 0.200</strong></td>
</tr>
<tr>
<td>GH</td>
<td>5.1 ± 3.7</td>
<td>–1.8 ± 5.5</td>
<td><strong>7.0 ± 4.7, p = 0.004</strong></td>
</tr>
<tr>
<td>SF</td>
<td>–0.6 ± 10.0</td>
<td>–0.5 ± 6.5</td>
<td><strong>0.1 ± 8.3, p = 0.900</strong></td>
</tr>
<tr>
<td>VT</td>
<td>2.9 ± 5.0</td>
<td>1.2 ± 6.1</td>
<td><strong>1.7 ± 5.6, p = 0.500</strong></td>
</tr>
<tr>
<td>RE</td>
<td>11.7 ± 11.1</td>
<td>–4.2 ± 10.2</td>
<td><strong>15.9 ± 10.6, p = 0.004</strong></td>
</tr>
<tr>
<td>MH</td>
<td>2.5 ± 5.0</td>
<td>–2.3 ± 4.6</td>
<td><strong>4.8 ± 4.8, p = 0.040</strong></td>
</tr>
<tr>
<td><strong>Steps/day</strong></td>
<td>–1413.1 ± 2367.8</td>
<td>411.4 ± 1258.4</td>
<td><strong>–1824.5 ± 1825.5, p = 0.020</strong></td>
</tr>
<tr>
<td><strong>RNB</strong></td>
<td>–15.0 ± 83.5</td>
<td>–109.5 ± 356.8</td>
<td><strong>–94.5 ± 217.0, p = 0.300</strong></td>
</tr>
<tr>
<td><strong>SDE</strong></td>
<td>–20672.6 ± 64688.3</td>
<td>–33.5 ± 1639.8</td>
<td><strong>–20639.1 ± 41393.9, p = 0.200</strong></td>
</tr>
</tbody>
</table>

**Note:** Values are mean ± standard deviation. O2 = supplemental oxygen; BP = bodily pain; FSS = Fatigue Severity Scale; GH = general health; LCQ = Leicester Cough Questionnaire; MH = mental health; PF = physical functioning; RE = role emotional; RNB = road network buffer; RP = role physical; SDE = standard deviational ellipse; SF = social functioning; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire; VT = vitality.
Table 3 shows results for the slope analyses: age-adjusted, gender-adjusted, and FVC-adjusted modeled slopes for change over time are displayed for each outcome for all subjects with available data (30 contributed data at T1, 38 at T2, and 25 at T3). Dyspnea and physical functioning (as assessed by the physical functioning domain of the SF-36 whose range is 0-100) declined from enrollment to just prior to starting O2. Supplemental O2 improved fatigue (adjusted FSS slope $-0.5 \pm 1.2$, $p = 0.03$) over 1 month. Fatigue increased from enrollment to T1; after O2 was started, fatigue declined (difference in slopes T0-T1 versus T1-T2 $= 2.9 \pm 1.4$; $p = 0.03$). For the entire cohort, from 1 month after starting O2 to 9 to 12 months later, worsening dyspnea trended toward statistical significance. Cough-specific quality of life, general health ratings, and vitality declined. There were no differences in steps per day. On subgroup analyses, there were differences in some outcomes between men and women and between subjects older than 65 versus those younger than 65 (Tables 2a and 2b).
## Table 3. Modeled Slopes for Change in Outcomes Over Time

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Slope 1 From T0 to T1 ± SE, p</th>
<th>Slope 2 From T1 to T2 ± SE, p</th>
<th>Slope 3 From T2 to T3 ± SE, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD</td>
<td>1.27 ± 0.47, 0.009</td>
<td>0.39 ± 1.78, 0.800</td>
<td>0.89 ± 0.44, 0.050</td>
</tr>
<tr>
<td>FSS</td>
<td>0.41 ± 0.32, 0.200</td>
<td>−2.5 ± 1.2, 0.030</td>
<td>0.49 ± 0.29, 0.100</td>
</tr>
<tr>
<td>LCQ</td>
<td>−0.09 ± 0.07, 0.100</td>
<td>0.41 ± 0.25, 0.100</td>
<td>−0.15 ± 0.07, 0.020</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>−0.54 ± 0.22, 0.010</td>
<td>0.50 ± 0.84, 0.500</td>
<td>−0.27 ± 0.21, 0.200</td>
</tr>
<tr>
<td>RP</td>
<td>−0.60 ± 0.30, 0.050</td>
<td>−0.25 ± 1.14, 0.800</td>
<td>−0.20 ± 0.28, 0.400</td>
</tr>
<tr>
<td>BP</td>
<td>0.21 ± 0.22, 0.300</td>
<td>−0.23 ± 0.80, 0.700</td>
<td>0.22 ± 0.19, 0.300</td>
</tr>
<tr>
<td>GH</td>
<td>−0.19 ± 0.17, 0.200</td>
<td>0.62 ± 0.6, 0.300</td>
<td>−0.38 ± 0.15, 0.010</td>
</tr>
<tr>
<td>SF</td>
<td>−0.10 ± 0.28, 0.700</td>
<td>−0.25 ± 1.08, 0.800</td>
<td>−0.17 ± 0.27, 0.500</td>
</tr>
<tr>
<td>VT</td>
<td>−0.02 ± 0.21, 0.900</td>
<td>0.94 ± 0.74, 0.200</td>
<td>−0.38 ± 0.19, 0.040</td>
</tr>
<tr>
<td>RE</td>
<td>−0.23 ± 0.38, 0.500</td>
<td>1.03 ± 1.6, 0.500</td>
<td>0.46 ± 0.40, 0.200</td>
</tr>
<tr>
<td>MH</td>
<td>0.14 ± 0.22, 0.500</td>
<td>0.17 ± 0.84, 0.800</td>
<td>−0.16 ± 0.21, 0.400</td>
</tr>
<tr>
<td>Steps/day</td>
<td>−19.49 ± 60.51, 0.700</td>
<td>−50.80 ± 218.77, 0.800</td>
<td>−68.53 ± 57.75, 0.200</td>
</tr>
<tr>
<td>RNB</td>
<td>5.24 ± 2.56, 0.040</td>
<td>−13.62 ± 10.89, 0.200</td>
<td>−0.83 ± 2.72, 0.700</td>
</tr>
<tr>
<td>SDE</td>
<td>1000.5 ± 538.8, 0.060</td>
<td>−1315.3 ± 2273.9, 0.500</td>
<td>−171.8 ± 581.8, 0.700</td>
</tr>
</tbody>
</table>

**Note:** Values are slopes ± standard error. O2 = supplemental oxygen; T0-T1 = slope from enrollment to immediately prior to starting O2; T1-T2 = slope from T1 to 1 month (± 1 month) after starting O2; T2-T3 = slope from T2 to 9 to 12 months after starting O2. BP = bodily pain; FSS = Fatigue Severity Scale; GH = general health; LCQ = Leicester Cough Questionnaire; MH = mental health; PF = physical functioning; RE = role emotional; RNB = road network buffer; RP = role physical; SDE = standard deviational ellipse; SF = social functioning; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire; VT = vitality.
Progression from needing O$_2$ only with exertion to needing it all the time (even at rest) 9 to 12 months later (i.e., T3), was associated with significantly worsened physical functioning and strong trends toward statistically significant worsening general health, mental health and social functioning, vitality, and the role physical domain of the SF-36 (Table 4). There were no such differences or trends among subjects whose O$_2$ needs did not progress (i.e., all SF-36 domains remained stable during the 9-12 months from T2 to T3). Dyspnea and fatigue worsened over time regardless of whether O$_2$ needs changed.

**Table 4. Differences in Outcomes From T2 to T3**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>O$_2$ at Rest at T3</th>
<th>No O$_2$ at Rest at T3</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2 Minus T3 N = 10</td>
<td>T2 Minus T3 N = 15</td>
<td>All Subjects</td>
</tr>
<tr>
<td>UCSD</td>
<td>$-13.0 \pm 20.9, p = 0.100$</td>
<td>$-7.2 \pm 15.0, p = 0.100$</td>
<td>$-9.5 \pm 17.3, p = 0.020$</td>
</tr>
<tr>
<td>FSS</td>
<td>$-9.4 \pm 12.4, p = 0.060$</td>
<td>$-9.4 \pm 12.8, p = 0.020$</td>
<td>$-9.4 \pm 12.3, p = 0.003$</td>
</tr>
<tr>
<td>LCQ</td>
<td>$0.7 \pm 2.8, p = 0.500$</td>
<td>$1.6 \pm 1.4, p = 0.004$</td>
<td>$1.2 \pm 2.0, p = 0.020$</td>
</tr>
<tr>
<td>SF-36 PF</td>
<td>$10.2 \pm 9.8, p = 0.020$</td>
<td>$-0.7 \pm 2.6, p = 0.300$</td>
<td>$3.7 \pm 8.3, p = 0.060$</td>
</tr>
<tr>
<td>SF-36 RP</td>
<td>$6.2 \pm 11.0, p = 0.100$</td>
<td>$-1.9 \pm 10.5, p = 0.500$</td>
<td>$1.5 \pm 11.2, p = 0.600$</td>
</tr>
<tr>
<td>SF-36 BP</td>
<td>$1.1 \pm 6.4, p = 0.600$</td>
<td>$-1.9 \pm 10.0, p = 0.500$</td>
<td>$-0.7 \pm 8.7, p = 0.700$</td>
</tr>
<tr>
<td>SF-36 GH</td>
<td>$4.6 \pm 5.8, p = 0.060$</td>
<td>$2.4 \pm 7.3, p = 0.200$</td>
<td>$3.3 \pm 6.7, p = 0.040$</td>
</tr>
<tr>
<td>SF-36 SF</td>
<td>$6.8 \pm 11.5, p = 0.100$</td>
<td>$-1.8 \pm 11.2, p = 0.500$</td>
<td>$-1.8 \pm 11.2, p = 0.500$</td>
</tr>
<tr>
<td>SF-36 VT</td>
<td>$4.7 \pm 7.4, p = 0.100$</td>
<td>$3.4 \pm 9.0, p = 0.200$</td>
<td>$3.9 \pm 8.2, p = 0.040$</td>
</tr>
<tr>
<td>SF-36 RE</td>
<td>$6.6 \pm 13.7, p = 0.200$</td>
<td>$-3.5 \pm 15.8, p = 0.400$</td>
<td>$0.5 \pm 15.5, p = 0.900$</td>
</tr>
<tr>
<td>SF-36 MH</td>
<td>$5.4 \pm 7.3, p = 0.070$</td>
<td>$-1.2 \pm 9.7, p = 0.600$</td>
<td>$-1.2 \pm 9.7, p = 0.600$</td>
</tr>
<tr>
<td>Steps/day</td>
<td>982.7 ± 2782.4, ( p = 0.200 )</td>
<td>764.6 ± 2370.3, ( p = 0.200 )</td>
<td>855.4 ± 2493.4, ( p = 0.100 )</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>RNB</td>
<td>−4.1 ± 25.9, ( p = 0.600 )</td>
<td>−16.3 ± 76.3, ( p = 0.400 )</td>
<td>−11.4 ± 60.7, ( p = 0.400 )</td>
</tr>
<tr>
<td>SDE</td>
<td>−331.1 ± 1008.7, ( p = 0.300 )</td>
<td>−4934.9 ± 18393.4, ( p = 0.300 )</td>
<td>−3093.4 ± 14248.9, ( p = 0.300 )</td>
</tr>
</tbody>
</table>

**Note:** Values are mean ± standard deviation. O2 = supplemental oxygen; BP = bodily pain; FSS = Fatigue Severity Scale; GH = general health; LCQ = Leicester Cough Questionnaire; MH = mental health; PF = physical functioning; RE = role emotional; RNB = road network buffer; RP = role physical; SDE = standard deviational ellipse; SF = social functioning; SF-36 = Medical Outcomes Study Short-form 36-item Questionnaire; UCSD = University of California San Diego Shortness of Breath Questionnaire; VT = vitality.

**E.1. Results for Aim 3—to identify primary supporters’ and prescribers’ expectations and perceptions of O2, and for patients, their expectations and perceptions of O2 before and after it is prescribed**

**E.1.a.** To understand how patients viewed O2 before and after starting it, we conducted serial interviews (at enrollment, T1, T2, and T3) with 5 subjects. Subjects had formulated (before O2 was prescribed) and realized (after O2 was prescribed) expectations about the benefits and hardships associated with O2 (Table 5). All 5 expected O2 to help with symptoms, and 4 of the 5 derived the benefit they expected. The hardships associated with O2 use included cumbersome equipment and social stigma attached to being seen with a cannula. Although all 5 subjects had a pulse oximeter, they were not instructed on its use, and self-reported desaturations were frequent.

We also interviewed 20 informal caregivers (ICs) of pulmonary fibrosis patients who had been using O2 during the day for at least 8 months to better understand the following: (1) how having O2 in the home affected other members of the household/family; (2) relationships between patient loved one (PLO) and caregiver; and (3) nonpatient views on O2 as helping or holding back their PF PLO. Their baseline characteristics are found in Table 6. **IC’s initial reactions to PLOs being prescribed O2.** Most ICs viewed their PLOs being prescribed O2 in a negative light. Reflecting back, many ICs recalled themselves being “devastated” or “shocked”—it was a time when “everything change[d]” for them and their PLO. One IC said, “[N]either of us ever thought [O2] would be part of our daily lives, and it felt like a really big change in things.” The wife of a patient who had been using O2 for 3
years recalled the first time O₂ was delivered to their home as “one of our most depressing
days.” Most other ICs saw the prescribing of O₂ to their PLO as “stressful,” adding an
“emotional toll” and “constant worry” for them. Suddenly, ICs found themselves worried
about things like a power outage (a common theme) or running out of O₂ when they were
away from home.
Table 5. Hopes/Expectations and Reality of Benefits of Using O₂ During the Daytime

<table>
<thead>
<tr>
<th>Subject</th>
<th>Enrollment</th>
<th>Just prior to O₂</th>
<th>1 month later</th>
<th>9-12 mos later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, 57 years old, IPF</td>
<td>Now, I have to...just walking across the house...I have to stop and rest. I'm just hoping that I can actually do something. Just now the doctor's concerned of what damage it has done to my heart, because I have gone down so far. So, that has me concerned. So, I'm hoping that eliminates that problem. My mobility mainly...better...I don't know. I'm at a point where I'm hoping I can exercise more and just feel healthier, I guess.</td>
<td>Not having to stop every time when you're out of breath...that's the hardest thing for me, the fact that I have to slow down and lie let other people do things for me. I don't like that. So, I'm hoping that will be a benefit for me. My mobility. My freedom...just mainly my mobility, because I'm not doing very much now. Go back to water aerobics. I'm planning on having my tank right beside me.</td>
<td>I feel better. I get a cough often, and when I start coughing, it's better to have the oxygen. I have more energy. I can actually walk across the house. Before, I actually wasn't doing much, not going anywhere, not even grocery shopping. I got my freedom back. It just gave me that feeling that I can accomplish something.</td>
<td>I do my housework now. I did pulmonary rehab last fall, and now it's getting to the point where I can do. Ans so I still will walk—I just finished with it, but now I have a club, and I've been walking every day on the treadmill. And before, I wouldn't even have dreamed of doing that. I wouldn't even have tried to do it.</td>
</tr>
<tr>
<td>Male, 67 years old, IPF</td>
<td>I feel like it would expand my ability to do more of the things that I want to do.</td>
<td>using oxygen, I hope, um, to be more physically active, um, able to do things that um, as I look back, I've, um, um stopped doing or done considerably less, or and were hesitant about...um, so I think it's going to bring a fullness, a richness, um, that has been declining, um, for a period of time.</td>
<td>I'm able to do more things out by the house. You know, I'm able to, to exercise now, which is something that I, I wasn't able to do before...I feel like I'm, um, getting stronger and, um, uh, more stamina.</td>
<td>Well, it certainly has expanded my ability to do the things I want to do. I am more comfortable pushing what might be the limits of my breathing ability...um, and knowing that there is, um, some relief available other than just trying to huff your way through it.</td>
</tr>
<tr>
<td>Male, 70 years old, IPF</td>
<td>It would probably help my coughing. Oh, I would hope to gain a better quality of life. More...more mobility...to be able to do more things, you know, that I can't do right now.</td>
<td>I'll be able to, uh, do more of the things that I went to do and probably feel less tired...I'll have a quality of life that is not there right now, so I'm confident oxygen will increase my quality of life. ...do [things] without getting tired and, you know, having everybody look at me and say why is this guy panting?</td>
<td>I've been able to do things that normally would have been really tiring for me and exhausting, so it's improved my quality of life from what it was a couple months ago. It makes you feel refreshed. Uh, without oxygen, I was coughing a lot and, uh, now, I don't have that added stress of coughing all the time like I was before.</td>
<td>Well, I can do more, but not as much as I used to before. But I can get along on my day to day routine.</td>
</tr>
<tr>
<td>Female, 53 years old, CHF</td>
<td>...my assumptions are that if I was on oxygen, I would be able to do those things (e.g., walking out of a play) and not need to stop and rest. ...on a daily basis, there would be things that I would—and would be easier for me to do. Um, you know, things around the house, um yard work, things like that that I tend not to do because I know it—it is too difficult for me.</td>
<td>Well, I would hope it that it makes things easier to do...and not get tired so quickly. ...the biggest benefit, I think, for me, is that it would increase my um, uh, stamina and energy level. Hopefully, it will help extend my life.</td>
<td>...it provides more oxygen to my body, so I know that...but from a...actual benefit for me personally, like, do I feel like I want to go run—a a marathon or you know, go for a hike? I don't. I don't notice any, um, any differences...any benefits.</td>
<td>Um, honestly, I think one of the benefits is it's made me more sympathetic to other people who might have medical conditions.</td>
</tr>
<tr>
<td>Female, 76 years old, IPF</td>
<td>If it gets to the point where I need oxygen, that will help me to go ahead and do some of the chores I do around here, you know. Making the bed, doing the laundry... Well, hopefully, it would, you know, maintain at least the level of exercise that I have now, maintain, you know, my independence being able to go out.</td>
<td>Well, hopefully, I will continue to live a little longer...I hope to—to live a little longer by using supplemental oxygen.</td>
<td>I don't think honestly I'll be doing a lot more. It just maintains my daily activities really. I probably don't get as tired if I'm using the oxygen, you know, like for shopping. I used to get—wear myself down and get weak, if I'm not using the oxygen and I'm walking too far.</td>
<td>Well, there are things that I would be unable to do if I did not have that option [of using oxygen].</td>
</tr>
</tbody>
</table>
Table 6. Demographics of Informal Caregivers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>17/3</td>
</tr>
<tr>
<td>Age (range) in years</td>
<td>62.2 ± 9.7 (44-76)</td>
</tr>
<tr>
<td>State of residence</td>
<td>2 California; 4 Colorado; 2 Washington; and 1 each from Florida, Georgia, Idaho, Illinois, Maryland, Minnesota, Nebraska, New Mexico, New York, Ohio, Pennsylvania, Utah</td>
</tr>
<tr>
<td>Duration of O2 use (years)</td>
<td>3.9 ± 3.0</td>
</tr>
<tr>
<td>O2 set-up</td>
<td>In-house 19 home concentrators, 1 liquid oxygen 9 compressed gas only</td>
</tr>
<tr>
<td></td>
<td>Portable 3 liquid oxygen only 4 POC only</td>
</tr>
<tr>
<td></td>
<td>3 compressed gas and POC available 1 liquid oxygen and POC available</td>
</tr>
</tbody>
</table>

Note: O2 = supplemental oxygen; POC = portable oxygen concentrator.

Some felt “mad” at the disease, or “sad” or “bad” for their PLO because “it [O2] is part of his life now.” The daughter of a patient with PF who had been using O2 for 2 years recalled how “vulnerable” needing O2 made her mother seem to her. Although some ICs mentioned they were initially scared about having O2 in the house or car (because it’s flammable), for many, fear arose from “what it [being prescribed O2] meant in terms of his lung status”—it was an “in your face” reminder that “meant he was sick”; an ever-present “thing that just sits there all the time . . . her need for oxygen.” A few patients were started on O2 at the visit where they were also given the diagnosis of pulmonary fibrosis; this was a particularly “overwhelming” circumstance.

ICs’ perceptions of specific benefits of O2 for their PLOs. The general theme that emerged was that O2 made PLOs “feel better.” The comment from a husband of a patient on O2 for 3 years captured the theme best: “[W]ith the oxygen, it makes it better. Not perfect, but better.” ICs perceived O2 as allowing PLOs to be more active— “[she] wouldn’t be able to do anything [without oxygen]”—even to exercise and participate in activities that they once enjoyed but had given up before starting to use O2 (e.g., play golf). ICs also noted improvements in fatigue (“[she] doesn’t get as tired as quick”; “[he can] function without . . . feeling totally exhausted all the time”; “[he’s] not . . . falling asleep all the time”) and energy (“[O2] helps him feel a little more energetic”; “[O2] helped [it] seems like a little bit with his energy”). To ICs, PLOs appeared “more comfortable” when using their O2: They were visibly less short of breath and
had “pink cheeks” or “color in his face”—things they didn’t have before O2. In 2 cases, PF progression seemed to outpace the benefits that O2 might have conferred, and ICs perceived no improvements at all in their PLOs.

ICs’ perceptions of adverse effects of O2 for their PLOs. Although most ICs perceived benefits from O2 for their PLOs, they also saw it as limiting. PLOs were better off using O2, but they still had to “drag” or “lug” their O2 around with them. As the daughter of a female patient on O2 for 2 years explained, “it limits her . . . in where she can go, how long she can go, how far she can go.” Inside, patients were “tied,” “tethered,” or on a “leash,” which was a source of frustration and irritation for them. Cannulas frequently got stuck on something (e.g., furniture) and in a couple cases did not allow patients to reach certain areas in their house. Limitations extended outside the home as well, some because of the equipment and some the PLOs self-imposed. The wife of a patient on O2 for 18 months recalled a time when her husband was using a portable oxygen concentrator and their 3-year-old granddaughter “came up to him and she goes, ‘Pops, run with me!’ and he says, ‘Well, I can’t. . . . I have to have this [O2],’ and she goes, ‘Well, take it out and run with me!’” Outside the home, O2 made PLOs self-conscious (“sometimes people notice it [O2] and that might make him feel uncomfortable”), even to the point of not using it when needed: The wife of 1 patient commented, “He would not . . . be caught dead walking around [grocery store name] hauling a tank behind him.” O2 was a visible reminder to PLOs that they were sick; it made them “feel very frail and fragile.” Some PLOs believed their O2 delivery device was too noisy, so they avoided public places (e.g., movie theater) because they did not want to disturb other people. This usually meant ICs did not go, either.

Life changes for ICs. For most ICs, the addition of O2 in the house meant a few extra physical duties related to O2, including filling and/or carrying tanks, loading tanks into the car prior to leaving home, helping care for and clean equipment, and making sure items (e.g., O2 tanks) were ordered on time. Typically, duties were met without resistance, but 1 daughter described being “annoyed” at having to carry tanks for her patient mother (she never mentioned this to her mother), and 1 husband IC had difficulty carrying tanks because his balance was poor. For some ICs, including the husband of a patient who rapidly declined and
died after less than a year on O₂, duties were more involved: “It was a 24/7 job that consumed all my time. . . . I didn’t think about doing anything but maintaining, maintaining her oxygen.” The wife of a patient who had been on O₂ for 9 years summed up her experience thusly: “[Y]ou have to work everything in your life around the oxygen . . . it’s changed [my] life a lot, but definitely not for the better.”

ICs were relegated to literally (and figuratively, in many cases) doing the heavy lifting around the house because they did not want their PLOs to overexert or “exert extra energy.” And they fell into the role easily, as 1 IC mentioned: “I mean, it’s my job, you know?” A handful of ICs commented that they had been ill earlier in life and their PLOs took care of them, so it was their turn to take care of their PLOs.

O₂ caused IC–PLO pairs to change their lifestyles as couples: O₂ “slowed [both of us] down.” It forced the couples to move at a slower pace but also put unwanted limitations on several aspects of their lives. Spontaneity was no longer an option. Some ICs were silently “frustrated” because their PLOs could not “keep up,” but most had accepted the change. Most pairs, even those in which the PLOs used a portable oxygen concentrator, traveled far less (or not at all) since O₂ was started. For pairs in which PLOs required high-flow systems (i.e., at least 6 liters per minute of continuous flow), out-of-home activities were particularly constrained. The wife of a patient mentioned how she and her husband brought their dog of 11 years to the veterinarian’s office to be euthanized; they had to leave before the dog was put down because the patient’s oxygen was going to run out.

Leaving home took some extra time and planning—greater oxygen needs required more thought and preparation. “You can’t just fly out the door,” said the wife of a patient on O₂ for 18 months. Another IC recalled, “Everything was an expedition if we were going out.” Before leaving, they had to consider where they had to go, how long it would take, and “figure out what your [O₂] needs are going to be while you’re gone.” Most patients who used a Portable Oxygen Concentrator (POC) took back-up tanks of compressed gas in case the POC malfunctioned or the battery ran out. Three ICs said leaving home with a patient on O₂
reminded them of running errands when they had a baby (packing up diapers, bottles, etc.).

ICs’ homes were different after O2 was brought in. Concentrators were noisy, and it was annoying to have “cords [cannulas]” throughout the house that got tangled and curled up and were “always in the way.” Several ICs referred to cannulas in the home as a “tripping hazard.” In the first few weeks after O2 was prescribed, some ICs worried about the O2 (feared it would “explode”; were concerned because it was “highly flammable”) or power outages, but these concerns did not persist for long.

Adapting and accepting. When O2 was first prescribed, ICs and PLOs found themselves attempting to simultaneously digest what the need for O2 was telling them about the disease’s status (it was serious); educate themselves about some of the practical issues about O2, like learning what they needed and figuring out how to navigate the system to get what they needed in a timely fashion; and begin the process of “embracing the new normal.” For the patient, ICs saw how O2 induced great uncertainty, representing a “major change in my health status and [left them questioning] how I’m going to be living my life.” Over time, ICs accepted and adapted to the change and developed strategies for living. But getting to this point took time and effort. ICs used several methods to cope, adapt, and “deal with whatever need[ed] to be dealt with.” A wife of a patient on O2 for 2 years commented, “It was hard at first, just getting used to it, just the adjustment period at first.” Although only 1 IC mentioned using a “team effort,” it was clear that ICs and PLOs worked together, relying on each other to adapt to the new life with O2:IC–PLO pairs had to find balance in their lives—it was impossible for them to completely disregard the presence of O2, but they realized they desperately wanted and needed to continue to live.

The leash and limitations never left; couples just learned to “not fight it,” “relax into it,” and deal better emotionally and physically with the limitations: “He has to live too, so it’s balancing things out.” Couples felt a strong motivation to maintain some sense of normalcy in their lives by getting out, remaining socially active, “enjoy[ing] every day,” and “enjoy[ing] life as much as you can.” A wife of a patient on O2 for 3 years said, “Well, we don’t ever think of it
as good or bad; it just is what it is and you deal with it.” Putting forth a conscious effort to maintain a positive outlook was vital. Some mentioned that keeping a sense of humor, laughing, and joking were important as they moved toward acceptance of O2. Acceptance required “chang[ing] the way you do things” or “taking baby steps” to prove to themselves that they could still live their lives as a couple. They—often subconsciously—adjusted routines around the home. One IC mentioned she did the cooking and her PLO did the preparing (e.g., chopping, mixing) of food. Ultimately, most ICs found that dealing with O2 eventually became “so routine and so much a part . . . of the way we live now” and although “it’s certainly different and somewhat cumbersome . . . it’s doable.” ICs of patients with progressive pulmonary fibrosis were required to reaccept and readjust as the PF worsened and oxygen needs increased. Increasing O2 requirements added physical limitations for PLOs, various duties and restrictions in social activities for ICs, and the need to conform to the new normal for them as couples. As 1 IC stated, “Before he was on it [O2] 24/7, it didn’t seem like a big deal.” ICs of patients who used O2 24/7 but whose needs could be met with pulsed flow still faced challenges, complexities, and constraints, but seemingly not as many as ICs of patients who required continuous high-flow O2. For most ICs, the prospect of their PLO’s health worsening was ever looming, as these quotes from ICs depict: “You’re kind of looking down the road . . . how long will we be able to continue to [use a pulsed flow regulator], and so . . . it changes your lifestyle, that’s for sure”; “When I think about people who have much higher O2 needs than he does, that the chance of them leaving the house would be slim . . . that’s a little frightening.”

F. DISCUSSION
In this mixed methods research program, we collected a cache of qualitative and quantitative data from patients with pulmonary fibrosis to advance understanding of the benefits and hardships associated with O2 use. To our knowledge, this is the first study to assess O2-associated change over time for a range of outcomes in patients with PF. The quantitative data confirmed variability in the response to O2—both the benefits and the hardships. Even in the underpowered longitudinal study, we observed how O2 was associated
with improvements in certain symptoms (fatigue) and domains of functioning (social functioning). In many cases, O2 conferred no benefits, but if the disease remained stable, despite O2, outcomes did not worsen. In other cases, disease progression outpaced the benefits O2 could deliver, thus magnifying the hardships of O2.

The rich qualitative data generated give a granular, personal view of the myriad ways O2 affects PF patients. These data also reveal that few, if any, patients use O2 exactly as prescribed and that O2 prescribers’ goal of having their patients maintain normoxia at all times may be unrealistic. Patients’ and caregivers’ perceptions show how big of a deal O2 is—a life-changer for both. Trying to manage O2 (particularly early on) frequently left patients and their caregivers feeling ignorant and overwhelmed with nowhere to turn.

Perhaps the greatest benefit of the data from this research program is that they shed light on a better path forward: Patients and their loved ones would benefit from more readily available, trustworthy, lay-friendly education about O2; O2 prescribers and suppliers could ease the transition to O2 through more detailed conversations about what to expect from O2 (i.e., the possible benefits and hardships patients and their loved ones might encounter); and reliable support resources that O2 users can turn to in times of need should be developed.

F.1. Decisional context. In isolation, the results of the various facets of this research program will not (and are not meant to) convince PF patients that O2 is a magic bullet against their disease. Nor can the results speak to whether O2 can prevent or forestall the onset of conditions associated with chronic hypoxemia, like pulmonary hypertension and cognitive dysfunction. But, in aggregate, they can help guide PF patients and their practitioners through informed decision making about O2. In the following paragraphs, we use PCORI’s 4 key questions for patient-centered research to discuss the specific ways this research advances the field.

• “Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?” The longitudinal study did not have adequate power to allow us to make definitive conclusions about the benefits of O2 at the group level. We needed 83
subjects to have 80% power to detect a 5-point difference in dyspnea (UCSD score) from immediately prior to starting O₂ to 1 month later. We had pre–post UCSD data for 19 subjects, giving us only 25% power to detect this difference. However, 6 of those 19 had a 5-point or greater improvement in dyspnea (see Figure 3, and 7 had a greater-than-10-point improvement in fatigue after O₂ was started.

Figure 3:

In contrast to our hypothesis, O₂ did not lead to increased day-to-day activity (as measured by triaxial accelerometer). It may be that the improved oxygenation that comes
with O₂ use (something we did not measure in the longitudinal study) may be offset (or overshadowed) by the added physical weight of the O₂ delivery apparatus. Additional research is needed to clarify this and identify ways to mitigate it if true.

Because this was a real-world study, we had no control over O₂. Thus, it is unknown whether O₂ was prescribed or used as scientific rationale would suggest is best (i.e., to maintain peripheral oxygen saturation > 89% at all times). Additional research is needed to settle this issue.

Over the first year after O₂ was started, subjects with IPF—the most common form of PF and, unfortunately, the most lethal—were the ones most likely to have their O₂ needs escalate (e.g., needed O₂ at rest). That progression was associated with significantly worse physical functioning and trends toward worsening in several other domains. In contrast, physical functioning did not worsen among subjects whose O₂ needs remained stable during the first year. The qualitative data suggest PF patients (and their loved ones) adapt reasonably well to O₂; the frustration and worsening outcomes lie in the need to constantly readapt as the disease progresses. For IPF, there are now 2 FDA-approved antifibrotic drugs that slow disease progression (as defined by decreasing the negative slope for forced vital capacity over 52 weeks). As more effective drug therapies emerge (e.g., those that halt the disease), we can anticipate fewer cases in which disease progression outstrips the ability of O₂ to maintain how PF patients feel and function.

So, in response to the question posed, PF patients who decide to start using O₂ have a decent chance of realizing improvements in various domains, particularly fatigue—one of the most troublesome but underappreciated symptoms of PF. But PF patients must also recognize—and the medical community should work to communicate more clearly—that O₂ will likely change things for them, their loved ones, and their home lives.

- “What are my options and what are the potential benefits and harms of those options?”

Currently, O₂ is typically recommended to patients with PF if oxygen saturation falls below 89%, but patients can (and some do) refuse to use it at all—predominantly because of the
stigma they perceive is attached to using O2 in public. To our knowledge, no harms are associated with O2 use. Aside from the potential benefits described above, the theoretical benefits of preventing long-term complications of hypoxemia remain. One of the subjects we interviewed before and after starting O2 captured the sentiment most subjects had about balancing the hardships and the benefits: “The tradeoff is well worth it.”

Subjects and caregivers spoke loud and clear about the challenges of using O2. Although not physically harmful, the use of O2 brought physical challenges for patients (who had to carry delivery devices) and their caregivers who chose—or were forced by circumstance—to embrace more physically active roles around the home. The use of O2 also strained the patient–caregiver relationship and had untoward mental health effects on some patients: They felt stigmatized and did not like how wearing the cannula created a constant reminder of their disease.

• “What can I do to improve the outcomes that are most important to me?” By enlisting the input of patients in all facets of this research, including the selection of outcome metrics, this study was guaranteed to assess outcomes important to PF patients. Although more research is needed, and the longitudinal study was underpowered, its data, in aggregate, suggest O2 offers PF patients the possibility to feel and function better.

On slope analysis—which, for multiple reasons, many would argue is a more sophisticated and robust method for analyzing the type of data we collected in the longitudinal study—O2 was associated with improvement in fatigue. For many PF patients, fatigue is the most intrusive, bothersome symptom.9

A key point that PF patients and O2 prescribers must keep in mind is that the manifestations of disease progression can (and often do) overshadow the benefits that O2 might confer. When PF progresses, and oxygen desaturation becomes frequent and/or profound, O2 needs rise. As flow requirements increase, portable oxygen concentrator batteries and compressed gas tanks run out sooner. Patients and loved ones who are accustomed to traveling or being out and about become acutely aware of the constraints.
And the blame is often placed on the O₂. True, longer-lasting POC batteries and alternative delivery devices would help matters, but the root of the problem is the disease, not the O₂. Getting better at halting disease progression—an incredibly lofty goal—would go a long way toward solving many problems related to O₂ use.

- “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?” Concerning O₂ in PF, prescribers must discuss realistic expectations and potential hardships and the medical community must have adequate educational and support resources for PF patients contemplating or starting O₂.

F.2. The study results in context. The published literature on O₂ for PF is extremely limited. A 2016 Cochrane review identified 3 studies (enrolling a total of 98 subjects, all with IPF) that met its inclusion criteria. All studies assessed the effect of O₂ on exercise capacity. The Cochrane review identified no study in which investigators examined symptoms or quality of life over the short or long term. To our knowledge, ours is the first study to do so.

In a recently published, landmark study of O₂ in patients with COPD who had moderate oxygen desaturation at rest or with exercise (the LOTT trial), the investigators found that O₂ did not prolong survival or provide durable improvements in measures of submaximal exercise, symptoms, or quality of life. However, these results must not be extrapolated to patients with PF, who typically desaturate more rapidly and more profoundly than COPD patients.

Prescribing O₂ for a PF patient only to maintain SpO₂ above 88% for 2 minutes of walking—as was the protocol in the landmark LOTT trial—is an unlikely safeguard against profound desaturation in ensuing minutes.

In previously published work, our group coined the term “shrinking world syndrome” to describe the effects of O₂ on PF patients and their caregivers. The results from the current study build on that work and highlight how many issues connected with O₂ use might be improved.

F.3. Implementation of study results. Not applicable.
F.4. **Generalizability.** One of the strengths of this research program is that it enrolled patients from across the United States. Inclusion criteria were left broad to enroll patients across the country and along the continuum of disease severity. Because PF is a relatively rare condition, most subjects were recruited from the centers of excellence where they receive their care. In the end, some degree of tertiary referral bias may be present, but based on prior observational studies and drug trials, the cohort is likely representative of the PF population at large.15,16,34-40

F.5. **Subpopulation considerations.** Given the small number of subjects, subpopulation analyses should be considered exploratory. Recognizing this, women’s fatigue scores improved to a statistically significant degree in response to O2 initiation, whereas men’s fatigue scores did not change, and the difference in fatigue change scores between women and men was statistically significant. Despite a decline of more than 1000 steps per day, younger subjects (those under 65 years) experienced improvements in certain quality of life domains.

F.6. **Study limitations.** There are limitations to the inferences that may be drawn from the results of this study. The primary cause of those limitations is subject number. To account for death and dropout, we enrolled 300 subjects, aiming to observe 83 whose physicians would prescribe O2 for use during the day. Fortunately for the patients, but unfortunately for us, the actual number was far lower, thus significantly limiting the power of our analyses. Among subjects with data at any time point, only 19 had questionnaire data available for the primary analysis and for secondary analyses using t tests. Thirteen subjects had T2 but not T1 data (i.e., we had data from 1 month after O2 was started but not from immediately prior to starting O2). We attempted to keep track of patients’ clinic visits, so we could check whether O2 had been prescribed (or was being contemplated). Unfortunately, in these subjects, O2 was started without our knowledge. We elected to keep them in the study, knowing they would be deleted case-wise from t test analysis for the primary endpoint but could contribute data to the secondary slope analyses. All 43 subjects who were prescribed O2 contributed data for at least 1 time point for the slope analyses.

   Based on clinical experience, scientific rationale, and a limited supply of published
data, we believe the benefits of O₂ are best realized when it is used to maintain a peripheral oxygen saturation > 89%. We had no control over how O₂ was prescribed or what, if anything, subjects were told about how to use it (e.g., whether to use a pulse oximeter to adjust flow). Nor did we possess the capability to assess whether O₂ was used as prescribed. This was not a study of “perfect use” O₂—if there is such a thing. A meter/detector that tracks O₂ flow into the nose combined with an apparatus capable of real-time flow adjustments to maintain a prespecified SpO₂ goal would be required.

By design, the longitudinal study was unblinded: Subjects knew they started O₂, and they also knew when they were wearing accelerometers and GPS units. Knowing about either or both elements could have influenced results. The pre–post design allows for subjects to serve as their own controls, so bias related to the wearables was less of a concern. However, we had no formal control group per se.

We did not track drug-related side effects during the study. In October 2014, 2 drugs were approved by the FDA to treat IPF. Both have significant potential side effects, the presence of which could have negatively affected certain symptoms (i.e., fatigue) and/or quality of life. Seven subjects with IPF were taking 1 of the 2 FDA-approved antifibrotic drugs, but whether and how those drugs affected outcomes is unknown. Likewise, subjects with non-IPF pulmonary fibrosis may have been receiving treatment with potent, immunosuppressive/modulatory drugs that, like the antifibrotics, have potential side effects.

F.7. Future research. Future research should seek to discover ways to make O₂ easier for patients to use. A delivery device that integrates real-time, biometric data and automatically adjusts to maintain a prespecified heart rate or SpO₂ target should be developed and tested, as should remote controls for regulators and concentrators.

G. CONCLUSIONS

In this pioneering research effort, we observed that, among patients with PF, O₂
prescribed for use during the day was not associated with improved dyspnea, cough, quality of life, day-to-day physical activity, or activity space. However, on slope analysis, O₂ was found to significantly improve 1 of the most distressing symptoms of PF—fatigue. Within the cohort were subjects for whom O₂ improved dyspnea and the other patient-reported outcomes, but the small sample size limited our ability to confidently identify predictors.

Subjects with IPF appeared to derive the least benefit from O₂; that likely stems from the progressive nature of their disease. Most subjects with IPF were started on O₂ only with exertion, but over the course of 9 to 12 months, they required it at rest as well. The qualitative data we collected reinforces that the leap from needing O₂ only with exertion to needing it at rest is quite large.

The qualitative data also remind us that O₂ affects patients’ loved ones and changes the entire home environment—for most PF patients, O₂ is a very big deal. Prescribers should better manage patients’ expectations about O₂; it will not alleviate dyspnea, but it may help considerably, and it has the potential to positively affect several other domains important to PF patients.

For the individual patient (and his or her caregiver), the decision of whether to use O₂ when a prescriber deems it necessary should be made in partnership with the prescriber and after a thoughtful discussion of the potential benefits and hardships. The results of this study tell us that the benefits of O₂ may outweigh the hardships, but not for some patients. Patients could consider a trial of O₂ to make the determination. As a system, improvements could come through better educational and support resources. Future research should focus on whether strict adherence to maintaining normoxia leads to improved outcomes.
H. REFERENCES


4. Submitted: Baseline characteristics and novel outcome-assessment-tool data for a cohort of patients with pulmonary fibrosis. Elisabeth Dowling Root, PhD; Bridget Graney, MD; Susan Baird; Tara Charney, MPH; Kaitlin Fier, MPH; Marjorie Korn; Mark McCormick; David Sprunger, MD; Thomas Vierzba; Frederick S. Wamboldt, MD; Jeffrey J. Swigris, DO, MS


7. Submitted: Tracking dyspnea up to supplemental oxygen prescription among patients with pulmonary fibrosis. my L. Olson, MD; Bridget Graney, MD, Susan Baird, Tara Churney, MPH, Kaitlin Fier, MPH, Marjorie Korn, Mark McCormick, David Sprunger, MD, Thomas Vierzba, Frederick S. Wamboldt, MD, Jeffrey J. Swigris, DO, MS
1.1 Purpose

As the name states, contact registries store contact information from groups of reasonably well-characterized patients who are interested in being informed about ongoing or future research opportunities. Pulmonary fibrosis (PF) is a condition for which effective therapies have remained elusive, making drug trials and interventional research studies a mainstay in the PF arena over the past decade and for the foreseeable future. A PF Contact Registry will be a conduit to collect, analyze, and disseminate deidentified, group-level data on the clinical phenotypes of PF patients and will house contact information from patients who wish to be informed about research opportunities for which they may qualify. Data contained in the registry will help inform research hypotheses and guide investigators as they develop research protocols by providing them with numbers of potential subjects who meet particular inclusion/exclusion criteria. The development of a PF Contact Registry will help study this disabling disease.

1.2 Background and Significance

Pulmonary fibrosis is a horrific, irreversible disease. While shortening patients’ survival, PF insinuates itself into their lives, leaving them breathless and unable to perform physical activities.\(^1\) Although understanding of the pathogenesis of PF remains murky, what is clear is that increasing age is a risk factor for PF.\(^2-4\) Because the US population is aging, PF will be an expanding health problem for the foreseeable future. Given its estimated US prevalence of about 50 per 100 000 persons,\(^5\) PF may not be a rampant burden on the US health care system, but it absolutely and unrelentingly weighs down patients. Patients with PF suffer. They have poor quality of life,\(^6-7\) and as the disease progresses, their ability to perform physical activities dwindles. Many are forced to stop working, and 50% of PF patients face death within 3 years of diagnosis. There are no Federal Drug Administration–approved drugs for PF and, to date, no therapy (medicinal or nonmedicinal) has been indisputably proved to benefit PF patients. Further research is needed to identify new drug treatments for PF, to examine the benefits of existing therapies such as supplemental oxygen, and to improve the quality of life of PF patients and their loved ones.

Having access to certain basic data (e.g., demographic, disease status, and contact information) from patients who wish to be contacted about research opportunities is vital to conducting all kinds of PF research studies, particularly those that require large, demographically diverse samples. A contact registry gives underserved and hard-to-reach populations (e.g., rural, minority, or low socioeconomic status)—and patients unwilling or unable to travel to a PF center of excellence—an opportunity to move the PF field by participating in research.
As more and more Americans, including those of underserved populations, are “plugged in” to the internet, a web-based contact registry will afford more PF patients than ever the chance to seek out and participate in groundbreaking research. According to the Pew Internet & American Life Project, 81% of American adults use the internet. Moreover, at least half of American seniors aged 65 and older report internet use, and 88% of the 79% of caregivers who have access to the internet look online for health information on behalf of someone else. Furthermore, caregivers are more likely than non-caregivers of the same age to use the internet, particularly to get and share health information. Overall, a 2012 poll showed that 72% of all adult internet users reported looking online for health-related information within the previous year of being surveyed. With the internet-savvy population growing (both in numbers and with age), web-based contact registries are more than justified, especially in the field of chronic disease.

1.3 Aims

Specific Aim 1:
Create and maintain a nationwide registry of up to 50,000 people, including PF patients or people who are primary supporters of PF patients, who are willing to be contacted when opportunities arise for participation in clinical research and/or with other forms for data dissemination (i.e., with a biannual newsletter detailing study results or advances in PF).

Specific Aim 2:
Use the registry as a source of potential subjects for the study “Observing the Effects of Supplemental Oxygen on Patients With Pulmonary Fibrosis.”

Specific Aim 3:
Use the registry as a source of possible subjects for future clinical research studies that require people with PF or their primary supporters.

1.4 Design and Methodology

Who will be in the registry
Anyone at least 18 years of age who either (1) has been diagnosed with PF or (2) is a primary supporter or caregiver of someone living with PF is eligible to enroll in the registry.

How the registry works
Patients with PF consent to be enrolled in the registry and may consent to be contacted by registry personnel about opportunities for them to participate in research studies. Some of these studies (e.g., “Observing the Effects of Supplemental Oxygen on Patients With Pulmonary Fibrosis”) will be conducted by Dr. Swigris and his research team—these studies will be considered registry-affiliated. Registry participants are free to enroll in any study they
wish—whether registry affiliated or conducted by investigators not affiliated with the registry (that is, non–registry affiliated studies). It is assumed the investigators conducting those studies will adhere to regulations governing the protection of human subjects in research. Consider a hypothetical example: An investigator in Michigan is conducting a study of the effects of oral honey on PF-related cough and would like registry participants to consider enrollment. The investigator would petition the registry and, if approved by the Registry Oversight Committee, registry personnel would contact potentially eligible registry participants to inform them of the study. The participants would then decide whether to contact the investigator in Michigan to be considered for enrollment. The investigator in Michigan would be responsible for discussing the study with any potential subject, obtaining informed consent, and conducting the study. All of these actions fall outside the purview of the registry or its personnel.

How subjects will enroll in the registry
Eligible participants must fill out an intake questionnaire/consent form. Contact information provided to receive a questionnaire is not stored by the registry data coordinating center (DCC) or by the study coordinator. Subjects have 4 options to obtain the intake questionnaire, complete it, and submit it:

- Complete the questionnaire/consent form and submit it online at http://www.pfresearch.org/p3f-Registry/Registry.htm. Participants will be encouraged to print a copy for their records.
- Enter a mailing address onto an online form (http://www.pfresearch.org/p3f-Registry/HardCopy.htm) and have a hard copy mailed to the subject. Once a signed questionnaire/consent has been sent back to the study coordinator, a copy will be made and mailed back to the subject for his or her records.
- Download a PDF file of the questionnaire/consent form from http://pfresearch.org/p3f-Registry/downloadform.htm and mail the completed questionnaire to the study coordinator, who will then hand it off to the DCC at National Jewish Health. Subjects will be encouraged to print a copy for their records.
- Call the study coordinator at a toll-free number (1-855-609-0010) and have him or her mail a hard copy of the questionnaire/consent form to the subject. Once a signed questionnaire/consent has been sent back to the study coordinator, a copy will be made and mailed back to the subject for his or her records.

Registry intake questionnaire/consent form
The information collected from registry participants will be submitted on the registry intake questionnaire/consent form. The following information will be included:

- Informed consent
- Demographics
- Cause of PF (if applicable)
- Medical symptoms related to PF (if applicable)
- Diagnostic tests
- Supplemental oxygen use
To stimulate study enrollment and discourage attrition rates, a biannual newsletter will be sent out to registry participants electronically. On the intake questionnaire, registrants will be able to give an email address where they wish to receive the newsletter. If they do not provide their email address, they will not receive the newsletter. With this newsletter, a request will be made to participants to update their contact information. Contact information for study personnel will be included in the newsletter. The newsletter will contain information relevant to PF, including research updates/results, information on interventions, resources, etc.

**Subject discontinuation**

Subjects’ participation in the registry is voluntary. Any subject may decline or discontinue participation in the registry at any time. Requests for discontinuation and removal of data from the registry must be made by phone or in writing. The registry will notify the DCC immediately of a subject’s withdrawal from the registry, and the DCC will delete all data related to the subject.

If a subject requests information about a particular non–registry affiliated study, enrolls in that study, and then later wishes to withdraw from that study, he or she must contact the study investigator and request to have his or her data removed from the study database. The registry and its personnel are not responsible for removing data collected in any non–registry affiliated study.

**Receiving protected health information**

As a part of the intake questionnaire/consent form, enrolling participants with PF (recall, primary supporters/caregivers may enroll as well) will have the option of filling out a HIP-024 form, which will allow registry personnel to obtain certain diagnostic and physiologic data from the participant’s health care provider. The registry study coordinator will oversee the collection of data on date of diagnosis, symptom onset, pulmonary physiology, chest imaging studies, lung biopsy reports, and supplemental oxygen use. We will not request such data for primary supporter/caregiver registry participants. All data collected will be stored in the registry by the DCC.

### 1.5 Data Entry, Editing, and Storage

Data will be collected, processed, and stored by the DCC in the Biostatistics Department of National Jewish Health (NJH) in Denver, Colorado.

The registry questionnaires are processed by Cardiff TeleForm™ Verification software.
Forms that are submitted in paper format are faxed to a computer fax machine and converted into images. The software package includes character recognition, which attempts to convert handwriting into text. These images are verified by DCC staff, using the TeleForm software. If the interpreted text is incorrect, the verifier can type in corrections, based on visual inspection of the form. Forms that are submitted electronically, including the website HTML form and PDF, are processed by the TeleForm software without human verification. The TeleForm software exports the data directly into a Microsoft SQL 2005 database.

Data written on the registry intake questionnaires is self-reported and voluntary. The respondent must sign and date the first section of the questionnaire; if a signature and date are not provided, the questionnaire will not be accepted into the system, the individual will not be able to participate in the registry, and the record will be deleted immediately. Electronic questionnaires that lack an electronic signature and date will not be saved in the system. Print questionnaires that lack a signature and date will be shredded, and the respondent will be notified that he or she needs to fill out another questionnaire if he or she wishes to participate. In general, the respondent may leave questions blank. The DCC may contact respondents to correct data if questions are left blank or if conflicting data are recorded. A maximum of 2 attempts to correct the data may be made via telephone, email, or mailings. The DCC is responsible for restoring any lost data by manual entry from questionnaires, if needed.

1.6 Data Security

Information given by registry participants will be maintained in a secure storage as described below. Likewise, any data collected from the participant’s health care provider (assuming the participant has signed a HIP-024 form) will be entered into the electronic database, and the hard copy will be securely filed. Paper consent or questionnaire forms (or any other hard copies with identifying or potentially identifying information) will be stored in locked file cabinets in locked offices at NJH’s main campus. Images of electronically submitted forms are stored on a secure server for future reference if errors in the data are found and confirmation of accuracy is desired.

Access protection
Access to the registry database is granted to the director of the DCC, the principal investigator (PI), and the registry coordinators. The registry database will be kept on a secure server; security consists of physical security measures, software security protections, database backup protections, and policies to ensure authorized use of the database. Each registry coordinator and the PI will have an individual password to the registry database. Assigned passwords must never be disclosed to anyone other than the intended user. Password(s) will be disabled immediately when no longer needed by registry personnel. Only the database administrator has the access needed to change passwords.
Software security protections
The director of the DCC or his or her designee will have administrative control of the registry database. The registry will remain on a server on the secure NJH network behind the NJH firewalls. The server, firewalls, and database will each remain password protected at all times.

Web applications’ security
The DCC will develop a password-protected, limited-access website for the registry that is located at a secure https URL. By definition, https websites are secured using Secure Sockets Layer (SSL) or Transport Layer Security technology standards. SSL is used to encrypt data transmissions between the web server and a user’s computer. In addition, the DCC maintains a security certificate that authenticates the website that resides within NJH.

1.7 Data Release of Deidentified Information

Deidentified, group-level data can be given to researchers on written request to—and approval by—the Registry Oversight Committee. These data will not include any individual protected health information (PHI). They may be used by researchers to learn about a larger PF patient population. This information may also help inform possible research hypotheses, assist with the creation of therapeutic clinical trials, and more.

No queries about subject-specific data will be accepted from any source.

Researchers who are granted access to deidentified, group-level data by the Registry Oversight Committee will be required to take the following actions:

1) A confidentiality and nondisclosure agreement must be signed by both NJH and the recipient institution/entity.
2) Researchers must agree to delete study subjects when notified of withdrawal and comply with human subjects protection.
3) The study investigator must maintain an up-to-date address and telephone number with the registry coordinator. This will enable the registry coordinator to provide subjects with the researchers’ direct contact information.

After a study investigator receives approval from the oversight committee for receipt of deidentified, grouped data, the DCC will create a password-protected and locked Excel file of the selected data from the secure database. The password-protected and locked Excel file will be sent to the researchers from the DCC. It is the researchers’ responsibility to store the Excel file in a secure location.

1.8 Linkage to Other Future Clinical Research Studies
Researchers who would like to have registry subjects contacted concerning a research study will make a formal request by letter or email to the chair of the Registry Oversight Committee. This formal request for registry subject contact must include the following information:

a) A research protocol that demonstrates a scientifically valid research proposal with eligibility criteria and details of human subjects protection
b) Current curriculum vitae for the PI that documents relevant research and publications
c) Documentation of IRB approval at the research sites
d) Letter of institutional support from a division chair, program director, or office of sponsored research that indicates home institution approval of the use of space, PI time, and use of equipment or services

The chair may also request additional information, including the following:

a) Funding source(s)
b) Research support personnel’s qualifications
c) Anticipated outcomes
d) Researchers’ previously published work

Once a researcher has been granted approval by the Registry Oversight Committee, the study coordinator will contact registry participants about the opportunity to take part in the clinical research. This contact will be made via email, mail, or phone. Contact information for the researcher will be provided to registry participants, and it is the responsibility of the registry participants to establish contact with the researcher.

1.9 Monitoring and Quality Assurance

Registry Oversight Committee
The Registry Oversight Committee will oversee the implementation, maintenance, and use of the registry. The committee may meet in person or via teleconference as needed, to be determined by the registry director. The following are the 4 primary functions of the committee:

a) Review and maintain the Pulmonary Fibrosis Registry Policies and Procedures
b) Provide oversight for Registry Data Coordinating Center
c) Review and take actions based on the Data Coordinating Center’s reports
d) Review and make approval decisions on proposed clinical studies that would use registry data

Members of the committee

Jeffrey Swigris, DO, MS
Chair of the Registry Oversight Committee
Autoimmune Lung Center and Interstitial Lung Disease Program
Associate Professor of Medicine
1.10 Registry Reports

The DCC will provide reports to the Registry Oversight Committee 3 times a year. These reports will include the number of participants and their age (all subjects older than the age of 89 will be labeled as 90+), sex, and state of residence. None of these reports will include PHI.

A quarterly progress report on the status of the Data Coordinating Center will be emailed to the chair of the Registry Oversight Committee. The DCC and registry research staff will maintain an accurate and complete file of these reports. The frequency of this report can be decreased with concurrence of all parties. The Registry Data Center director will remain available to discuss any concerns of the Registry Oversight Committee.
2.1 Inclusion Criteria

Anyone who self-reports a diagnosis of pulmonary fibrosis and is older than 18 years of age will be included in the registry.

Anyone who self-reports being a primary supporter or caregiver of someone living with pulmonary fibrosis and is older than the age of 18 will be included in the registry.

Those who consent to be enrolled in the registry will presumably be able to read and write in English.

2.2 Exclusion Criteria

Anyone younger than the age of 18 will not be included in the registry.

Anyone who does not self-report having PF or being a primary supporter or caregiver of someone living with PF will not be included in the registry.

Anyone who does not read and write in English will not be included in the study. It will be assumed that anyone who cannot read or write in English will not be able to fill out the form correctly and therefore will not make it into the registry.

2.3 Determining Eligibility

DCC staff will determine eligibility by the completeness of questionnaires/consents. Potential participants whose questionnaires/consents are not filled out appropriately (e.g., missing a signature), will not be considered eligible to be in the registry.

3.0 Consent

All individuals whose data are maintained in the registry will have given their consent to participate in the registry, as well as their consent to store PHI in a database and to be contacted for future studies. The consent process is integral to the submission of their data to, and storage of their data by, the DCC. If an electronic questionnaire is submitted without providing a signature and date in the first section, the form will not be accepted into the system and no identifying information will be retained. If a print questionnaire is submitted without a signature and date in the first section, the form will be shredded and no identifying information will be retained. The questionnaire form includes a prompt before the signature block that advises participants to retain a copy for their records. Data from the intake questionnaires will be entered into the database after the forms are sent to the DCC. Participants may withdraw their information from the registry at any time by contacting registry personnel or the DCC either by phone or in writing.
3.1 Research Procedures

The information collected from registry subjects will be submitted on the registry intake questionnaire/consent form. This information includes the following:
- Informed consent
- Demographics
- Contact information (primary, alternative, address, email, phone number)
- Cause of PF (if applicable)
- Medical symptoms related to PF (if applicable)
- Diagnostics
- Supplemental oxygen use
- Smoking history
- Medication
- Family history

4.0 Administration and Enrollment

The web page for the Participation Program for Pulmonary Fibrosis (P3F) will advertise the registry and provide enrollment instructions and access to the online version of the intake questionnaire/consent form.

5.0 Advertising

Advertising for the registry will be done through the P3F website, flyers, announcements, newsletters, and word of mouth with the help of National Jewish Health, the Pulmonary Fibrosis Foundation, the Coalition for Pulmonary Fibrosis, www.clinicaltrials.gov, and other PF patient advocacy groups. Letters to colleagues across the United States will also be sent requesting advertisement of the P3F and the registry at local clinics.

6.0 References


