Protocol

An Evaluation of Telenursing with or without Remote Monitoring to determine impact of Hospitalization Rate when compared to Usual Care for patients diagnosed with Idiopathic Pulmonary Fibrosis

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Wendi R. Mason, MSN, RN, ACNP-BC; Anne F. Turner, JD, BSN, RN; Lisa H. Lancaster, MD

Vanderbilt Medical Center, Nashville, Tennessee

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Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a serious progressive lung disease. The pathophysiology is not well understood but current theories rest on an inciting event or trigger that causes a cascade of fibrotic activity that is not responsive to treatment with anti-inflammatories or well known autoimmune agents. The most recently published demographics show that this chronic lung disease continues to affect men greater than women (1.2: 1) and in the sixth decade of life (median age 66) (1). A rare disease only affecting 120,000 persons, or 3 to 9 in 100,000 persons, but with incidence increasing due to our increasing aging population. (2) Unfortunately, due to the progressive fibrotic process, survival is only 3.5 years from the point of diagnosis, or stated otherwise, survival to 5 years is only 30% to 50% (3).

IPF can be challenging to manage clinically as many patients have multiple comorbidities, respiratory complications requiring hospitalization, and development of other lung diseases. Common comorbidities seen in the IPF population that also require additional healthcare specialty management include gastroesophageal reflux disease (GERD), pulmonary hypertension (PH), obstructive sleep apnea (OSA), and emphysema. Patients are at increased risk for developing other respiratory complications (pulmonary embolus, pneumothorax), and are more prone to respiratory illnesses such as pneumonia or bronchitis, or other lung diseases (PH or forms of lung cancer). A proportion of patients will also succumb to their disease every year due to acute exacerbation of IPF (AExIPF). (4)

Depression and anxiety are additional significant and common comorbidities associated with IPF. (5,6) A prevalence study consisting of 112 Korean patients with IPF showed that 25% experienced symptoms of depression and 21% experienced symptoms of anxiety. Survival rates and rates of hospitalization did not significantly differ between patients with and without depression and/or anxiety, however patients with depression and/or anxiety reported poorer quality of life. (7)

Quality of life is significantly affected due to the grim outcomes associated with the diagnosis, disease symptoms (shortness of breath, hypoxia, and cough), managing multiple comorbidities, hospitalization rates and disease severity. (8) Hypoxia requiring long-term oxygen therapy (LTOT) has a particularly

large influence on quality of life, as patients must maneuver heavy equipment that typically includes tanks and machines in order to perform the most basic activities; restrictions on mobility and activities of daily living continue to rise as oxygen liter flow requirements persistently increase throughout disease progression.

Hospitalizations are common in patients diagnosed with IPF, with hospitalization frequently resulting in death. An observational study in France examined a hospital database to describe reasons, outcomes, and costs of hospitalizations of patients diagnosed with IPF. Of over 6,000 patients identified, 87% were admitted for one or several acute events (including respiratory infections, pneumothorax, pulmonary embolism, myocardial infarction and other cardiac events such as heart failure, rhythm disorders, or pulmonary hypertension) with 36.5% of these being an acute respiratory worsening. 12% died on first admission with mortality increasing to 36.8% by Year 3. (9) A retrospective analysis of IPF patients managed by the University of California at Los Angeles reported 25.3% of their patients were hospitalized over the course of their lung disease, with 77.3% of these being respiratory-related. Mean survival following hospitalization for a respiratory-related event was very low at 2.8 months. (10)

Upon diagnosis of this rare lung disease, there is much education to deliver to the patient and their care givers to help them adjust to their diagnosis. Educational topics include understanding the disease, medications, management of comorbidities, importance of long-term oxygen therapy, consideration of lung transplant, and the critical avoidance of respiratory illness and hospitalization. This has typically been performed in the out-patient clinic setting; however, this can be very time consuming and nearly impossible for busy community practices. To help patients understand their lung disease, healthcare providers direct patients to trusted websites and provide them with ample educational materials provided by industry and not-for-profit organizations, relying on the patients and family members to read and learn on their own. Pharmaceutical companies have clinical educators available to educate patients about disease and their company's own medications to assist healthcare providers in educating patients.

In 2014, two oral medications were approved by the Food and Drug Administration (FDA) for the treatment of IPF. Both medications showed a similar ability to slow disease progression - as measured by forced vital capacity - by about 50%. Both medications have similar side effects as well (predominantly GI) and require routine liver function assessment. In the clinical trials, dose reduction and/or discontinuation were common (pirfenidone 16% dose reduction, 20% discontinuation; nintedanib 15% dose reduction, 26% discontinuation). (11,12) Utilization of these drugs post-approval in the United States depends largely on the geographical location and the ability of the practice to manage the patient on therapy. Unfortunately, the disease continues to progress and many patients must consider the option of lung transplantation or choose palliative care and hospice.

As researchers continue to make discoveries in areas of genetics, pathways of fibrolinosis, and search for further medications to reverse the process of fibrosis, we strive to find other ways in which to improve quality of life, reduce hospitalizations, respiratory illnesses and complications, as well as increase compliance with medications, oxygen, and pulmonary rehabilitation.

Telemedicine is the use of telecommunication and information technology to provide clinical healthcare through offsite diagnosis and management. Telemedicine has also been referred to as or telehealth or e-health. **Remote monitoring** is a category within telemedicine, also known as self-monitoring, that enables healthcare professionals to monitor a patient remotely using various technological devices.

Remote monitoring has been shown to provide comparable outcomes to traditional in-person patient encounters, supply greater satisfaction to patients, and may be cost-effective. This method is primarily used for managing chronic diseases. **Telenursing** refers to the use of telecommunications and information technology in order to provide nursing services in healthcare. The use of telenursing is increasing in many countries due to attempts to reduce costs of healthcare, increases in the number of aging and chronically ill persons, and less healthcare available in rural and sparsely populated areas.

Numerous studies show that remote monitoring and/or telenursing improves outcomes for patients especially those with chronic diseases. (13) There are ample telehealth-related studies in respiratory medicine, including chronic obstructive pulmonary disease, cystic fibrosis, and idiopathic pulmonary fibrosis, and include education via telenursing models. Polisena, et al, who has published multiple articles related to telehealth, completed a meta-analysis of randomized clinical trials with COPD patients utilizing telehealth studies. (14) In this meta-analysis they report various studies where patients received weekly or monthly planned telephone calls post-hospital discharge, or individualized teaching from a case manager on the day of discharge with subsequent contacts, who were then compared to patients who received usual care from their primary physician. Across the studies, home telehealth (home telemonitoring with telephone support) was found to reduce rates of hospitalization and emergency room visits. A 2003 study conducted in Canada created a model of telephone calls that consisted of an Educational Period of scheduled weekly phone calls for 8 weeks, followed by a Management Period of monthly phone calls for 10 months for COPD patients. (15).

Telemonitoring with hand-held home spirometry has been shown to be a reliable and valuable tool for monitoring health in respiratory illnesses. Russell demonstrated that daily measurement of FVC in IPF patients is more sensitive than hospital-based measures in predicting prognosis and at time points earlier than had been possible with traditional periodic monitoring (16). Respiratory patients benefit from home spirometry use by predicting re-exacerbation (17), allowing earlier tapering of steroids (18), and decreased healthcare costs in both compliant and non-compliant cystic fibrosis patients. (19) Asthma patients reported home use of spirometry was 'not complicated' and the vast majority remained interested in using a home system of monitoring their lung disease. (20)

Combined structured telephone calls with telemonitoring demonstrate further benefit across chronic care conditions including respiratory-related diseases. Celler demonstrated significant drops in healthcare expenditures, reduced admission rates to hospitals, and reductions in hospital stays among patients with COPD, CAD, HTN, DM, and asthma (21). Inglis completed a meta-analysis of 41 randomized clinical trials of heart failure patients and showed that structured telephone calls with non-invasive home monitoring reduced the risk of all-cause mortality and heart failure related hospitalizations as well as improved quality of life, overall disease knowledge, and self-care behavior (22)

We propose that structured telenursing with non-invasive remote monitoring of newly diagnosed IPF patients will, due to improved levels of patient education and understanding, decrease hospitalizations for respiratory illness, decrease visits to emergency centers or urgent care centers, increase compliance with therapies such as medication, oxygen, and rehab, and ultimately increase quality of life. This increased education and oversight of patients by nurses and nurse practitioners trained in the management of patients with Idiopathic Pulmonary Fibrosis will allow for earlier recognition of complications and exacerbations that we hypothesize will ultimately show an impact on mortality.

Hypothesis

Telenursing with or without remote monitoring will reduce the rate of hospitalization, and positively affect other variables, as compared to usual care (control group).

Endpoints

Primary Endpoint

1. To determine if the total number of hospitalizations related to respiratory event is lower in the interactive arms (Arm 2 and Arm 3) than in the control group (Arm 1).

Secondary Endpoints

1. To recognize, evaluate, and treat respiratory events through telecommunications with or without remote monitoring before the requirement of hospitalization or result of death.
2. To improve compliance in multiple areas noteworthy to IPF patients as measured by various means during clinic appointments to help guide further understanding and education:
    a. IPF medication compliance – by patient report/diary
    b. Laboratory follow up – by patient report and collection of laboratory reports
    c. Attendance in pulmonary rehab or other formal exercise program – by patient report and/or collection of rehabilitation records
    d. Supplemental oxygen use – by patient report
    e. Management of comorbidities
        i. GERD – by patient report of medication use and lifestyle changes
        ii. OSA – by collection of compliance reports of pap therapy, or notes of such contained in office notes
    f. Vaccines – by patient report
3. To improve quality of life scores as demonstrated by QOL questionnaires
4. To compare hospitalization parameters of “time to first hospitalization”, length of stay, number of hospitalizations per individual, and outcomes (such as quality of life post-hospitalization), discharge status [alive, deceased], discharged to [home, hospice facility].
5. To improve patient knowledge of lung disease, treatments, and management as demonstrated by self-report
6. To compare measurements obtained by clinic spirometry and home spirometry and clinic pulse oximetry and home oximetry.

Exploratory Endpoints

Exploratory endpoints will be collected to determine if the activities related to telehealth and remote monitoring will positively affect physiology and mortality.

1. To evaluate the difference in forced vital capacity (FVC) from baseline/diagnosis among the groups and as stratified by class
2. To evaluate the difference in walk distance in six minutes from baseline/diagnosis among the groups and as stratified by class

3. To compare findings in annual echocardiography in regards to right ventricular size and function and pulmonary hypertension from baseline/diagnosis among the groups and as stratified by class
4. To evaluate mortality differences among the groups and as stratified by class
5. To evaluate patient management at ILD Center compared to outlying community centers among the groups and as stratified by class.
6. To evaluate a standardized protocol that includes a structured educational curriculum followed by a regularly timed disease-focused phone calls with protocolized interventions when disease progression is recognized.

Study Design

This is a single-center prospective randomized study to compare outcomes on hospitalization, healthcare compliance, and quality of life of telenursing with or without remote monitoring as compared to usual care. All patients diagnosed with IPF at the Vanderbilt Medical Center outpatient Pulmonary Clinic, who meet inclusion and exclusion criteria, will be asked to participate. Patients who agree to participate and sign consent will be randomized into one of three treatment arms: usual care (the control group), usual care with telenursing, usual care with telenursing and remote monitoring. Patients will be asked to participate in the study for at least one year. We expect to enroll 150 patients, or 50 patients into each arm.

Usual care (Arm 1) – Patients will continue to receive education in the clinic and telephonically about their lung disease, medications, and oxygen use. At the point of diagnosis, patients will be given our current educational materials to take home and review, as well as our contact information. Patients will continue to attend face-to-face visits in the out-patient setting. The frequency of visits will be based on the discretion of the provider. During these visits, the patient will continue to receive individualized standard of care, which may include some or all of the following: a face-to-face visit with a healthcare provider, vital signs, with pulse oximetry at rest, weight measurement, pulmonary function testing, a six-minute walk, and laboratory testing. Other testing, such as echocardiography or chest radiography, may be required based on need. If patients do not return to Vanderbilt Medical Center beyond the point of diagnosis, they will still be allowed to participate. The usual care of local healthcare providers will be collected.

In addition to usual care, patients will be asked to answer five questionnaires to provide information about quality of life, depression, anxiety, dyspnea, and compliance and disease-state knowledge. These questionnaires will be given at the point of diagnosis, at 3 months, then 6 months, and then at 6-month intervals until the patient dies or is transplanted. Patients will be given paper-based questionnaires if they do not have the ability to complete them on-line via the RED Cap portal. These questionnaires to be conducted are the St. George's Respiratory Questionnaire-IPF Specific (SGRQ-I), Living with IPF (L-IPF for symptoms and impact), the modified Medical Research Council dyspnea scale (mMRC), a Depression Self-Screen (adapted from the Mental Health America Depression and Anxiety Screening Tools), an Anxiety Self-Screen (adapted from the New Zealand Health Promotion Agency Anxiety Self-Test), and the IPF Treatment Compliance and Knowledge Questionnaire. These are located in Appendices 1-6.

Usual Care with Telenursing – Patients will continue to receive 'usual care' as outlined above (with the questionnaires), however, will also receive scheduled one-on-one teaching support telephone calls with a nurse or nurse practitioner who have clinical expertise in the treatment and management of idiopathic pulmonary fibrosis. Telenursing will consist of an 8-week "Educational Phase" followed by periodic phone calls during the "Management Phase". During the Educational Phase telephone dialogue will be streamlined and remain on the topic of education, while only briefly discussing symptoms or side effects of medications as needed. During the Management Phase telephone dialogue will be focused on assessing symptoms of acute exacerbation or other respiratory concerns, adherence to treatments, including oxygen therapy and pulmonary rehabilitation, as well as follow up regarding known associated comorbidities. Re-education of previous modules will be provided as needed. The mMRC will be assessed with each phone call. Telenursing visits will be scheduled with the patient during an Introductory Phone visit from the nurse practitioner. Visits will be conducted telephonically or via a secure portal (ZOOM). An outline of Educational Phase topics as well as the plan for Management Phase telephone calls is provided in Appendix 7.

If patients do not return to Vanderbilt University Medical Center beyond the point of diagnosis, they will still be allowed to participate. Usual care will be completed as described above, with the telenursing arm incorporated. Participants will sign for agreement for their local pulmonary and/or primary care healthcare team to be advised of outcomes of structured telenursing calls.

Usual Care with Telenursing and Remote Monitoring – Patients will continue to receive usual care and telenursing as described above, however, will also be given devices to assist in monitoring objective data points. Patients will receive a hand-held spirometer for home use and a pulse oximeter.

patientMpower. patientMpower is a digital healthcare company providing technology solutions for people with chronic illness who are making strides toward helping patients with idiopathic pulmonary fibrosis. The patientMpower platform is an electronic health journal developed for patients with pulmonary fibrosis to enable them to record objective health data (spirometry, blood pressure, pulse, oxygen saturation and weight), appointments and keep a health journal, medications and obtain reminders to take medications, health surveys, and set exercise goals. The platform is downloaded as an app (free of charge) to the patient's smartphone or tablet and connected wirelessly to the spirometer and pulse oximeter to allow daily longitudinal monitoring.

After downloading the app, the patient will be able to pair his smartphone or tablet with the spirometer and the pulse oximeter and begin to capture objective data. The mMRC is included within the patientMpower app. Patients will be asked to answer this question as often as they would like, but at least during the telenursing visits. The nursing staff will assist the patient with this process. Recent studies show that pulmonary fibrosis patients are willing and able to use the app to record spirometry and pulse oximetry, as well as symptoms questionnaire (23). More information about the patientMpower app is located in at https://info.patientmpower.com/ipf/.

Daily Pulse Oximetry and heartrate. Patients will be given a Nonin 3230 Bluetooth Smart pulse oximeter to measure oxygen saturation at rest on room air or prescribed resting oxygen liter flow. Resting heartrate will be captured simultaneously.

If the patient has smartphone technology, he will be assisted with pairing his smartphone or tablet to the pulse oximeter, and then utilizing the app to take a measurement. If the patient does not have smartphone technology, he will still be able to participate in this portion of the study, but rather than allow the app to record the value, the patient will record the value in the Data Diary.

The patient will be asked to measure his oxygen saturation at about the same time every day. To do this, the patient will be asked to sit at rest and breathe room air or their prescribed resting oxygen liter flow for 5 minutes. They will place the finger probe on the finger of their choice, and after 15 seconds, record their pulse oximetry and heartrate, then remove the finger probe. The data captured will be immediately seen by the patient as well as transferred to the app. If the patient does not have smartphone technology, he will be asked to record his oxygen saturation and heartrate (and liter flow of oxygen if required) in the Data Diary each day. The diary pages will be mailed in on a monthly basis or turned in at the next office visit.

During each healthcare provider directed appointment, patients will be given specific individualized instruction regarding when to contact their healthcare team should their results begin to decline. Each patient will be instructed to contact the office if their oxygen saturation drops 4 percentage points from their baseline for 3 days in a row (example: from 93% to 89%). More information about the pulse oximeter is located in Appendix 8 and the Data Diary is located in Appendix 9.

Daily Spirometry. Patients will be given a Spirobank Smart hand-held home spirometer to measure pulmonary function (specifically FVC).

If the patient has smartphone technology, he will be assisted with pairing his smartphone or tablet to the spirometer, and then utilizing the app will be instructed how to take a measurement. If the patient does not have smartphone technology, he will not be able to participate in this portion of the study. Through Bluetooth technology, data is instantly transmitted to a smartphone or tablet. The patient will be able to see his result.

The patient will be asked to measure his pulmonary function at about the same time every day, preferably after completion of the pulse oximetry measurement. Patients will be asked to sit and complete spirometric maneuvers by following the directions and instructions provided by the device and telehealth team. The data will immediately be seen by the patient on his or her smartphone or tablet.

During each healthcare provider-directed appointment, patients will be given specific individualized instruction regarding when to contact their healthcare team should their results begin to decline. Each patient will be instructed to contact the office if their FVC drops by 5% for 3 days in a row (example: from 3.0L to 2.85L). More information about the Spirobank Smart spirometer is located in Appendix 10.

A Flowchart that simplifies the decision-making and assigning of tools is located in Appendix 11.

Patient Selection

Every patient who is diagnosed with IPF by a Vanderbilt physician, who is scheduled for an out-patient visit will be pre-screened to ensure inclusion criteria are met and exclusion criteria are not met.

Inclusion Criteria. The patient must meet all inclusion criteria.

1. Patient must be diagnosed with IPF by a Vanderbilt pulmonologist according to the 2011/2018 ATS Guidelines (3/24).
2. FVC >= 40%.
3. Willingness to complete Quality of Life and Compliance Questionnaires at 6-month intervals either via an on-line process (RED Cap survey) or paper-based.
4. Willingness to participate in phone calls/video calls with the nurse practitioner or nurse case manager, if assigned to Arm 2 or Arm 3.
5. Willingness to complete and monitor daily physiologic assessments, if assigned to Arm 3.
6. Willingness to share objective data via a provided electronic web-based portal, electronically via email, fax, or regular mail.
7. Willingness to notify, or allow notification, of study involvement with local pulmonary practices.

Exclusion criteria. If the patient meets any of the following exclusion criteria, he or she cannot participate:

1. Diagnosed with any other interstitial lung disease.
2. Listed for lung transplant.
3. Requires supplemental oxygen > 5L at rest.
4. Experiencing an acute exacerbation of IPF.
5. Recently hospitalized for respiratory event.
6. Not willing to complete questionnaires.
7. Not willing to participate in educational and management phone calls/video calls.
8. Not willing to complete and share objective data via a provided electronic web-based portal, electronically via email, fax, or regular mail.
9. Not willing to notify, or allow notifications, of study involvement with local pulmonary practices.
10. Any comorbidity or other reason why the investigator believes the patient would not be an acceptable candidate to enter the study.

If the patient meets candidacy during pre-screening, his or her potential participation will be reviewed with the healthcare provider to ensure eligibility on the day of the out-patient visit, preferably after the provider has completed the health history and physical examination. Once confirmed, the study team will consult the patient, advised him or her of the study, and determine if he or she would be willing to participate. Those who do not consent, will be asked their reason why, and these will be recorded (see Appendix 12). Those who agree will sign the consent.

<u>Randomization</u>

The randomization schedule will be generated prior to study initiation using a permuted-block randomization with varying block sizes of 2 to 3 assignments per arm. Patients who sign consent will be randomized by this schema to one of the three arms of the study. The permuted block will be set up in RED Cap and available for the study team to utilize. Randomizations will be structured so that patients will be stratified by degree of illness and then randomized in order to have equal numbers of patients in

each of the severities of illness. The randomization schedule will be uploaded to the RED Cap module so that a study participant's intervention assignment is only revealed after entry of consent documentation. Pre-screening and enrollment activities will begin upon Vanderbilt Human Research Protection Program (IRB) approval.

Confidentiality

All attempts will be made to ensure patient confidentiality.

Patients who agree to participate and sign the consent will be assigned a study identifier known only to the study staff for data entry purposes. The code for study identifiers will be the arm of the study and next sequential two-digit number of enrollment, therefore, a patient who is consented to the study and was sequentially randomized to Arm 2, would have the next sequential two-digit participant number, so that the third participant into Arm 2 would be assigned a study identifier of 2-03.

Data Collection

Data will be collected in RED Cap.

Data collected will include the following: demographics (gender, race, ethnicity, age at diagnosis, date of birth, miles from our center, classification of rural, suburban, or urban, tobacco use and status), diagnosis (date of diagnosis, where made, physician overseeing, where IPF healthcare will occur), longitudinal physiological components of IPF collected in the clinic or hospital (measures of pulmonary function, 6-minute walk, echocardiography, heartrate at rest, oxygen saturation at rest on room air/liter flow of oxygen, and body weight, as well as provider's interpretation of IPF classification/stage), daily physiological components as captured at home (FVC in liters, FEV1/FVC ratio, heartrate at rest, oxygen saturation at rest on room air/liter flow of oxygen), staging at clinic visits, use of FDA approved medications for IPF, hospitalizations (dates of admission and discharge to determine length of stay and time to hospitalization, and the admitting diagnosis), cost of hospitalizations, outcomes of telenursing calls, quality of life and other questionnaire scores, compliance measures (related to medications, pulmonary rehabilitation, oxygen use, and comorbidities such as GERD and OSA), and health status (living, deceased, transplanted). PHI collected will include date of birth, medical record number, date of diagnosis, and dates of service. No other standard PHI will be included.

Statistics

Power calculations for telenursing project

Simulation

In order to understand the operating characteristics of the proposed telenursing project, we constructed a simulation study. Using the Brown-2015 paper as the basis of the simulation study, we generated a hypothetical study cohort of 300 subjects (100 in each arm). The one-year hospitalization event rate was

set to 25% in the usual care arm (A1). The event rate in arm 2 (A2) and arm 3 (A3) was set to a range of values, as noted in results table below ("A2 risk" and "A3 risk").

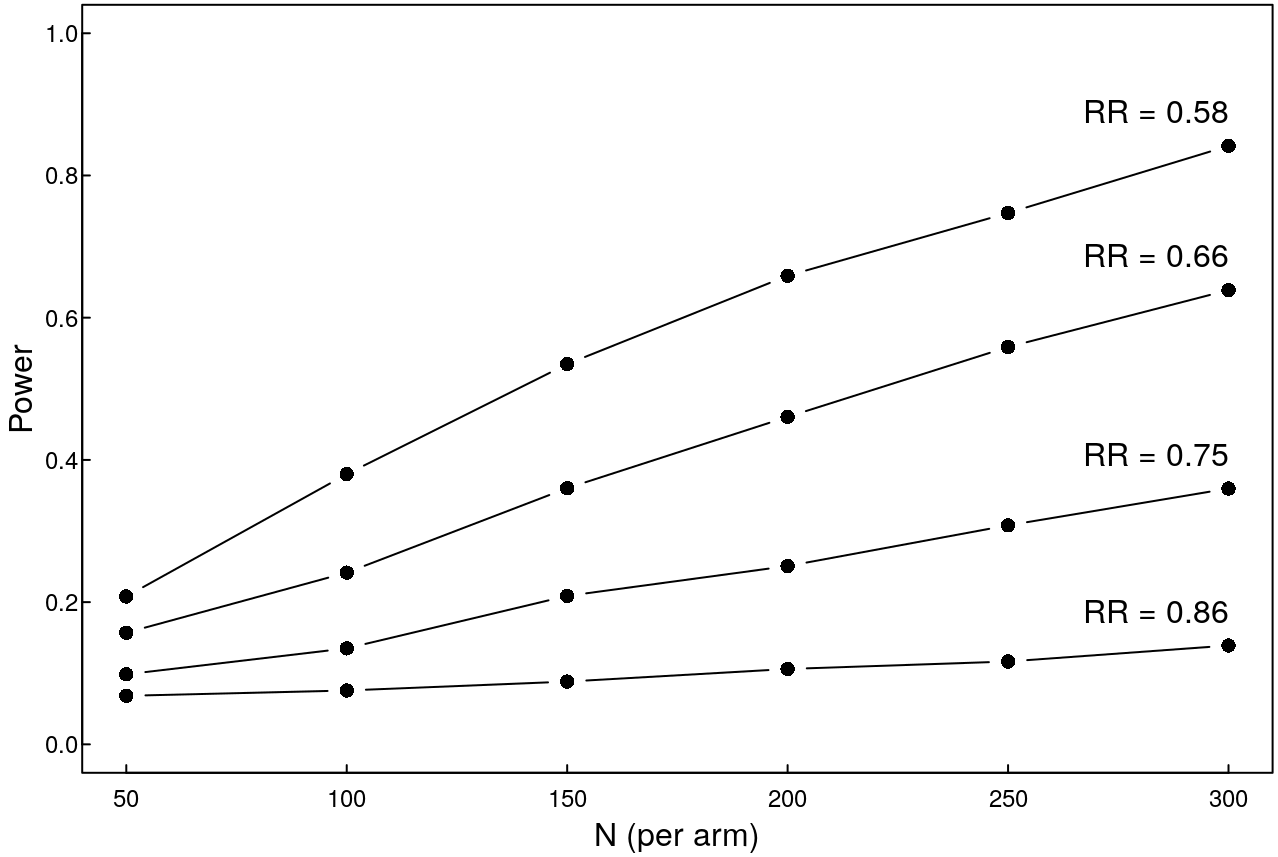
We generated 4000 replicates of the hypothetical study cohort for each combination of event rates, i.e., the rows of the results table. In each replicate, we calculated the (a) overall treatment effect, (b) the A2 vs A1 effect, and (c) the A3 vs A1 effect. The effect estimates were calculated by fitting a logistic regression model, and corresponding tests were calculated with the Wald method. Power was calculated as the proportion of the 4000 replicates in which the treatment effect was significant at α=0.05α=0.05 type I error rate.

Results

The results are provided in the table below. In the plot, RR refers to the relative risk of arm 3 to arm 1. In the table and in the plot, relative risk (RR) is simply the ratio of the risk in arm 2 (or 3) divided by the risk in arm 1.

Code

```
plotstyle(style = upright); par(mar = c(3,3,2,1))
plot.new()
plot.window(xlim = sim_settings$N %>% range, ylim = c(0,1))
g <- sim_settings %>%
  as.data.table %>%
  `[`(,lines(copy(N), copy(power), type = "b"),p2)
axis(1, at = sim_settings$N %>% unique)
axis(2)
box()
title(xlab = "N (per arm)", ylab = "Power")
g <- sim_settings %>%
  filter(N == max(N)) %>%
  as.data.table %>%
  `[`(, text(N, power, "RR = " %|% round(rr2,2), adj= c(1,-1)))
```



The table and plot report the same information.

Sample Size	A1 risk	A2 risk	A3 risk	RR 2:1	RR 3:1	Power 3:2:1	Power 2:1	Power 3:1
50	0.25	0.23	0.22	0.93	0.86	0.07	0.05	0.06
100	0.25	0.23	0.22	0.93	0.86	0.08	0.06	0.08
150	0.25	0.23	0.22	0.93	0.86	0.09	0.06	0.10
200	0.25	0.23	0.22	0.93	0.86	0.11	0.07	0.13
250	0.25	0.23	0.22	0.93	0.86	0.12	0.07	0.15
300	0.25	0.23	0.22	0.93	0.86	0.14	0.08	0.17
50	0.25	0.22	0.19	0.87	0.75	0.10	0.05	0.10
100	0.25	0.22	0.19	0.87	0.75	0.14	0.08	0.17
150	0.25	0.22	0.19	0.87	0.75	0.21	0.10	0.26
200	0.25	0.22	0.19	0.87	0.75	0.25	0.11	0.32
250	0.25	0.22	0.19	0.87	0.75	0.31	0.14	0.39
300	0.25	0.22	0.19	0.87	0.75	0.36	0.15	0.45

Sample Size	A1 risk	A2 risk	A3 risk	RR 2:1	RR 3:1	Power 3:2:1	Power 2:1	Power 3:1
50	0.25	0.20	0.16	0.82	0.66	0.16	0.08	0.17
100	0.25	0.20	0.16	0.82	0.66	0.24	0.12	0.31
150	0.25	0.20	0.16	0.82	0.66	0.36	0.15	0.44
200	0.25	0.20	0.16	0.82	0.66	0.46	0.19	0.55
250	0.25	0.20	0.16	0.82	0.66	0.56	0.24	0.66
300	0.25	0.20	0.16	0.82	0.66	0.64	0.27	0.73
50	0.25	0.19	0.15	0.77	0.58	0.21	0.09	0.23
100	0.25	0.19	0.15	0.77	0.58	0.38	0.16	0.46
150	0.25	0.19	0.15	0.77	0.58	0.53	0.23	0.64
200	0.25	0.19	0.15	0.77	0.58	0.66	0.29	0.74
250	0.25	0.19	0.15	0.77	0.58	0.75	0.33	0.83
300	0.25	0.19	0.15	0.77	0.58	0.84	0.38	0.90

At least 80% power for the joint treatment effect and the A3 vs A1 effect was achieved when the event rate was .25, .19, and .15 for the three arms, respectively. The power for the comparison between A2 and A1 was 0.38, which was the highest of all the situations considered.

Proposed statistical analysis plan for the primary endpoint

The primary endpoint will be an ordinal variable that is a composite of hospitalizations and death within one year of diagnosis. The categories of the ordinal variable will be: 0 hospitalizations & no death, 1 hospitalization & no death, …, K hospitalizations & no death, and then death as the final category. This will order the patients from best to worst outcomes in a way that incorporates the possibility of death.

The primary endpoint will be analyzed with a cumulative probability ordinal regression model which includes treatment assignment indicators and relevant covariates, such as age, gender, race, and other measures of baseline disease severity like **time-since-diagnosis**. Continuous variables, such as age, will be included in the model with restricted cubic splines in order to allow for the possibility of a non-linear association with the outcome. Model diagnostics, such as DFBETAs, will be generated to identify overly influential observations.

Once the regression model diagnostics indicate the model is reasonably fit, the treatment effect will be tested with Wald statistics at the α=0.05α=0.05 type I error level. The first effect to be tested is the joint treatment effect. If the joint effect is significant, then A3 vs A1 and A2 vs A1 will be tested. If the joint effect is not significant, no additional pairwise comparisons will be tested. The sequential test strategy ensures that the type I error rate is preserved.

As a sensitivity analysis, we will analyze hospitalization rates (not the composite hospitalization and death) with a model similar to the one described above.

Every effort will be made to collect covariate information; however, if missing data exists in the analysis dataset, we will adjust the analysis described above and implement multiple imputation with predictive mean matching. At least 30 imputations will be generated.

Power for proposed analysis. The proposed analysis is expected to be more powerful than the analysis simulated above because it uses an ordinal instead of a binary outcome. As such, the power calculations above serve as a lower bound for the analysis of the primary endpoint.

APPENDICES

APPENDIX 1: QUALITY OF LIFE QUESTIONNAIRE: SGRQ-I (25)

(Attachment)

APPENDIX 2: QUALITY OF LIFE QUESTIONNAIRE: L-IPF (26,27)

(Attachment)

APPENDIX 3: DYSPNEA QUESTIONNAIRE: mMRC (28,29)

The modified Medical Research Council dyspnea scale is a simple one question tool to evaluate the patient's current state of dyspnea. It will be provided via multiple formats (available electronically via a RED Cap survey invitation, available on the patientMpower app, and in paper form.

Please choose the one best response to describe your shortness of breath.

Grade

0 "I only get breathless with strenuous exercise."

1 "I get short of breath when hurrying on the level or walking up a slight hill."

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level."

3 "I stop for breath after walking about 100 yards or after a few minutes on the level."

4 "I am too breathless to leave the house" or "I am breathless when dressing."

An increased score reflects impaired quality of life and a high symptom burden. In practice, this scale may be used to help identify increased need for palliative care. (29)

APPENDIX 4: DEPRESSION SELF-SCREEN TOOL

Grief & Depression

Everyone who is diagnosed with a serious lung disease, as well as their loved ones, will experience episodes of deep sadness & grief, and these feeling will usually wax & wane throughout the disease process.

It's important to reach out for help if these feelings become prolonged or otherwise start to interfere with your quality of life; asking for help is not a sign of weakness – it is a sign of strength that you are taking back some control over your own life and health. Take the Depression Self-Screen below to see how sadness & grief may be affecting you, then turn to the end of this booklet for a list of resources to help.

Depression Self-Screen*

	Not At All	**Several Days**	**More Than Half the Days**	**Nearly Every Day**
Over the last two weeks, how often have you been bothered by feeling little interest or pleasure in doing things?				
Over the last two weeks, how often have you been bothered by feeling down, depressed, or hopeless?				
Over the last two weeks, how often have you been bothered by having trouble falling or staying asleep, or sleeping too much?				
Over the last two weeks, how often have you been bothered by feeling tired or having little energy?				
Over the last two weeks, how often have you been bothered by a poor appetite or overeating?				
Over the last two weeks, how often have you been bothered feeling bad about yourself – or that you are a failure or have let yourself or your family down?				
Over the last two weeks, how often have you had problems with moving or speaking so slowly that other people could have noticed?				
Over the last two weeks, how often have you had thoughts that you would be better off dead, or of hurting yourself?				
If you checked off any problems, how difficult have these problems made it for you at work, home, or with other people?	**Not Difficult**	**Somewhat Difficult**	**Very Difficult**	**Extremely Difficult**
Add	0 For each box checked	1 For each box checked	2 For each box checked	3 For each box checked

Total For Each Column				
Total of All Columns = Depression Score				

0 – 6: None to Mild Depression

7 – 15: Moderate Depression ***(seeking outside help is recommended)***

16 – 24: Severe Depression ***(it is critically important that you seek outside help as soon as possible)***

**Adapted from the Mental Health America Depression Screening Tool*

APPENDIX 5: ANXIETY SELF-SCREEN TOOL

Anxiety

Feelings of anxiety are very common with a diagnosis of serious disease, especially serious lung disease because our bodies naturally experience intense anxiety when we feel very short of breath or see a loved one experiencing severe shortness of breath. Patients and loved ones often experience periods of anxiety throughout the disease process, and these symptoms may occur separate from or together with feelings of grief or depression.

It's important to reach out for help with symptoms that are interfering with your quality of life; asking for help is not a sign of weakness – it is a sign of strength that you are taking back some control over your own life and health. Take the Anxiety Self-Test below to see how anxiety may be affecting you, then turn to the next page for a list of resources to help.

Anxiety Self-Test*

	Not At All	**Several Days**	**More Than Half the Days**	**Nearly Every Day**
Over the last two weeks, how often have you been bothered by feeling nervous, anxious or on edge?				
Over the last two weeks, how often have you been bothered by not being able to stop or control worrying?				
Over the last two weeks, how often have you been bothered by worrying too much about different things?				
Over the last two weeks, how often have you been bothered by having trouble relaxing?				
Over the last two weeks, how often have you been bothered by being so restless that it is hard to sit still?				
Over the last two weeks, how often have you been bothered by becoming easily annoyed or irritable?				
Over the last two weeks, how often have you been bothered by feeling afraid as if something awful might happen?				
Over the last two weeks, how often has worrying caused you physical symptoms, such as stomach upset, rapid breathing or heart rate, etc.?				
Add	0 For each box checked	1 For each box checked	2 For each box checked	3 For each box checked
Total For Each Column				
Total of All Columns = Anxiety Score				

0 – 8: None to Mild Anxiety

9 – 15: Moderate Anxiety

16 – 24: Severe Anxiety

**Adapted from the New Zealand Health Promotion Agency Anxiety Self-Test*

APPENDIX 6: TREATMENT COMPLIANCE QUESTIONNAIRE

The following questionnaire will be given to patients at Baseline, Month 3, Month 6, then every 6 months. This will be given as a survey via the RED Cap database, or as a paper-based product for the patient to complete and return. The purpose of this survey is to evaluate patient-reported compliance with IPF treatments and therapies, as well as evaluate the patient's general knowledge about his disease. Both sections of the questionnaire will be scored. The values of the answers for the Compliance Section are recorded in parenthesis below. The scoring of the Educational Section is as follows: Completely agree = 3 points, Mostly agree = 2 points, Somewhat agree = 1 points, Do not agree = 0 points. A higher score will reflect an overall greater compliance or knowledge level.

Compliance section

Do you take your IPF medication (nintedanib or pirfenidone) daily and as prescribed?

A. Yes, I take my medication for IPF daily (3)
B. Yes, I take my medication for IPF daily, but not always as prescribed. (3)
C. No, I do not take my medication daily, but take it most days of the week. (2)
D. No, I only take my medication less than half the days in a week. (1)
E. No, I do not take my medication. (0)
F. This is not applicable to me because I am not currently prescribed IPF medication. (n/a)

Do you get your safety labs completed for your IPF medication monthly or quarterly?

A. Yes, I get my safety labs completed monthly. (3)
B. Yes, I get my safety labs completed quarterly. (3)
C. No, I get my safety labs completed less frequently than quarterly. (1)
D. No, I do not get any lab work completed regularly for my IPF medication. (0)
E. This is not applicable to me because I am currently not on prescribed IPF medication. (n/a)

Do you wear your oxygen as prescribed?

A. Yes, I wear my oxygen as prescribed. (3)
B. No, I wear my oxygen according to how I need it. (1)
C. No, I do not wear my oxygen. (0)
D. This question does not apply to me because I am currently not prescribed oxygen. (n/a)

Do you exercise most days a week?

A. Yes, I exercise every day. (3)
B. Yes, I exercise most days a week (at least 4 days a week). (2)
C. No, I exercise less than 4 days a week. (1)
D. I do not exercise. (0)

Do you take your medication to control reflux / GERD daily?

A. Yes, I take my medication for reflux / GERD daily and as prescribed. (3)
B. No, I do not take my medication for reflux / GERD daily, but take it most days of the week. (2)

C. No, I only take my reflux / GERD medication less than half the days in a week. (1)
D. No, I only take my reflux / GERD medication when I need it. (1)
E. No, I do not take my reflux / GERD medication. (0)
F. This is not applicable to me because I am currently not prescribed reflux / GERD medication. (n/a)

Do you wear your cpap or bipap mask every time you sleep?

A. Yes, I wear my cpap or bipap every night. (3)
B. No, I wear my cpap or bipap most days a week (at least 4 days a week). (2)
C. No, I wear my cpap or bipap less than 4 days a week. (1)
D. No, I do not wear my cpap or bipap. (0)
E. This is not applicable to me because I do not have sleep apnea that requires treatment with cpap or bipap. (n/a)

<u>Knowledge section</u>

I understand my lung disease.

A. Completely agree
B. Mostly agree
C. Somewhat agree
D. Do not agree

I understand how my IPF medication has been shown to help me.

A. Completely agree
B. Mostly agree
C. Somewhat agree
D. Do not agree

I understand the side effects associated with my IPF medications.

A. Completely agree
B. Mostly agree
C. Somewhat agree
D. Do not agree

I understand the importance of regular exercise.

A. Completely agree
B. Most ly agree
C. Somewhat agree
D. Do not agree

I understand why I need (or may need) to wear oxygen.

A. Completely agree
B. Mostly agree

C. Somewhat agree
D. Do not agree

I know when to call my IPF healthcare provider.

A. Completely agree
B. Mostly agree
C. Somewhat agree
D. Do not agree

APPENDIX 7: TELENURSING OUTLINE AND SCRIPTS FOR EDUCATIONAL, MANAGEMENT, and RECOGNIZED RESPIRATORY EVENT TELEPHONE CALLS

Introductory Phone Call – with the nurse practitioner and within the first week of the initial visit

Purpose 1: IF NOT CONSENTED TO THE STUDY IN THE CLINIC – the NP will discuss this study with the patient during the usual care appointment follow-up phone call. If the patient verbally agrees, a consent will be sent to the patient for signature and randomization will occur.

Purpose 2: IF ASSIGNED TO TELENURSING OR TELENURSING WITH REMOTE MONITORING: the phone call will not only be the usual care appointment follow-up phone call, but will explain telenursing (and remote monitoring, as randomization requires), and set up Educational Phase phone call times, as well as introduce available support groups (local, internet). IF POSSIBLE: The Educational Phone Call # 1 may occur at this time.

Education Phase

Educational phone contact should be scheduled with the patient at his or her convenience and at weekly intervals. The goal is to complete all 8 phone calls within 3 months of enrolling. Please see the power point slide decks associated with each phone call for teaching and script.

Education Phone Call # 1 – review of disease state / procedures / team

Education Phone Call # 2 – IPF FDA-approved medication benefits / risks (or side effects)

Education Phone Call # 3 – tobacco cessation / pulmonary rehabilitation

Education Phone Call # 4 – symptoms management / Importance of wearing your oxygen / AEx

Education Phone Call # 5 – clinical trials

Education Phone Call # 6 – comorbidity management – refer to GI, Sleep, PH (echo)?

Education Phone Call # 7 – lung transplant team (if applicable)

Education Phone Call # 8 – integrative health / palliation / hospice

Management Phase

Management Phone Calls will occur within one week following known provider visits and at intervals between known provider visits to begin within one-week of the post-~3 month follow up visit to discuss outcomes of visit / unanswered or new questions / assurance of follow up. Management Phone Calls will continue until the patient dies or is transplanted. Please see the Management Call power point slide deck or the scripts written below regarding the below topics of discussion:

Med review (side effects, dosing, labs)

Office visits / hospitalization review

Comorbidity review

Assessment of symptoms of AEx IPF / pneumonia / bronchitis /mMRC

PR/Exercise routine?

Oxygen use?

PRN Reminders regarding vaccines

Respiratory Event

If during the process of an educational or management call, the nurses recognizes the symptoms of disease progression or respiratory event, the nurse will utilize the following intervention. Please see the power point slide deck for scripts regarding respiratory event and disease progression.

Associated Script for Telenursing Management Visits

Visit A – within one week of office appointment

Focus is on ensuring understanding of diagnosis, inform of test results, ensure all orders have been started/completed (medications, referrals, etc), follow-up established.

Greeting

Hello. I'm calling to follow up on your appointment with Dr. ____ / NP ____ this past week at Vanderbilt Medical Center. How are you doing?

General understanding from visit

I just want to follow up to ensure you understand everything about your visit at Vanderbilt. I see from your healthcare provider's note, you were in the office for a ____ visit. Do you have any questions or concerns about your visit?

Review Medical Note – symptom review

your visit you informed your doctor about your ___symptoms____. During the visit, Dr. ___ stated you could do ____ to control these symptoms. How are your symptoms today?

Review Medical Note – procedures / test results

*test results only advised when approved on by the ordering physician.

During your office visit, Dr. ___ ordered some __blood tests / xrays / etc. These are / are not back yet. May I review them with you?

Review Medical Note – all follow up

During your office visit, Dr. ___ wanted you to _____. Have these been set up yet?

(referrals for pulmonary rehab, other doctors to evaluate other problems, other studies, medications).

Review of phone call and End of call

Ensure all items have been completed, or are in the works. Ensure understanding of visit / diagnosis. Remind that you will call prior to next appointment.

Visit B – At midpoint between scheduled office appointment

Focus is on health status – is the patient well, or improving, or declining. Also touching compliance regarding medication, oxygen use, and exercise.

Greeting

Hello. This is _____, the _____ at Vanderbilt. I'm calling to check in with you. How are you doing?

Compliance measures

You are taking _____ - are you remembering to take it as prescribed? Any trouble with side effects? How are you managing this? Your pharmacy is _____. Any problems with getting your medications?

Double check lab schedule – have they had labs / need labs?

You are wearing oxygen? Current liter flow is __ with rest and __ with exercise. Your current DME is _____. Any changes to this? Do you have enough oxygen for your needs both inside and outside of your home?

You are exercising? Pulmonary Rehabilitation or at home? How many days a week?

Do you have sleep apnea and need PAP therapy? Are you wearing your mask? Any problems with this? Your DME is _____.

IPF Symptom Control – stable, worsening?

How is your shortness of breath? What makes you short of breath?

How is your cough?

How is your fatigue level?

Touchpoints to look for worsening.

Have you had any fever / chills / sweats?

Any change to your cough?

Any change to your shortness of breath?

Anyone in the home or family been ill?

IF + findings concerning for URI or worse –

Obtain as much information about start of illness.

If concerns for viral illness – ensure appropriate OTC symptom relief.

If concerns for bacterial illness – prescribe abx with/without steroid burst

If concerns about significant illness – call to obtain follow up visit with local pulmonary.

If concerns about acute worsening such as an AEx, may need to go to hospital for admit / testing.

Review phone call and follow up appt reminder

Today I will _____. Remember your follow up appointment is scheduled with Dr. _____on _____at _____.

Make sure everything is scheduled – should have PFTs and 6 MWT and labs q 3 months.

APPENDIX 8: NONIN 3230 BLUETOOTH SMART PULSE OXIMETER

The Nonin 3230 is a small, lightweight, portable device indicated for use in measuring and displaying functional oxygen saturation of arterial hemoglobin (%SpO2) and pulse rate of patients who are well or poorly perfused. The device is FDA approved (FDA 510(k):K072979) and has been shown to have the same accuracy of a clinical setting. The device is easy to set up with Bluetooth technology to a tablet or smartphone. It requires two AAA batteries. The device has a display, but no memory, however, information is transmitted directly to the smartphone or tablet.

APPENDIX 9: DATA DIARY

The Data Diary is a paper-based tool for collecting objective data points for those patients who do not have smartphones or tablets with Bluetooth capability. This paper-based tool will be given to patients at Baseline and as needed over the course of their involvement in the study and will collect the same data points as are collected in the patinetMpower application.

Example:

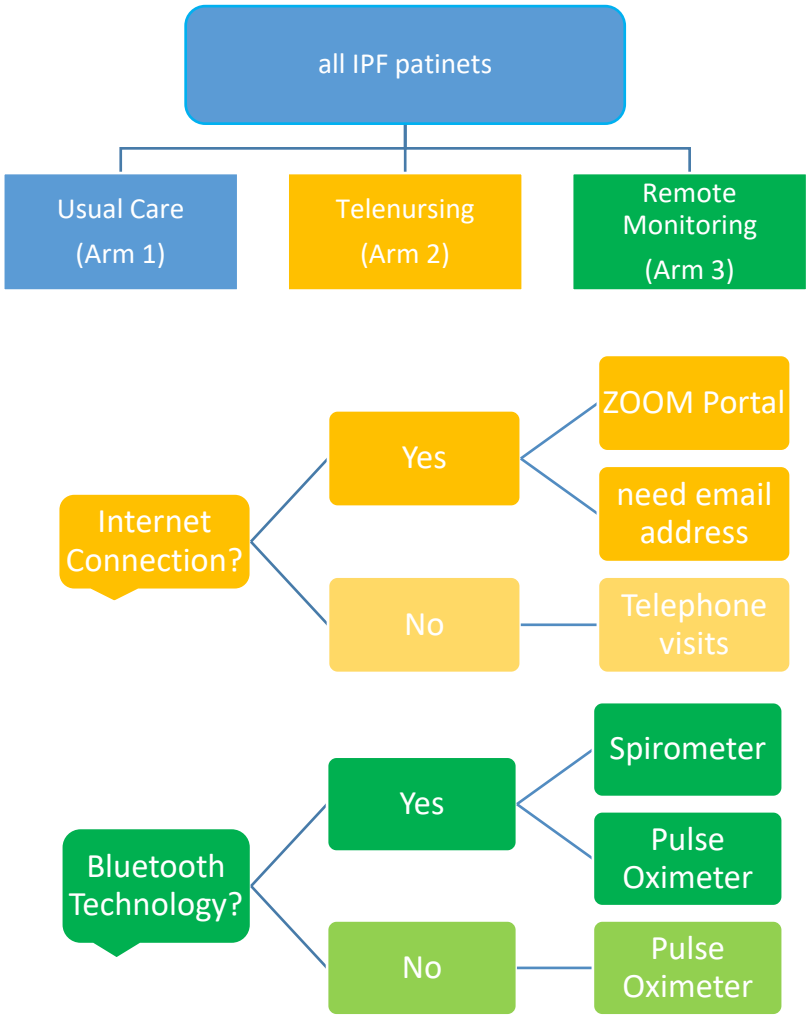
Date	Day	Time	% Ox Sat	Room Air or L/min	Pulse	FVC
1-Aug	Wednesday					
2-Aug	Thursday					
3-Aug	Friday					

APPENDIX 10: SPIROBANK SMART SPIROMETER

The Spirobank Smart is a handheld daily use spirometer used in for monitoring respiratory illnesses such as COPD, CF, and asthma, as well as managing the healthcare of lung transplant recipients. The spirometer measures PEF, FVC, FEV1, FEV1/FVC ratio, FEV6, and FEF25/75. The spirometer is one of several products manufactured by Medical International Research (MIR). The device is FDA approved (FDA 510(k):K072979) and has been shown to have the same accuracy of a clinical setting. The device is easy to set up with Bluetooth technology to a tablet or smartphone. It requires two AA batteries. There is no display or memory on the device, as all information is communicated in real time to the smartphone or tablet. The attached flowmeter is reusable for a single patient and can be cleaned in soapy water. Disposable turbines are available. More information is available at www.spirometry.com/eng/Products/spirobank_smart.asp

13 patients diagnosed with interstitial lung disease recorded daily spirometric measurements with this device and the patientMpower app in a proof-of-concept observational study conducted in Ireland. The patients were able to install the app and use the device independently and continued daily use for a minimum of 6 weeks, with several members continuing to use the device regularly (Edwards 2017).

APPENDIX 11: STUDY FLOWCHART



APPENDIX 12: SCREENING AND ENROLLMENT LOG / DEVICE LOG

The purpose of the Screening and Enrollment Log is to document each newly diagnosed patient agreement or non-agreement to participate in the study. This log will match all participants to their study identifier. All patients who agree to participate will have their Medical Record, last name, date and time of appointment, and study identifier recorded. All patients who deny participation will have their last name, date of appointment, and reason for denial recorded. The log will be kept on a password-protected excel spreadsheet located on a secure server in the Pulmonary Division only accessible by the IPF Study Team.

Last Name	Appt Date	Appt Time	Screen Number	Agree	Deny	Study ID / Reason Refused	ARM	ID	MR
			1						
			2						
			3						
			4						
			5						
			6						

The purpose of the Device Log is to record and assign the device(s) to the patient. The log will also help us record what devices have been returned.

ID	Last Name	Intro phone call date	spirometer assigned	pulse ox assigned	date given/shipped	date returned

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