An observational study of self-monitoring of spirometry and symptoms via the patientMpower app in patients with idiopathic pulmonary fibrosis.

IPF patientMpower 03

Statistical Analysis Plan

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Authors:
Principal investigator:
Dr. Katherine O'Reilly, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland.

Co-investigator:
Dr. Colin Edwards, patientMpower Ltd, 21 Denzille Lane, St. Peters, Dublin D02 EY19, Ireland.

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PROTOCOL SUMMARY

PRODUCT	patientMpower intervention (+ home spirometry)
CLINICALTRIALS.GOV IDENTIFIER	NCT 03544598
PROTOCOL TITLE	An observational study of self-monitoring of spirometry and symptoms via the patientMpower app in patients with idiopathic pulmonary fibrosis.
COORDINATING INVESTIGATOR	Dr. Katherine O'Reilly, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland.
NUMBER OF TRIAL SITES	One
CLINICAL PHASE	Not applicable
STUDY OBJECTIVES	1. Characterise longitudinal trends of patient-reported Forced Vital Capacity (FVC) and outcome measures in patients with idiopathic pulmonary fibrosis (IPF). 2. Determine the correlation between patient-reported FVC and outcome measures with clinic-observed measurements. 3. Assess if longitudinal trends in patient-reported FVC predict clinical outcomes. 4. Characterise the acceptability and utility of the patientMpower app from patient and healthcare professional perspectives.
METHODOLOGY	Prospective, open-label, single-arm observational study. Usual care for all patients throughout study.
NUMBER OF SUBJECTS	Total randomised: target = 25

	Actual intention-to-treat: 21. Treated dataset: 20
DIAGNOSIS	Confirmed diagnosis of IPF
MAIN CRITERIA FOR INCLUSION	Age ≥18 years, daily access to smartphone or tablet device, email address, demonstrated understanding of use of patientMpower app and home spirometry, written informed consent
TEST PRODUCT	patientMpower intervention (defined as patientMpower app + home spirometer) used daily + usual care
COMPARATOR PRODUCT	None
DURATION OF OBSERVATION	Sixteen ± eight weeks (corresponding to interval between usual care visits)
END OF STUDY DEFINITION	Date of first usual care visit after baseline visit (typically at sixteen ± eight weeks)
PRIMARY ENDPOINTS	Trend of patient-measured FVC over time. Degree of correlation between patient-measured FVC with clinic-observed measures
SECONDARY ENDPOINTS	Trends of patient-reported outcomes over time. Degree of correlation between patient-reported outcomes with clinic-observed measures. Patient and healthcare professional perspectives on preference for and difficulty using the app and helpfulness in managing IPF. Impact of app on patient self-management of IPF and daily living.
INTERIM ANALYSIS	Analysis of data up to 18 October 2019 to prepare abstract for American Thoracic Society 2020
STATISTICAL METHODS	Descriptive statistics tables prepared for all endpoints

FLOW CHARTS

Flow chart 2: Assessments during observation period

	Baseline (clinic visit)	**Install app & pair spirometer**	***Daily (patient - reported)**	**16 (±8) weeks End study (clinic visit)[1]**
	day 0	day 0-2	daily	week 16 (approx.)
Informed consent	X			
Start of study	X			
Spirometry, assess dyspnoea	X			X
Demographic data (include IPF history & medicines history[3])	X			
Patient training & encouragement	X			
Installation of patientMpower app & pair spirometer		X		
Record compliance or changes (IPF medicine)[2]	X		X	X[3]
Patient-measured FVC[2]	X		X	X
Record impact of IPF (PROM)[4,5]	X[4]		X[5]	X[4]
Patient outcomes (e.g. oxygen consumption, dyspnoea, pulse oximetry, symptoms, vital signs)[6]			X	
Utility & acceptability of app[7]				X
Clinic-reported outcomes (e.g. exacerbations)				X
End of study				X

[1] End of study visit will be date of usual scheduled clinic visit.

[2] Reported by patient on patientMpower app every day. Goal is for patient to record one FVC measurement (seated) per day.

[3] Clinic to record changes in IPF medication or other medicines prescribed for respiratory conditions.

[4] Impact of IPF on daily life (Patient Reported Outcome Measure; PROM) to be assessed by clinic team at baseline and end of study visit and recorded on patientMpower app.

[5] Impact of IPF on daily life (PROM) to be reported by patient on patientMpower app every week.

[6] Reported by patient as often as possible, ideally each day. These measurements are optional and will only be recorded where practical for the patient.

[7] Patient and healthcare professional perspective. If patient is withdrawn prematurely, try to capture patient perspective of utility and acceptability of app at time of withdrawal.

List of abbreviations

AE	Adverse event
ATS	American Thoracic Society
COVID19	Coronavirus disease 19
ERS	European Respiratory Society
EU	European Union
EWMA	Exponentially Weighted Moving Average
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
IPF	Idiopathic pulmonary fibrosis
ITT	Intention to treat
JRS	Japanese Respiratory Society
MIR	Medical International Research
mMRC	modified Medical Research Council
pMp	patientMpower application
PROM	patient reported outcome measure
US	United States

1. Study protocol

1.1 Protocol

The study protocol was finalised on 11 January 2018 [1].

This was an open-label, single-group observational study of a population of idiopathic pulmonary fibrosis (IPF) patients treated with usual care. There was no control group.

1.2 Protocol amendments

Not applicable.

1.3 Dates of study conduct

The first patient gave informed consent and entered the study on 28 November 2018. In-clinic visits were cancelled at the study centre in March 2020 because of the COVID19 pandemic and the last two patients did not have end-of-study clinic visits. Data for all patients who had completed the study by 30 April 2020 and for the two patients who were still on study on 30 April 2020 are included in this analysis.

1.4 Data management plan

The preparation of listings and tables for analysis is described in the data management plan dated 09 July 2020.

2. Datasets for analysis

2.1 Dataset definitions

The patient populations to be included in the analyses were defined as follows.

- Intention-to-treat dataset: all patients who gave informed consent.
- Treated dataset: all patients in the intention-to-treat dataset who downloaded the patientMpower application (pMp), and used pMp with a MIR Spirobank Smart spirometer at least once.

2.2 Protocol deviations

There was no definition of significant protocol deviations. Data from all patients in the treated dataset were analysed irrespective of adherence to the protocol. The primary analysis was of the treated dataset.

2.3 Duration of follow-up

It was planned that each patient would be followed up for the duration of the interval between usual care clinic follow-up visits (expected to be 8-24 weeks). Because of the Covid19 pandemic starting March 2020, end-of-study clinic visits for two patients were not conducted and end-of follow-up for these patients was arbitrarily defined as 30 April 2020. The duration of follow-up varied for each patient.

3. Study design

3.1 Summary of design, including control

Open-label, single-arm observational study of patients treated in a usual care environment.

There was no control group.

3.2 Study population

Adult patients with a diagnosis of idiopathic pulmonary fibrosis [2].

3.3 Observational intervention

The observational intervention was an electronic health diary (pMp) supplied with a Bluetooth-connected home spirometer (MIR Sprobank Smart).

pMp+home spirometry was developed specifically for patients with IPF. pMp is an electronic application downloaded to the patient's mobile phone or tablet device. It is designed to allow the patient to report various parameters relevant to IPF and record these on a regular basis. The information recorded by the patient is stored in a secure cloud and is available to the patient through their phone or mobile device at all times. No personal health data are stored on the phone or mobile device itself.

Patients were asked to report measurements on pMp each day e.g. Forced Vital Capacity (FVC; (one reading once/day), dyspnoea, activity (steps/day), distance walked per day and compliance with IPF medication. Patients were prompted to report the impact of IPF on daily life using a Patient Reported Outcome Measure (PROM) developed specifically for IPF [3]) once every week.

3.4 Concomitant therapy, restrictions and rescue treatment

There were no restrictions on concomitant treatment. All concomitant treatments as prescribed by the patient's healthcare professionals were allowed. Patients continued to take all medicines as prescribed by their healthcare professionals.

There were no restrictions on diet or life-style. Patients continued to follow all instructions on diet, exercise and lifestyle as directed by their healthcare professionals.

4. Variables for assessment

4.1 Efficacy variables

The objectives of this observational study were:

- to assess and characterise the longitudinal trends of patient-measured FVC and PROMs in a cohort of patients with IPF
- to determine the correlation (if any) between patient-measured FVC and PROMs with clinic-observed measurements
- to assess if longitudinal trends in patient-measured FVC outcomes are predictive of clinical health outcomes in IPF
- to assess the acceptability and utility of pMp

The primary endpoint was the longitudinal trend in patient-reported FVC. The correlation between patient-reported FVC and clinic-reported measures and outcomes were also assessed.

The primary endpoint variable was the daily patient-reported FVC.

The secondary endpoints included:

- the longitudinal trend in PROMs
- the correlation between PROMs and clinic-reported measures and outcomes.
- assessment if patient-measured FVC predicts clinical health outcomes
- the impact of active engagement and self-monitoring using pMp on the impact of IPF on daily life (PROM)
- the effect of pMp on medication compliance
- the acceptability and utility of pMp (from patient and healthcare professional perspective)

The secondary endpoint variables (reported by patients) were:

- maximum level of dyspnoea each day (ideally linked to description of activity causing maximum dyspnoea)
- activity (number of steps/day)
- distance walked per day
- compliance with medicines prescribed for treatment of IPF
- addition of any new prescribed medicines for treatment of IPF
- impact of their medical condition on their daily life (once/week; PROM)

Additional secondary endpoint variables which can be recorded by the patients (if measurement devices are available to the patient and it is practical for the patients to record these variables) include:

- duration of walking per day
- number of episodes of walking per day
- cough (worst severity each day)
- heart rate (if patient has access to wearable fitness device)
- blood pressure (if patient has access to measurement device)
- temperature (if patient has access to measurement device)
- body weight (once/week)
- oxygen saturation at rest (if patient has access to pulse oximetry device and wishes to record saturation)
- oxygen consumption (cylinders/month)

Patients assessed dyspnoea with the mMRC dyspnoea scale which may be a useful prognostic indicator in IPF [4].

The secondary endpoint variables (assessed and recorded by the clinic) are:

- FVC
- dyspnoea
- impact of the patient's medical condition on their daily life (using the same PROM questions used by the patient)
- health outcomes e.g.

  - medication adherence
  - change in IPF medication (dose change or new medicine prescribed)
  - oxygen usage
  - exacerbations of IPF
  - hospitalisations due to IPF

The patient's opinion of the utility and acceptability of pMp as assessed by their response to questions:

- the instructions given in using pMp were clearly understandable (strongly agree/agree/disagree/strongly disagree)
- using pMp helped me to take the correct dose of my medicines for lung fibrosis every day (strongly agree/agree/disagree/strongly disagree) [only asked if patient is taking medication specifically prescribed for IPF]
- using pMp helped me to reach my personal exercise goal every day (strongly agree/agree/disagree/strongly disagree)
- using pMp helped me to walk further (or exercise more) compared with before (strongly agree/agree/disagree/strongly disagree)
- using pMp gave me more confidence/a greater sense of control in managing my lung health (strongly agree/agree/disagree/strongly disagree)
- I found it useful to be able to record the impact of lung fibrosis on my daily life (strongly agree/agree/disagree/strongly disagree)
- I liked using pMp (strongly agree/agree/disagree/strongly disagree)
- pMp was easy to use (strongly agree/agree/disagree/strongly disagree)
- the effect of using pMp on the impact of lung fibrosis on my well-being and daily life (positive, negative)
- I found it tiring or irritating to use pMp (strongly agree/agree/disagree/strongly disagree)
- I want to continue using pMp after the end of the study (yes, no)
- I would recommend other people with my condition to use pMp (yes/no)
- what other measurements, reminders or information would be useful to have on pMp? (Open text for participant to give opinion)
- describe the benefits and/or disadvantages of using pMp (Open text for participant to give opinion)

The secondary endpoint will also be assessed by the healthcare professional's response to the following questions:

- preference for using pMp versus not using it (yes, no preference, no)
- difficulty rating in using pMp (very easy, easy, difficult, very difficult)
- did using pMp help me to help the patient manage their IPF better? (yes, no)

- did using pMp help the patient to take their IPF medicines at the correct dose every day (yes, no) [only asked if patient is taking medication specifically prescribed for IPF]
- do I believe the patient should continue using pMp after the end of the study (yes, no)
- what other measurements, reminders or information would be useful to have on pMp? (Open text for healthcare professional to give opinion)
- describe the benefits and/or disadvantages of using pMp (Open text for healthcare professional to give opinion)

4.2 Safety

All observed adverse events were listed.

4.3 Other variables

Demographic data (date of birth, gender, ethnicity, height, weight, concomitant diagnoses, medication prescribed).

Engagement of patients with pMp was assessed by analysis of the numbers of patients who used pMp and the frequency of recording study measurements.

5. Statistical methods and determination of sample size

5.1 Statistical design and model

The study was an open-label, prospective, single-arm observational study of patients treated in a usual care environment.

There was no control group.

5.2 Null and alternative hypotheses

Not relevant.

5.3 Planned analysis

All data from the Treated data set were included in the analysis. The list of variables, data formats, data presentations, statistical comparisons and statistical tests used are shown in Appendix 1 (section 7).

Results were summarised for descriptive statistical display. No imputations of missing data were made.

The primary efficacy endpoints were assessed by analysis of changes in patient-reported FVC, clinic-derived parameters and health outcomes over time.

Patient-reported FVC and other patient-reported measures were compared with the clinic-derived measures and health outcomes to determine if there were any correlations between them.

The secondary endpoints data were assessed by analysis of changes in the patient-reported health parameters, clinic-derived parameters and health outcomes over time.

Data on the level of engagement with pMp and the patient opinions were described and tabulated.

Patient-recorded FVC data were screened to detect outlier values (e.g. where a patient did not blow forcefully enough or may have coughed during the forced expiratory maneuver). The average patient-recorded FVC was tracked over time via the Exponentially Weighted Moving Average (EWMA) adjusted for irregular time indices [5,6]. Control limits were constructed via the EWMA variance, which accounted for the stochasticity around the mean, plus an adjustment 0.15*log(max(delta_t, 1)), where delta_t is the time since the last observation, for the purpose of modelling our uncertainty due to lack of engagement during periods where the patient was not inputting spirometry values. Any values outside these control limits were considered outliers. Scatter plots of patient-recorded FVC versus time were prepared for each patient.

Correlation between clinic-observed and patient-recorded FVC was assessed as follows. The means of the first seven days of patient-recorded FVC after baseline and of the last seven days of patient-recorded FVC before the end-of-study clinic visit were calculated. Outlier values were detected by inferring a rolling average of the patient-recorded data using the EWMA algorithm and removing values far away from this average, taking into account heightened uncertainty of the average during periods of poor engagement. Outlier values were excluded and

the means of spirometry values within the first seven days after the baseline clinical FVC (mean baseline spirometry) and the last seven days before their end-of-study clinical FVC (mean endpoint spirometry) were calculated. Patients without a single spirometry value in either 7 day window were excluded.

For both baseline and end-of-study, the correlation between in-clinic FVC and patient-recorded FVC was calculated by randomly sampling from the data with replacement and calculating the usual Pearson correlation coefficient. This process was repeated 1000 times, giving an empirical distribution for correlation. This process is known as bootstrapping [7]. The mean of this distribution is the inferred correlation, and the standard error is the standard deviation of this distribution divided by the square root of 1000.

5.4 Interim analysis

An interim set of data listing was prepared in October 2019 to submit an abstract for American Thoracic Society 2020. There was no formal statistical analysis of these data.

5.5 Determination of sample size

This was a pilot-scale study. The proposed sample size of 25 subjects was chosen arbitrarily based on the expected patient population who would participate at this site over a one-year period.

6. References

1. O'Reilly K, Costello E, Edwards C. An observational study of self-monitoring of spirometry and symptoms via the patientMpower app in patients with idiopathic pulmonary fibrosis. Study protocol dated 11 January 2018. www.clinicaltrials.gov NCT 03544598.
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7. Appendices

7.1 Variables, data formats, data presentations, statistical comparisons and tests

Listed in NCT03744598 statistics analysis plan appendix 1