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

IPF patientMpower 03

Protocol date: 11 January 2018

Number of pages: 37

Version 1.0

Authors:

Colin Edwards PhD, patientMpower, Dublin, Ireland.

Eamonn Costello, patientMpower, Dublin, Ireland.

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

NCT 03744598

# Table of Contents

# PROTOCOL SUMMARY

| | |
|---|---|
| PRODUCT | patientMpower app |
| WWW.CLINICALTRIALS.GOV IDENTIFIER | NCT 00000000 |
| PROTOCOL TITLE | An observational study of self-monitoring of spirometry and symptoms via the patientMpower app in patients with idiopathic pulmonary fibrosis |
| CO-ORDINATING INVESTIGATOR | Dr. Katherine O'Reilly, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland (Principal investigator) |
| NUMBER OF STUDY SITES | One |
| CLINICAL PHASE | Not applicable |
| STUDY OBJECTIVES | Characterise longitudinal trends of patient-reported Forced Vital Capacity (FVC) and outcome measures in patients with idiopathic pulmonary fibrosis (IPF).<br>Determine the correlation between patient-reported FVC and outcome measures with clinic-observed measurements.<br>Assess if longitudinal trends in patient-reported FVC predict clinical outcomes.<br>Characterise the acceptability and utility of the patientMpower app from patient and healthcare professional perspectives. |
| METHODOLOGY | Multi-center, prospective, single-arm, open design |
| NUMBER OF SUBJECTS | Total randomised: up to 25<br>Each treatment:<br>patientMpower app: 25 |
| 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 app (via patient's smartphone or tablet device) |
| DURATION OF OBSERVATION | Sixteen (± eight) weeks |
| END OF STUDY DEFINITION | Sixteen (± eight) weeks |
| PRIMARY ENDPOINTS | Trend of patient-measured FVC over time.<br>Degree of correlation between patient-measured FVC with clinic-observed measures. |
| SECONDARY ENDPOINTS | Trends of patient-reported outcomes over time.<br>Degree of correlation between patient-reported outcomes with clinic-observed measures.<br>Patient and healthcare professional perspectives on preference for and difficulty using the app and helpfulness in managing IPF.<br>Impact of app on patient self-management of IPF and daily living. |
| INTERIM ANALYSIS | None planned |
| STATISTICAL METHODS | Descriptive statistics tables will be prepared |

# FLOW CHARTS

## Flow chart 1: Patient recruitment process

| Step | Day | Action |
|---|---|---|
| 1 | 0 (Baseline) | At a usual care visit to study centre, research team discusses study with patient (face-to-face), confirms patient's understanding of the study processes and willingness to participate.<br>Obtains written informed consent[A].<br>Study centre conducts usual clinical assessments.<br>Study starts. |
| 2 | 0 (Baseline) | Study centre advises patientMpower Ltd. of email address of patients who have given consent to participate. |
| 3 | 0 -2 | patientMpower sends information pack (electronic; includes instructions on installation of app) and home spirometer to patient[B]. |
| 4 | 0 - 2 | Patient starts to use patientMpower app and home spirometry as soon as possible after installation of app and pairing of spirometer. |

[A] Includes explicit consent by patient for patientMpower to know their identity and email address and collect, store and analyse data reported by the patient on the patientMpower app.
[B] On request by the patient, patientMpower Ltd can contact patient to offer help with installation of patientMpower application and pairing of spirometer (so that application and spirometer are installed and operating correctly).

## 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.

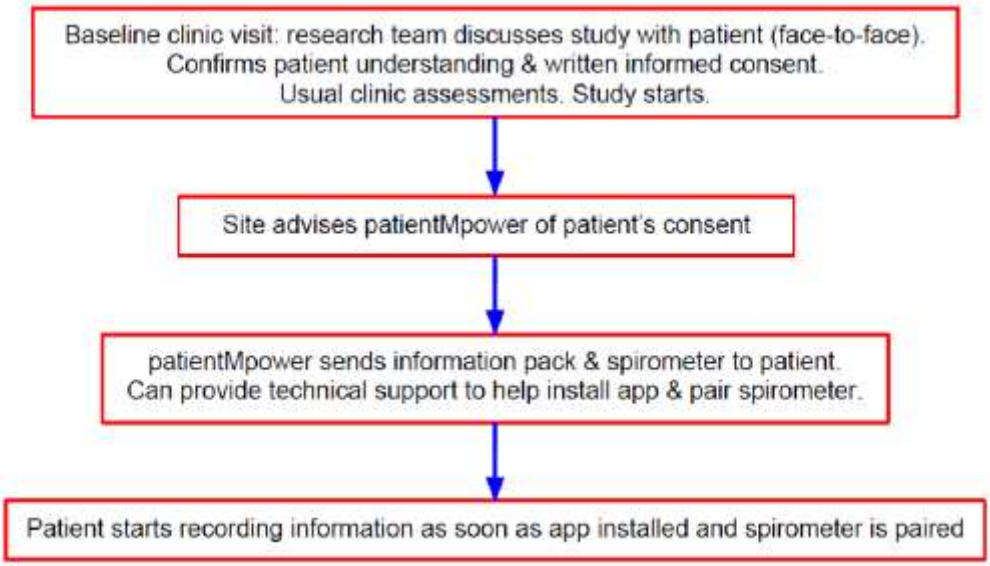
[7] Patient and healthcare professional perspective. If patient is withdrawn prematurely, try to capture patient perspective of utility and acceptability of app at time of withdrawal.

# List of Tables

None

# List of Figures

## Figure 1: Patient recruitment process



# List of Abbreviations

| | |
|---|---|
| ADR | Adverse reaction |
| AE | Adverse event |
| ATS | American Thoracic Society |
| BI | Boehringer Ingelheim |
| DLCO | Diffusing Capacity of the Lung for Carbon Monoxide |
| ERS | European Respiratory Society |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| IEC | Independent ethics committee |
| ILFA | Irish Lung Fibrosis Association |
| IP | Internet Protocol |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Institutional review board |
| JRS | Japanese Respiratory Society |
| K-BILD | King's Brief Interstitial Lung Disease Questionnaire |
| MIR | Medical International Research |
| mMRC | modified Medical Research Council |
| PEF | Peak Expiratory Flow |
| PFW | PF Warriors of Texas |
| PROM | patient reported outcome measure |
| SSH | Secure Shell |
| SSL | Secure Sockets Layer |
| TLS | Transport Layer Security |
| UCSD | University of California San Diego |

# 1. Introduction

## 1.1 Medical background

Idiopathic pulmonary fibrosis (IPF) is an irreversible lung disease leading to progressive dyspnoea and a deterioration of pulmonary function reflected by a progressive decline of forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Progression of the disease results in serious limitation of physical activities and has a major impact on the patient's quality of life [1].

Digital medicine platforms which directly record patient experiences (e.g. symptoms, impact on daily life, medication compliance) and measurements (e.g. blood pressure, blood sugar levels) have been developed for chronic medical conditions and may be valuable in helping the patients to manage their condition. To date, no digital platform has been specifically developed for patients with IPF.

At the time of writing, there are few simple disease-specific instruments to assess health-related quality of life in patients with IPF. A modified version of the St. George's Respiratory Questionnaire has been developed for IPF [2]. Another group has developed and tested the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) in an interstitial lung disease population [3,4]. The Brompton Hospital, London has recently developed a patient reported outcome measure (PROM) specifically to capture the impact of IPF on the patients' daily life [5]. This PROM can be used on a regular basis (e.g. every week) and could provide information on longitudinal trends on the impact of IPF on daily life. It is possible that patient-reported information may be more useful than clinic-reported assessments in characterizing the impact of IPF on quality of life.

## 1.2 Product profile

The product evaluated in this study is an electronic health diary developed by patientMpower Ltd., The Digital Depot, Thomas Street, Dublin 8, Ireland. The patientMpower electronic health diary has been developed for and is already used in providing support to patients post-renal transplant or with IPF. The patientMpower electronic health diary is downloaded as an application or "app" to a mobile phone or tablet device and patients record various parameters (e.g. blood pressure, symptoms, medication compliance, impact of their medical condition on daily life) on a daily basis. The patient has a permanent health diary of their self-reported measurements available to them on their mobile device. The app includes a health journal which allows patients to record symptoms at the time they occur. This is helpful for the patient in monitoring their health and in preparing them for appointments

with their healthcare professionals, particularly if there is a long interval between clinic visits. If appropriate, certain clinic-derived measurements (e.g. therapeutic drug levels, spirometry data) can be shared with the patient via the app.

The patientMpower app for renal transplant recipients is now offered as standard care at the national renal transplantation centre in Ireland. In the renal transplant setting, patients use the patientMpower app every day to monitor health parameters (e.g. medicines adherence, blood pressure, body temperature) which are important in maintaining the health of the transplanted kidney. The data collected on the patientMpower app is identifiable (i.e. the identity of the patients is known to patientMpower Ltd) so that it can be shared with the renal transplant clinical centre to aid in the post-transplant care of the patients. The patientMpower app has been in use at the national renal transplantation centre in Ireland since summer 2015 and has also been used at renal transplant centres in other countries. To date, over 200 renal transplant patients have used the patientMpower app.

However, it is important to recognise that patient demographic factors vary by medical condition and this can have an impact on the utility and acceptability of digital health platforms in the patient user group.

This observational study will evaluate a version of the patientMpower app which has specifically been developed to capture parameters which are relevant for patients with IPF. Examples of measures which can be recorded by the patient include dyspnoea [modified Medical Research Council (mMRC) Dyspnoea Scale], activity (steps/day), vital signs, temperature, oxygen use, type of activity linked to maximum dyspnoea, medication compliance and cough. In addition, patients can report measures linked to the recently developed PROM specifically developed to capture the impact of IPF on patients' daily life [5].

A recent study in patients with IPF has suggested that daily home monitoring of FVC by patients is clinically informative and daily FVC may be of value as a primary endpoint in short proof-of-concept studies [6,7]. The patientMpower app can link to home spirometry devices to allow longitudinal collection and upload of long-term patient-measured FVC data to the app. The Spirobank Smart spirometer [Medical International Research (MIR), Via del Maggiolino 125, 00155 Roma, Italy. www.spirometry.com] is one example of a home spirometer which can collect and wirelessly upload FVC and other spirometry data to the patientMpower app.

The patientMpower app (including daily patient-recorded spirometry using the MIR Spirobank Smart spirometer) has been assessed in user experience surveys (42-day observation period) in over 50 patients with lung fibrosis. These surveys were conducted in collaboration with two patient advocacy

groups [Irish Lung Fibrosis Association (ILFA), Dublin, Ireland and PF Warriors (PFW), Plano, Texas, USA]. The identity of each participant in these surveys is known to patientMpower Ltd. Knowledge of the participant's identity is needed in order to maintain access for the participant to the app, provision of individualised technical support and to enable later deletion of the participant's data if they were to request deletion at a later stage. Feedback from the surveys' participants demonstrated that daily home recording of spirometry and symptoms is feasible and acceptable to people with lung fibrosis. In the ILFA study, the majority of participants (9/11; 82%) wished to continue using the patientMpower app after the end of the study [8] and at least 8 participants (73%) continued to use the app for at least 200 days [9]. The PFW study is currently being analysed.

The patientMpower app (including daily patient-recorded spirometry using the MIR device) is also being evaluated in an open-label, usual care controlled clinical trial in patients with IPF at Galway University Hospital, Ireland [10, www.clinicaltrials.gov NCT03104322]. This study has received ethics committee approval, patient recruitment is complete and follow-up is ongoing at the time of writing. The identity of each patient in this study is known to patientMpower Ltd.

Another version of the patientMpower application will shortly be evaluated in a pilot-scale study in haemodialysis patients [11, www.clinicaltrials.gov NCT03403491]. This study has been approved by the independent research ethics committee of the study centre in Ireland.

The study described in this protocol will capture longitudinal data on home measurement (by the patient) of FVC and PROMs within the same cohort of patients. This will enable assessment of the degree of correlation (if any) between patient-reported spirometry and the impact of IPF on daily life (as assessed by the PROM).

# 2. Rationale, objectives and benefit-risk assessment

## 2.1 Rationale for performing the study

There are few data on longitudinal trends in patient-measured FVC and PROMs in IPF. It is possible that these data may be predictive of important health outcomes (e.g. exacerbations). The patientMpower app provides a tool to collect and share this type of information between patients and their healthcare professionals.

In addition, as no specific digital patient support platform for patients with IPF is available and validated, there is sufficient justification in testing the effectiveness and acceptability of the patientMpower app in a controlled observational setting.

### 2.2 Study objectives

The objectives of this observational study are:

- 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

An additional purpose of this observational study is to assess the acceptability and utility of the patientMpower app in helping IPF patients and their healthcare professional caregivers manage their condition. These will be assessed from both the patient and healthcare professional perspective.

### 2.3 Benefit-risk assessment

The patientMpower app has been used in other clinical settings (post renal transplant). The renal transplant version of the patientMpower app is now offered as standard care at the national renal transplantation centre in Ireland. It has been positively received by patients and healthcare professionals and studies of its use are ongoing.

Initial feedback from participants in the user experience surveys and clinical trial in lung fibrosis indicates that patients are willing to use the app and record spirometry at home on a very regular basis (usually daily) and that they find it helpful in managing their health. These studies are ongoing at the time of writing.

It is not expected that the study or patientMpower app will create any additional risks for IPF patients.

## 3. Description of design and study population

### 3.1 Overall design and plan

This is an open-label, single group observational study of a population of IPF patients treated with usual care. Patients who enter the study will be trained in correct use of the patientMpower app and the Spirobank Smart home spirometer and encouraged to use them on a daily basis. The study will not make any other changes to the therapeutic interventions offered to the patients.

### 3.1.1 Administrative structure of study

This is a single centre study in Ireland. The study centre is an expert centre for the diagnosis, staging and treatment of IPF.

The patientMpower app was developed and is owned by patientMpower, Dublin 8, Ireland. The Spirobank Smart home spirometer was developed by Medical International Research, Via del Maggiolino 125, 00155 Roma, Italy. The protocol was designed by Dr. Katherine O'Reilly, Mater Misericordiae University Hospital, Dublin (the principal investigator) and patientMpower Ltd.

Financial support for the study will be provided as an unrestricted research grant from Boehringer Ingelheim Ltd. The financial sponsor will not play any role in the design, conduct or analysis of the study.

## 3.2 Discussion of study design

This is an open-label, single group observational study. There is no control group.

Patients will follow their usual care programme throughout the study. The study observation period (16 ± 8 weeks) is approximately equal to the interval between clinic visits in the usual care of IPF.

This design will enable assessment of longitudinal trends in FVC and PROMs in a cohort of patients with IPF undergoing usual care.

Patients enrolled in the study will capture information on relevant health outcomes related to IPF on a regular basis (daily for some parameters) using the patientMpower app. Patients will also measure FVC at home once per day using the Spirobank Smart spirometer. The patient measured FVC and other spirometry data will be captured automatically by the patientMpower app. These data will form the patient-reported outcome database.

Clinical assessments (e.g. FVC, dyspnoea) in the same cohort of patients will be assessed at the beginning and end of the study. PROMs will also be recorded at the clinic at the beginning and end of the study.

This design allows comparison of patient-reported data and their longitudinal trends with clinic-reported data in a cohort of patients with IPF. The correlation between the two types of data and the value of patient measurements in predicting health outcomes can be assessed and quantified.

This design will also allow evaluation of the utility and acceptability of the patientMpower app in a patient population managed by centres with expertise in the diagnosis and management of IPF. This will be assessed from both the patient and healthcare professional perspectives.

The patientMpower app will include key questions derived from a PROM developed specifically for patients with IPF [5] and will help to evaluate the utility of an electronic health diary in capturing PROM data in IPF patients.

## 3.3 Selection of study population

### 3.3.1 Main diagnosis for study entry

Idiopathic pulmonary fibrosis

### 3.3.2 Inclusion criteria

Aged at least 18 years

Confirmed diagnosis of IPF [according to American Thoracic Society (ATS), European Respiratory Society (ERS) or Japanese Respiratory Society (JRS) criteria] [1].

Has daily unrestricted access to a suitable smartphone or tablet device at home*.

Has an e-mail address.

Has home broadband and/or mobile data as part of their mobile phone service

Demonstrates understanding of correct use of the Spirobank Smart spirometer and the patientMpower app.

Able and willing to perform spirometry at home and record information on the patientMpower app on a daily basis.

Willing to give written informed consent.

(*patientMpower Ltd will provide a suitable tablet device if the patient does not have access to their own device.)

### 3.3.3 Exclusion criteria

Significant confusion or any concomitant medical condition which would limit the ability of the patient to record symptoms or use a home spirometer on a regular basis.

New prescription of antifibrotic therapy for IPF (e.g. pirfenidone, nintedanib) within the four weeks before the baseline visit.

Recent exacerbation of IPF or other clinically significant change in the patient's medical condition in the four weeks before the baseline visit.

### 3.3.4 Discontinuation of patients from study or assessments

#### 3.3.4.1 Discontinuation of individual patients

Patients are free to withdraw from the study at any time without any impact on their ongoing medical care. Patients can continue to use the patientMpower app and spirometer after withdrawal from the study of they wish.

Investigators may withdraw a patient from the study at any time if they believe that further participation in the study is not in the best interests of the patient.

#### 3.3.4.2 Discontinuation of the study as a whole.

The study may be terminated early if recruitment is significantly behind schedule or if for any other reason, it is unlikely that the study can be completed.

# 4. Treatments

All patients will continue to receive all usual care throughout the study as prescribed by their healthcare professionals.

## 4.1 Study observational intervention

#### 4.1.1 Identity of study observational intervention

The study observational intervention is an electronic health diary, the patientMpower app. This has been developed specifically for patients with IPF. The patientMpower app is an electronic application downloaded to the patient's mobile phone or tablet device. The app is designed to allow the patient to report various parameters relevant to IPF and record these on a regular basis, ideally daily. The information recorded by the patient will be stored in a secure cloud system and will be 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 will be asked to report measurements on the patientMpower app each day. Patient-reported measures (at a minimum) will include FVC (one reading once/day), dyspnoea, activity (steps/day), distance walked per day and compliance with IPF medication. In addition. the impact of IPF on daily life (as response to PROM questions) should be reported once every week.

Additional patient-reported measures which can be reported on the patientMpower app include vital signs (e.g. heart rate, blood pressure), temperature, pulse oximetry, cough severity, activity causing worst dyspnoea and oxygen consumption. These are optional measurements and will only be recorded where practical for the patients.

#### 4.1.2 Method of assigning patients to study observational intervention

All patients who give informed consent and enter the study will be given access to the patientMpower app and Spirobank Smart home spirometer and will be encouraged to use them on a daily basis.

There is only one treatment group in this study. The same study-related observations will be assessed and recorded for all patients who are eligible and who give written informed consent.

#### 4.1.3 Blinding and procedures for unblinding

The study is open-label.

### 4.2 Management of exacerbations or adverse events and guidance on concomitant treatments

#### 4.2.1 Management of acute exacerbations or adverse events

Any exacerbations of the patient's IPF or any other underlying medical condition(s) should be treated according to standard procedures.

Any other adverse events should be treated according to standard procedures.

Any adverse events observed with medical treatments should be reported to the manufacturers of those treatments. (See Section 8.4 for further information on the process.)

#### 4.2.2 Guidance on concomitant treatments

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

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

### 4.3 Treatment compliance

Patients will use the patientMpower app to record daily compliance with medications prescribed for treatment of their IPF (if they are receiving medications for treatment of IPF).

## 5 Variables and their assessment

### 5.1 Efficacy

The objectives of this observational study are:

- 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 the patientMpower app

#### 5.1.1 Efficacy endpoints

#### 5.1.1.1 Primary endpoint

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

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

#### 5.1.1.2 Secondary endpoints

The secondary endpoints include

- the longitudinal trend in PROMs
- the correlation between patient-reported measures (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 the patientMpower app on the impact of IPF on daily life (PROM)
- the effect of the patientMpower app on medication compliance
- the acceptability and utility of the patientMpower app (from patient and healthcare professional perspective)

The secondary endpoint variables (reported by patients) are:

- 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; responses to questions in 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 will assess dyspnoea with the mMRC dyspnoea scale [12] which may be a useful prognostic indicator in IPF [13].

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

- FVC
- Dyspnoea [e.g. University of California San Diego (UCSD) Shortness of Breath Questionnaire or other measure usually used by the research sites] [14]
- 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 the patientMpower app as assessed by their response to questions:

- the instructions given in using the patientMpower app were clearly understandable (strongly agree/agree/disagree/strongly disagree)
- using the patientMpower app 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 the patientMpower app helped me to reach my personal exercise goal every day (strongly agree/agree/disagree/strongly disagree)
- using the patientMpower app helped me to walk further (or exercise more) compared with before (strongly agree/agree/disagree/strongly disagree)
- using the patientMpower app 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 the patientMpower app (strongly agree/agree/disagree/strongly disagree)
- the patientMpower app was easy to use (strongly agree/agree/disagree/strongly disagree)
- the effect of using the patientMpower app on the impact of lung fibrosis on my well-being and daily life (positive, negative)
- I found it tiring or irritating to use the patientMpower app (strongly agree/agree/disagree/strongly disagree)

- I want to continue using the patientMpower app after the end of the study (yes, no)
- I would recommend other people with my condition to use the patientMpower app (yes/no)
- what other measurements, reminders or information would be useful to have on the patientMpower app? (Open text for participant to give opinion)
- describe the benefits and/or disadvantages of using the patientMpower app (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 the patientMpower app versus not using it (yes, no preference, no)
- difficulty rating in using the patientMpower app (very easy, easy, difficult, very difficult)
- did using the patientMpower app help me to help the patient manage their IPF better? (yes, no)
- did using the patientMpower app 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 the patientMpower app after the end of the study (yes, no)
- what other measurements, reminders or information would be useful to have on the patientMpower app? (Open text for healthcare professional to give opinion)
- describe the benefits and/or disadvantages of using the patientMpower app (Open text for healthcare professional to give opinion)

### 5.1.2 Assessment of efficacy

The primary efficacy endpoint data will be assessed by analysis of changes in the patient-reported FVC over time and comparison with the clinic-measured FVC at beginning and end of the study, clinic-derived parameters and health outcomes over time.

The secondary efficacy endpoint data will be assessed by analysis of changes in the patient-reported health parameters (including PROMs) over time and comparison with clinic-derived parameters and health outcomes over time (described above in 5.1.1.2).

The acceptability and utility of the patientMpower app will be assessed by analysis of the responses to the patient and healthcare professional questionnaires (described above in 5.1.1.2).

## 5.2 Safety

It is not anticipated that any safety issues will arise from use of the patientMpower app or the Spirobank Smart spirometer.

Any adverse events (AEs) observed in patients who have received medical treatments should be reported to the manufacturers of those treatments. The process for reporting AEs is described in section 8.4 and further information on the definitions of and reporting requirements of AEs is given in Appendix 10.3.

There are no safety endpoints in this study.

## 5.3. Other variables

Demographic data (date of birth, gender, date of IPF diagnosis, other respiratory conditions, medication prescribed for IPF or respiratory conditions).

Type of smartphone or tablet device (i.e. iPad or Android tablet, iPhone or Android phone)

Engagement of patients with the patientMpower app will be assessed by analysis of the numbers of

- patients asked to take part in the study
- patients who give informed consent to take part in the study.
- consented patients who download the app application to their smartphone or tablet device
- patients who use the app at least once after downloading
- patients who use the app more than once
- frequency of use by each patient
- date intervals between informed consent, download, first use
- date intervals between first and subsequent uses
- frequency of recording FVC at home
- frequency of recording PROM at home
- frequency of recording other measures at home

### 5.3.2 Other assessments

Data on the air quality at the patients' geographical location can be made available to them via the patientMpower app during the study. It is possible that these data may be analysed retrospectively to see if there is any correlation between air quality and impact of IPF on patient quality of life, respiratory measurements or exacerbations.

Data on the ultraviolet index at the patients' geographical locations over the duration of the study may be captured. These data may be analysed retrospectively to see if there is any correlation between possible ultraviolet exposure and impact of IPF on patient quality of life or possible side-effects of IPF treatment.

### 5.4 Appropriateness of measurements

The primary endpoint parameter FVC is an important measure of disease severity in IPF and a decline in FVC is consistent with disease progression [1, 15].

The secondary endpoint parameters are measurements which are affected by the patient's IPF and respiratory health.

The questionnaires used to assess usefulness and patient acceptability have been used to assess these parameters for other patient support platforms.

## 6 Investigational plan

Patients who participate in the study will follow their usual care programme and will be encouraged to use the patientMpower app and MIR Spirobank Smart spirometer every day to record parameters relevant to their health status (described in section 5.1.1.2 above).

### 6.1 Visit schedule

The total observation period will be sixteen (16) ± eight (8) weeks. This time interval coincides with the interval between usual clinic visits.

### 6.2 Details of study procedures at all visits

#### 6.2.1 Patient recruitment process

The patient recruitment process is summarized in the flow-chart 1 on page 6 and in Figure 1 on page 10.

At a usual care visit to the study centre, the research team will discuss the study with the patient (face-to-face), confirm their understanding of the study processes and their willingness to participate. During the informed consent discussion, it will be made clear to the patient that their identity and email address will be made known to patientMpower Ltd and that data collected on the app will be stored and analysed by patientMpower Ltd.

Written informed consent will be obtained before any study-specific procedures and before installation of the patientMpower app.

The study starts at this visit (baseline visit).

After the patient has given written informed consent to participate, the study centre will advise patientMpower Ltd. of the email address of patient and that they have consented to participate.

patientMpower Ltd. will send an information pack via e-mail to the patient. This will include instructions on installation of the patientMpower app and Bluetooth pairing of the spirometer. patientMpower will also send a MIR Spirobank Smart spirometer to the patient. These will be sent to the patient within two working days of the baseline visit.

If requested by the patient, patientMpower Ltd will contact them to offer help with installation of patientMpower app and pairing of spirometer.

### 6.2.2 Baseline clinic visit

The study procedures and assessments during the observation period at each clinic visit are summarized in flow-chart 2 on page 7.

At a usual care visit to the study centre, the research team will discuss the study with the patient (face-to-face), confirm their understanding of the study processes and their willingness to participate.

Written informed consent will be obtained before any study-specific assessments and before installation of the patientMpower app.

The study starts at this visit.

The patient will be instructed in the correct use of the Spirobank Smart home spirometer and uploading of data to the patientMpower app. The patient's understanding of the patientMpower app, Spirobank Smart home spirometer and the study procedures should be checked before they leave the clinic.

Demographic data, medical history and concomitant therapy for IPF and other respiratory conditions will be recorded.

The following parameters will be assessed and recorded in the clinic records:

- spirometry (to include FVC)
- dyspnoea (e.g. UCSD Shortness of Breath Questionnaire or other measure usually used by the investigator sites)
  impact of IPF on daily life (using the same PROM as in the patientMpower app)

The study centre will advise patientMpower Ltd that the patient has consented to participate in the study and provide the patient's contact details.

patientMpower Ltd. will send the patient an information pack (via email) and a home spirometer (via regular mail or courier). The information pack will give instructions (including video clips) on how to install the patientMpower app onto your smartphone or tablet device and how to pair the spirometer with the app. During the installation, some information on the patient (e.g. date of birth and gender) will be recorded on the patientMpower app. If necessary, the patient may be loaned a tablet device (like an iPad) which will have the patientMpower app installed. If requested by the patient, patientMpower Ltd. will provide technical support to the patient in downloading the app and pairing with the spirometer.

### 6.2.3 Treatment and observation period

Patients will be encouraged to record the parameters described in section 5.1.1.1 and 5.1.1.2 on a regular basis.

The following should be recorded by the patient each day:

- FVC (one spirometry manoeuvre each day ideally at approximately the same time each day but this is not essential)
- compliance with medication prescribed for IPF (if prescribed)
- any changes to medication taken for IPF
- activity (number of steps per day)
- distance walked per day
- maximum level of dyspnoea

Impact of IPF on daily life (PROM) should be recorded by the patients every week.

Patients will receive reminders (via the patientMpower app) at appropriate intervals to record study parameters.

Other parameters should be recorded by the patient (if suitable measurement devices are available to the patient and where practical for the patient) frequently. Examples include duration of walking, number of episodes of walking, cough, heart rate, blood pressure, temperature, body weight, oxygen saturation and oxygen usage (e.g. cylinders/month).

If requested by the patient, patientMpower Ltd will provide technical support on correct use of the app or spirometer at any time during the study.

#### 6.2.4 End of treatment clinic visit (16 ± 8 weeks) and follow-up period

The following parameters will be assessed and recorded in the clinic records:

- spirometry (to include FVC)
- dyspnoea (e.g. UCSD Shortness of Breath Questionnaire or other measure usually used by the investigator sites)
- impact of IPF on daily life (using the same PROM as in the patientMpower app)
- medication adherence (if prescribed for IPF)
- changes in or addition of any new medicines for the treatment of IPF (if prescribed)
- exacerbations of IPF since previous visit
- hospitalisations due to IPF since previous visit

The patient and healthcare professional opinion on the usefulness and acceptability of the patientMpower app will be assessed and recorded. (The questions are described in section 5.1.1.2 above.)

# 7. Statistical methods and determination of sample size

This a pilot study to assess the feasibility of patients with IPF using the patientMpower app including home-based FVC to monitor their health.

## 7.1 Statistical design and model

Open-label, single-arm observational study.

## 7.2 Null and alternative hypotheses

Not relevant.

## 7.3 Planned analyses

Results will be collected and summarized for descriptive statistical display.

### 7.3.1 Primary analyses

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

The patient-reported FVC will be compared with the clinic-derived measures and health outcomes to determine if there are any correlations between them.

### 7.3.2 Secondary analyses

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

The patient-reported health parameters and will be compared with the clinic-derived measures and health outcomes to determine if there are any correlations between them.

The acceptability and utility of the patientMpower app will be assessed by analysis of the responses to the patient and healthcare professional questionnaires (described above in 5.1.1.2).

### 7.3.3 Safety analyses

None planned.

### 7.3.4 Interim analyses

None planned.

### 7.3.5 Health economic analyses

Health outcomes (e.g. exacerbations of IPF) will be recorded.

## 7.4 Handling of missing data

No imputations of missing data will be made.

## 7.5. Randomisation

Not relevant.

## 7.6 Determination of sample size

This is pilot study. The proposed sample size of 25 subjects has been chosen arbitrarily.

# 8. Informed consent, data protection and study records

## 8.1 Study approval, patient information and informed consent

The study will be approved by the relevant ethics committee(s) for the participating centre.

The study will be discussed with each patient and they will be provided with written information (both electronic and paper) describing the study conditions and procedures.

All patients will give electronic written informed consent before participation.

## 8.2 Data quality assurance

All endpoint data will be stored on a central database for analysis. The data as reported by the patients will not be queried before descriptive statistical analysis tables are prepared.

## 8.3 Records

### 8.3.1 Source documents

The original electronic data recorded in the patientMpower application will be the source document.

### 8.3.2 Direct access to source data and documents

Source data verification will not be performed.

### 8.3.3 Storage of records

Medical data relating to patient care will be stored in the medical records according to the usual procedures of the investigator sites.

The endpoint data collected by the participants and recorded on the patientMpower app will be stored in a secure cloud database managed by patientMpower Ltd. These data will be available to patients indefinitely to aid them in self-management of their medical condition. Patients can request deletion of their data from the patientMpower cloud database at any time.

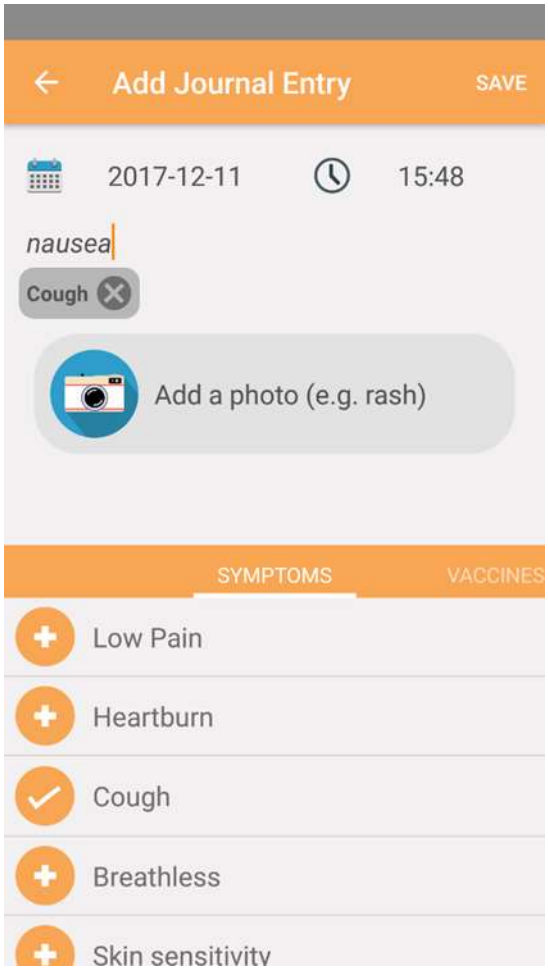
## 8.4 Reporting of adverse events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All observed AEs must be reported to the manufacturers of the medicinal product(s) administered (irrespective of causal relationship).

The patientMpower app contains a journal entry page where a patient can enter information from a list of pre-defined symptoms (e.g. cough) or can enter free text (e.g. “nausea”) in example screenshot shown below in Figure 8.4: 1. Therefore, it is possible that the patient can record AEs which may or may not be related to drug treatment.

**Figure 8.4: 1 Screenshot of journal entry page:**




As there could be a delay of up to sixteen weeks between the patient recording an AE on the journal entry page and the investigator becoming aware of the event, the following process is proposed to facilitate timely reporting of AEs to medicine manufacturers.

- On the first working day of each month, patientMpower Ltd will prepare a listing of all events reported on the journal entry page for each patient. This listing will contain the following information: date of preparation of listing, patient identification number and all reported events (with date and time) per patient.

- patientMpower Ltd will send the listing to the principal investigator at the study centre..

- The investigator will review the listing of events and compare with the medicinal treatments given to each patient and determine if any of the events recorded by patients are AEs (as defined above).

- Any AEs temporally associated with the use of a medicinal product should be reported to the manufacturers of the relevant medicinal treatments.

If an AE is associated with a Boehringer Ingelheim (BI) medicinal product, the event should be reported to the BI contact address described in section 10.3.3 of Appendix 10.3.

## 8.5 Statement of confidentiality

Patients will only be identified by a unique identification number on the study database and data will be anonymised. All data will be treated as confidential.
Each patient's data is linked to their unique identification number.

The patientMpower app is designed with stringent security protocols. The solution is hosted in Google Compute Engine. The security protocols used include:

- app uses a PostgreSQL database (https://www.postgresql.org/) which is backed up nightly
- app is patched regularly to ensure it is maintained against security vulnerabilities
- only certain Internet Protocol (IP) addresses can login to the cloud infrastructure using Secure Shell (SSH) with IP whitelists and public/private key access only
- built-in firewalls
- encrypted data storage
- patientMpower staff access to the PostgreSQL database, and content system is restricted and monitored
- a unique username and password for each user.
- audit and accounting of all access to the system is recorded. In the event of any staff looking at data without proper authorisation, there is an audit trail of what data was viewed
- data transfer between the patient mobile device and cloud server is sent securely via Transport Layer Security (TLS) and the app's cloud infrastructure uses an Extended Validation Secure Sockets Layer (SSL) Certificate issued by Digicert (https://www.digicert.com)
- data on the server is encrypted, only authenticated users can access the server

## 8.6 Completion of study

The study will be complete when 25 patients have completed the 16-week observation period.

If it appears to be unlikely that the target number of patients can be achieved (e.g. because of slow recruitment) a lower target will be set (after discussion and agreement with the investigator).

### 8.7 Protocol violations

All data will be analysed on an intention-to-treat basis without regard to protocol violations.

## 9 References


1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement — idiopathic pulmonary fibrosis: evidence based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
2. Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St. George's Respiratory Questionnaire. Thorax 2010; 65: 921-6.
3. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax 2012. Doi 10.1136/thoraxjnl-2012-201581.
4. Patel AS, Siegert RJ, Keir GJ, Bajwah S, Barker RD, Maher TM et al. The minimal important difference of the King's Brief Interstitial Lung Disease (K-BILD) and forced vital capacity in interstitial lung disease. Respir. Med. 2013; 107: 1438-43.
5. Russell A-M, Jones G, Sabella R, Cassidy N, Burge G, Lines S et al. Health status and impact of living with idiopathic pulmonary fibrosis (IPF): UK and Ireland Delphi survey. Eur Resp J 2016 48 OA4573 doi 10.1183/13993003congress-2016.OA4573
6. Russell A-M, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, Wells AU, Maher TM. Daily home spirometry: an effective tool for detecting progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2016. 10.1164/rccm.201511-2152OC.
7. Johansson KA, Vittinghoff E, Morisset J, Lee JS, Balmes JR, Collard HR. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. Eur. Respir. J. 2017 50 1602406 https://doi.org/101183/13993003.02406-2016.
8. Edwards C, Cassidy N, Costello E, Russell A-M. Pilot study to test the utility and acceptability of an electronic health record

(patientMpower) for patients with lung fibrosis. iproc 2017;3(1): e10) doi:10.2196/iproc.8389
9. Edwards C, Cassidy N, Costello E, Russell A-M. A longitudinal approach to supported self-management: sustainability of the idiopathic interstitial pneumonia (IIP) electronic health journal (patientMpower) with integrated home spirometry. Ir. J. Med. Sci. 2017 186 (Suppl 10) S440.
10. O'Regan A, Edwards C, Costello E. A pilot-scale observational study of self-monitoring of symptoms and spirometry via the patientMpower platform in patients with idiopathic pulmonary fibrosis. www.clinicaltrials.gov NCT 03104322.
11. O'Seaghdha C, Edwards C, Costello E, Sexton D. A pilot-scale, randomized study comparing self-monitoring of weight and blood pressure via an electronic health journal (patientMpower platform) with usual care in haemodialysis patients. www.clinicaltrials.gov NCT 03403491.
12. Stenton C. The MRC breathlessness scale. Occupational Med. 2008; 58: 226-7.
13. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K et al. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur. Respir. J. 2010; 36: 1067-72.
14. Eakin EG, Resnikoff PM, Prewitt LM, Ries AL, Kaplan RM. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. Chest 1998; 113: 619-24.
15. Richeldi L, du Bois R, Raghu G, Azuma A, Brown KK, Costabel U et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl. J. Med. 2014; 370: 2071-82.

# 10 Appendices

## 10.1 modified Medical Research Council Dyspnoea Scale

| Grade | Description of breathlessness |
|---|---|
| 0 | I only get breathless with strenuous exercise |
| 1 | I only get short of breath when hurrying on level ground or walking up a sight hill |
| 2 | On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace |
| 3 | I stop for breath after walking about 100 yards or after a few minutes on level ground |
| 4 | I am too breathless to leave the house or I am breathless when dressing |

## 10.2 Instructions for performing spirometry at home

Patients will perform one spirometry reading at home once per day (ideally at the same time each day).

Each patient will be supplied with a Spirobank Smart home spirometer (Medical International Research, Via del Maggiolino 125, 00155 Roma, Italy. www.spirometry.com). This spirometer will automatically upload Peak Expiratory Flow (PEF), Forced Expiratory Volume in 1 second ($FEV_1$), FVC and FEV1/FVC data directly to the patientMpower app.

## 10.3 Management and reporting of adverse events/adverse reactions

### 10.3.1 Definitions of adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a

causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. ADRs may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

### 10.3.2 Adverse event and serious adverse event collection and reporting to regulatory authorities and ethics committees.

The investigator shall maintain and keep detailed records of all AEs in their patient records.

The investigator will be responsible for reporting AEs which occur during the conduct of the study to the competent regulatory authorities, accredited Institutional Review Boards and/or Independent Ethics Committee(s) [IRB/IEC(s)] in accordance with the applicable laws and regulations.

### 10.3.3 Adverse event reporting to Boehringer Ingelheim (for adverse events associated with BI products)

All adverse events associated with use of any Boehringer Ingelheim medicinal products must be reported to Boehringer Ingelheim.

The investigator will report

1. all ADRs (serious and non-serious)
2. all AEs with fatal outcome
3. pregnancies in female subjects and partners of male subjects

which are associated with nintedanib by fax to the BI Unique Entry Point as specified in Safety Data Exchange Agreement using the BI NIS AE report form with the following timelines.

Report to:
Dr Mike Warwick-Sanders
Boehringer Ingelheim UK and Ireland Pharmacovigilance Department
Phone: 01 2913960
Fax: +44 1344 742661
E-mail: PV_local_UK_Ireland@boehringer-ingelheim.com

All Serious ADRs and AEs with fatal outcome shall be forwarded immediately [within twenty-four (24) hours or next business day whichever is shorter]. All non-serious ADRs and Pregnancy Monitoring Forms shall be forwarded within seven (7) calendar days

The investigator will carefully assess whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event:
The definition of an ADR implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Causality should be assessed for each event as either “yes” or “no”. No other variation should be reported.

Intensity of adverse event
The intensity of the AE should be judged based on the following:

- mild: awareness of sign(s) or symptom(s) which is/are easily tolerated
- moderate: enough discomfort to cause interference with usual activity

- severe: incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken BI Drug administered for the disease in scope of the study, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to BI by means of BI Pregnancy Monitoring Form provided.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Reporting of related Adverse Events associated with any other BI drug
The investigator is encouraged to report all adverse events related to any BI drug other than nintedanib according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

# 11 Summary of clinical study protocol modifications

None to date.