Supplementary material

- S1. EMERGE guideline
- S2. Variables and data collection methods
- S3. Descriptive results of the variables

Supplement 1 (S1). EMERGE guidelines [1]

Section	Item No	Recommendation	Reported on page No / line No
Minimum reporting criteria			
	1a	**Phases of medication adherence**: State the phase(s) of medication adherence studied (i.e. initiation, implementation, and persistence) and justify, where possible, the reasons the study focuses on this/these phase(s).	**6**
	1b	**Operational definition**: Provide the precise operational/working definition for each phase of medication adherence studied (i.e., initiation, implementation, and persistence).	**6**
	1c	**Measurement**: Specify the methods of measuring medication adherence (e.g., self-report, claims data, blood sampling, electronic monitoring). Consider each phase studied (i.e., initiation, implementation, and persistence), with details on the performance of the measures (e.g., validity, reliability, and potential bias).	**5, Supplement**
	1d	**Results**: Describe the results of the analysis appropriate to each phase of medication adherence studied (i.e., initiation, implementation, and persistence).	**9-10**
Abstract			
	2a	Present in the abstract, in as much detail as space permits, information on the 4 minimum reporting criteria (i.e., items 1.a- 1.d).	**2**

Background/introduction			
	3a	Summarize what is known about the topic with appropriate reference to the phase(s) of medication adherence (i.e., initiation, implementation, and persistence).	3,4
	3b	Describe the rationale and/or framework guiding the medication adherence study (e.g., theoretical framework and implementation science model).	4
Study objectives or hypotheses			
	4a	State the study objectives or hypotheses with reference to the phase(s) of medication adherence studied and context (patient population and setting).	4

Methods			
Design & participants	5a	Describe the setting in which the study was done. Refer to factors relevant to medication adherence, such as characteristics of the healthcare system, organization, and the team.	4
	5b	State whether medication adherence was an eligibility criterion (e.g., inclusion/exclusion). If so, define the measures and rules used.	4
	5c	Describe routine care related to the management of medication adherence, if applicable (e.g. routine assessment of medication adherence, adherence support programs, and provider training).	NA
Measurement	*PLEASE REFER TO ITEM 1.C. IN ADDITION TO THE "MEASUREMENT" ITEM BELOW*		
	6a	Measurement methods can themselves affect medication adherence (e.g., questionnaires, blood sampling, and electronic monitoring). Address this problem as appropriate.	4,6
Intervention (where applicable)	7a	For intervention and comparator groups, describe each relevant level of the medication adherence intervention (e.g., healthcare system, organization, and provider and patient/caregiver).	NA
	7b	Describe any implementation strategy that contributes to the translation (e.g., uptake, delivery, and sustainability) of the medication adherence intervention in clinical practice, if applicable.	NA
Statistical analysis	8a	If medication adherence is an outcome variable, justify the statistical methods, given the characteristics of the variable (e.g., phases of medication adherence, data type, statistical distribution, data censoring, longitudinal dependence).	7,8
	8b	If medication adherence is an explanatory variable, describe how it is related to the outcome(s) (e.g., causal pathway, temporal sequence).	7,8

Results			
	PLEASE REFER TO ITEM 1.D IN ADDITION TO THE "RESULTS" ITEMS BELOW		
	9a	Determine whether non-participation and/or dropout are associated with non-adherence, and provide any relevant data.	NR
	9b	Present sample characteristics relevant to medication adherence (e.g., those related to socio-demographics and therapy, condition, patient, caregiver, healthcare team/healthcare system).	9

Discussion			
	10a	Discuss study strengths and limitations with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, and persistence).	13,14
	10b	Discuss the study findings in the context of existing evidence on medication adherence (e.g., theory, measurement, intervention effects).	11,12
	10c	Discuss the generalizability (external validity) of the study findings with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, and persistence).	13

Supplement 2 (S2): Variables and data collection methods

Variables	Data collection method	Additional note
Predictors		
Age	Medical file	Collected at baseline
Marital status	Self-reported questionnaire developed for the purpose of this study	Response options: Partner, no partner (anymore)
Education level	Self-reported questionnaire developed for the purpose of this study	Response options: -Lower education (Primary school not finished, Primary school finished (till the age of 12), Lower secondary school finished (till the age of 15) -Moderate education (Higher secondary school finished (till the age of 18), Continuing vocational training) -High education (Bachelor, Masters, Doctor)
Health Literacy	Subjective health literacy screener (SHLS)	- **Definition** health literacy: "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions" [2]. - **Background information**: Single-item variant with the question 'how confident are you in filling out medical files by yourself' scored significantly better than two other investigated questions to detect patients with inadequate health literacy. - **Response options**: 5-point likert scale (i.e. none, a little, somewhat, most, all of the time). Score between 0 and 2 (i.e. none, a little or somewhat of the time) was seen as inadequate health literacy [3,4]. - **Self-reported** - **Recall period**: current state - **Psychometric properties**: Threshold of "somewhat" response: optimized sensitivity and specificity in a veteran outpatient population [3] and a primary care population [4].
Intentions to be adherent and the level of motivation	Investigator-developed questionnaire based on the manual for health services researchers and the stages-of-change theory [5].	- **Background information**: This questionnaire consists of 2 parts. - **Self-reported** - **Recall period:** current state - **Part 1:** Intentions are seen as the precursors of a specific behaviour and were therefore assessed using a three-item questionnaire based on 'the manual for health services researchers' of Francis J et al. [5]. The three

		statements are: 'I expect to […]', 'I want to […]' and 'I intend to […]'. o **Response options:** Each statement had to be scored on a scale ranging from 1 (i.e. strongly disagreeing) to 7 (i.e. strongly agreeing). The mean score for every statement was reported with a higher score reflecting a higher intention to do a specific behaviour. - **Part 2:** In the line with the stages-of-change theory, we used a two-item questionnaire to classify patients according to their level of motivation and readiness to change their medication taking habits. - **Response options:** Question 1 asks about the importance of always taking the medication as prescribed. Scale ranging between 0 (not important at all) to 10 (very important). A score below 8 suggests that patients are in the pre-contemplation phase, meaning that they do not intent to take actions to change or do the behaviour. If the score is 8 or higher, a second question on their perceived confidence or capability in following the regimen correctly will be asked. Scores again range from 0 (not at all confident) to 10 (very confident), with a score below 8 indicating that patients are in the contemplation phase, meaning they intent do act or to the behaviour. Higher scores reflect sufficient motivation.
Knowledge	Self-reported questionnaire developed for the purpose of this study	- **Background information:** Investigator developed with questions on IPF and pirfenidone treatment. - **Response options:** Six true/false/I don't know questions. Correct answers received a point resulting in a score ranging between 0 and 6. - **Self-reported** - **Recall period**: current state
Barriers to taking pirfenidone	Inventory of Medication Adherence Barriers (IMAB) Note: this questionnaire was adapted for use in pirfenidone	- **Definition barrier**: 'a person's estimation of the level of challenge of social, personal, environmental, and economic obstacles to a specified behaviour or their desired goal status on that behaviour' [6]. - **Background information**: The questionnaire consists of 27 items - **Response options**: 5-point likert scale (i.e. never, rarely, sometimes, often, always) resulting in a median score for all patients, a range of reported barriers and the percentage of patients reporting at least one barrier. Additionally, the percentage of patients experiencing a specific barrier was assessed by considering the barrier 'absent' if scored as 'never' and

		'present' if scored otherwise. - **Self-reported** - **Recall period**: not applicable (barriers currently experiencing)
Side effects to pirfenidone	Self-reported questionnaire developed for the purpose of this study	- **Background information**: Investigator developed - **Response options**: We asked patients if they have experienced any side effects and if yes, they were asked to specify which one. Also, they were asked how frequent it occurred (4-point likert scale: '1=rarely' to '4=always') and how much discomfort it gave (6-pont likert scale: '0=not disturbing' to '5=very disturbing'). - Preferably taken in **interview style** with investigator. If not possible: self-reported - **Recall period:** 1 week
Depression	Patient Health Questionnaire (PHQ)	- **Background information:** The PHQ-9 was used to assess symptoms of depression, as it is a reliable and validated self-administered nine-item questionnaire based on the nine diagnostic criteria for DSM-IV depressive disorders. The PHQ-2 was used as a first-step approach to screen for depressed mood. It contains the first two questions of the PHQ-9, representing the core symptoms of major depressive disorder. In case of a positive score on PHQ-2, the PHQ-9 was given to the patient. - **Response options**: 4-point likert scale (0 =not at all, to 3 =nearly every day) o PHQ-2: score ranging from 0 to 6 (Patients with a positive result, i.e. a score of 3 or more were further screened with the PHQ-9) o PHQ-9: Score ranging from 0 and 27. Cut-off points of 5, 10, 15, and 20 represent the lower limits of mild, moderate, moderately severe, and severe depression, respectively [7]. In case of a positive score of 10 or more, the patient's pulmonologist was alerted. o Note: In this study, results were dichotomized based on the cut-off point of 10. - **Self-reported** - **Recall period**: 2 weeks - **Psychometric properties:** Internal validity: Cronbach's alpha of 0,87 in primary care population [7]. Cut-off point of 10: sensitivity of 88% and

		specificity of 88% for major depression in primary care population [7,8]
Medication adherence to pirfenidone	Basel Assessment of Adherence to Immunosuppressive medication Scale (BAASIS©) [9] Note: We adapted the questionnaire to pirfenidone.	- **Definitions**: o Taking adherence: whether there was an omission of at least one dose. If yes, the patient was asked how many times this had happened. o Drug holiday: whether at least two consecutive doses were missed o Dosing adherence: whether the prescribed dose had been adapted o Discontinuation: whether the prescribed medication had been discontinued. - **Response options**: Questions were scored dichotomously and all deviating answers (i.e. questions answered by 'yes') were scored as non-adherent. In case of dosing nonadherence or discontinuation, patients were asked whether they decided to change their dose or discontinue on their own or someone else initiative. - **Interview style** when possible. The patient was interviewed by the researcher at each study visit. In case this was not possible, the patient self-reported his/her adherence behaviour. - **Recall period**: 4 weeks - **Psychometric properties:** Internal consistency: Cronbach's alpha of 0,70 in kidney transplant population [10].
Outcomes		
DLco% predicted	Medical file	Collected at visit 1, visit 3, visit 4, visit 5 and visit 6
DLco% predicted change	Computed variable	A difference of 15% is considered significant. Options: stable, negative decline, positive increase. Calculated between pre-specified time points (between visit 1 and visit 4, between visit 1 and visit 6)
FVC% predicted	Medical file	Collected at visit 1, visit 3, visit 4, visit 5 and visit 6
FVC% predicted change	Computed variable	A difference of 10% is considered significant. Options: stable, negative decline, positive increase. Calculated between pre-specified time points (between visit 1 and visit 4, between visit 1 and visit 6)
Perceived health status	EQ-5D-5L (EuroQol Research Foundation questionnaire) [11,12]	- **Background information:** The questionnaire consists of 2 parts - **Self-reported** - **Recall period**: current state - The EQ descriptive system comprises five dimensions: mobility, self-care,

		usual activities, pain/discomfort, anxiety/depression. ○ **Response options:** Each dimension has 5 levels of response options (i.e. 1= no problems, 2= slight problems, 3=moderate problems, 4= severe problems and 5= extreme problems) and the combined answers of the dimensions result in a five-digit number describing the patient's health. This five-digit number can be converted in a single index value. We report the individual domains as well as the single index value. For that, we used the Belgian reference value set [13]. **-Psychometric properties:** Good psychometric properties across a range of populations [14] Internal validity: Cronbach's alpha of 0,80 in a fibrotic ILD population [15]
Quality of life	King's Brief Interstitial Lung Disease questionnaire (K-BILD) [16]	- **Background information**: The K-BILD is a 15-item questionnaire measuring the health-related quality of life (HRQoL) of patients with interstitial lung diseases [16]. It consists of three domains: breathlessness and activities, psychological and chest symptoms. - **Response options**: Each question has a seven-point response scale resulting in a total score ranging between 0 and 100 with a higher score reflecting a higher HRQoL. The mean and standard deviation are calculated for all items as well as the scores of each individual domain. - **Self-reported** - **Recall period**: 2 weeks - **Psychometric properties:** -Cronbach's alpha for the total score: 0,94 in ILD population 16] The minimal important difference of 8 points for the K-BILD total score [17]

Legend S2: Abbreviations: BAASIS: Basel Assessment of Adherence to Immunosuppressive medication Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; ILD: interstitial lung diseases; IMAB: Inventory of Medication Adherence Barriers ; IPF: idiopathic pulmonary fibrosis; HRQoL: health-related quality of life; K-BILD: King's Brief interstitial lung disease; PHQ: patient health questionnaire; SHLS: Subjective health literacy screener

Supplement 3. Descriptive results variables

		Baseline (Visit 1)	Six weeks (Visit 2)	Three months (Visit 3)	One year (Visit 4)	One year and a half (Visit 5)	Two years (Visit 6)
Predictors							
Health literacy	N Inadequate n (%)	53 11 (20)					
Knowledge	N Median total score (IQR) Mean (SD) Range Score lower than 6, n (%)		47 6 (0) 5.7 (1) 1-6 6 (12.8)		33 6 (1) 5.6 (0.9) 2-6 8 (24.2)		9 6 (1) 5.6 (0.7) 4-6 3 (33.3)
Side effects to pirfenidone	N Patients experiencing min 1 side effect, n (%) Number of side effects/patients Median (IQR) Range		50 37 (74) 1 (2) 0-5	44 35 (79.5) 1 (2) 0-7	37 23 (62.2) 1 (3) 0-5	22 15 (68.2) 1.5 (3) 0-4	11 9 (81.8) 3 (4) 0-6
Depression	N Total score: median (IQR) Total score: range Moderate depression n (%)		47 3 (5) 0-17 8 (17)	44 4 (7) 0-14 8 (18.2)	33 3 (6) 0-13 2 (6.1)		9 2 (4) 0-7 0
Intentions to be adherent to treatment[#]	N 'I expect to […]' Mean (SD) Range 'I want to […]' Mean (SD) Range 'I intend to […]' Mean (SD) Range	50 6.7 (1) 1-7 6.9 (0.9) 1-7 6.9 (0.9) 1-7	48 6.8 (0.5) 5-7 6.9 (0.1) 5-7 6.9 (0.1) 5-7		34 6.7 (1.1) 1-7 6.8 (1) 1-7 6.8 (0.9) 2-7		10 7 (0) 7 7 (0) 7 7 (0) 7
Level of motivation[#]	N Pre-Contemplation n Contemplation n Sufficient motivation n	50 0 1 49	48 0 0 48		34 0 0 34		10 0 0 10

Pirfenidone medication adherence	N Taking nonadherence n (%) N Drug holiday n (%) N Dosing nonadherence n (%) N Discontinuation n (%) N Omitted to take pirfenidone n (%) 1 time 2 times 3 times 4 times More than 4 times		52 11 (21.2) 11 2 (18.2) 52 0 52 0 10 7 (70) 1 (10) 0 1 (10) 1 (10)	44 11 (25) 11 2 (18.2) 44 0 44 0 11 6 (54.5) 3 (27.3) 1 (9.1) 0 1 (9.1)	36 12 (33.3) 12 0 35 0 35 0 12 7 (58.3) 2 (16.7) 1 (8.3) 2 (16.7) 0	24 8 (33.3) 8 1 (12.5) 24 1 (4.2) 24 0 8 4 (50) 2 (25) 1 (12.5) 0 1 (12.5)	11 4 (36.4) 4 0 11 0 11 0 4 2 (50) 1 (25) 0 1 (25) 0
Barriers to medication adherence[#]	N Total numbers of barriers Median (IQR) Mean (SD) Range Persons having min 1 barrier n (%)		48 1 (4) 3.2 (4.3) 0-15 34 (70.8)		34 4 (5) 3.8 (3.4) 0-11 26 (76.5)		8 4 (6) 5.8 (5.9) 1-19 8 (100)
Outcome variables							
DLco % predicted	N Mean (SD) Range Median (IQR)	54 58.1 (14.7) 24.2-111 58.5 (18.3)		49 58.4 (14) 29-103 57 (12)	41 56.1 (15.4) 23-99 56 (17)	21 54.2 (17.4) 25-102 51 (19)	11 58.3 (17.6) 42-98 51 (22)
FVC % predicted	N Mean (SD) Range Median (IQR)	54 88 (18.3) 50-126 88 (29)		50 89.6 (21.4) 42-147 89 (31)	41 87.6 (19.3) 54-120 89 (28)	21 85.1 (23.5) 39-116 89 (28)	11 79.9 (17.8) 46-101 84 (23)
Perceived health status EQ-5D-5L	Descriptive health index, N Median (IQR) Mean (SD)	53 0.849 (0.191) 0.805 (0.193)		45 0.847 (0.232) 0.803 (0.190)	34 0.860 (0.192) 0.829 (0.161)	22 0.797 (0.278) 0.752 (0.190)	10 0.824 (0.183) 0.794 (0.205)
Quality of life K-BILD	N Total score Mean (SD) Range Breathlessness/activities Mean (SD) Range Psychological Mean (SD)	55 58.9 (11.5) 33.3-100 50.7 (18.4) 0-100 57 (14.6)		44 61.3 (10.5) 35.5-84.6 52.3 (19.5) 0-100 60.6 (15.7)	34 62.5 (12.7) 36.5-90.8 51.8 (17.3) 0-79.9 64.5 (18)	23 60 (12.3) 36.5-90.8 49.3 (17.6) 0-79.9 59 (17.2)	10 62.5 (11.4) 47.8-84.6 55.7 (13.5) 39.9-79.9 61.6 (18.2)

	Range	28-100		32.2-100	33.9-100	25.3-100	41.2-100
	Chest symptoms						
	Mean (SD)	75.2 (19.1)		77.5 (18.9)	75.5 (20.2)	72.8 (16.3)	79.8 (18.1)
	Range	17.3-100		17.3-100	32.1 (100)	32.1-100	44-100

List of references from the supplement

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