Digital home resources in clinical trial management

Marlies Wijsenbeek
Erasmus MC

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Disclosures

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- Boehringer Ingelheim; Hoffman-La Roche; Galapagos; Respivant; Novartis; Savara

All fees and grants were paid to my institution

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Digital home resources in clinical trial management

Experiences from the ILD field

- Why do we want home based measurements in trials ?
- What have we learned so far?
- What are the challenges?

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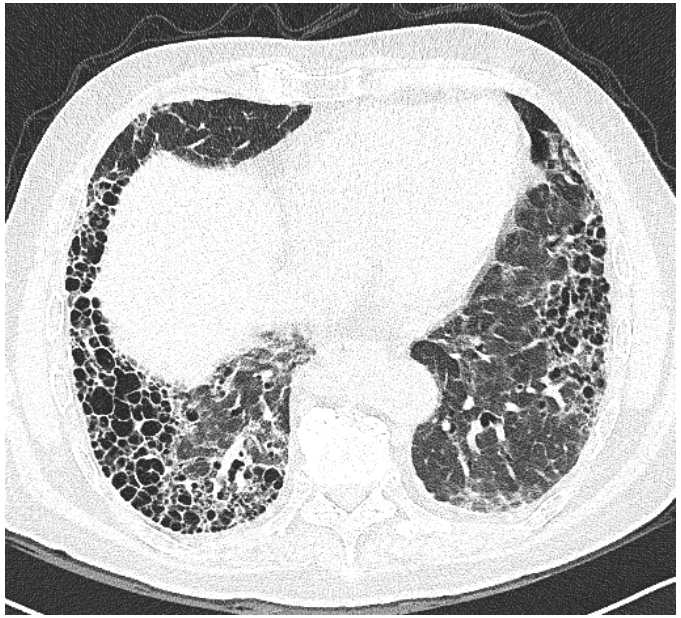
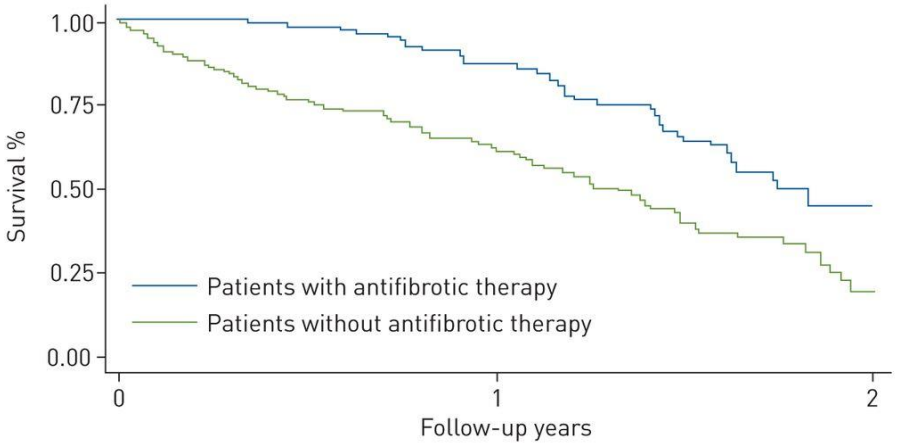
The patient with a progressive deadly disease, in need for better treatments



Included with permission of patient

Idiopathic Pulmonary Fibrosis



Patients at risk n			
With antifibrotic therapy	281	129	57
No antifibrotic therapy	252	139	93

Jürgen Behr et al. Eur Respir J 2020;56:1902279

Outcomes of clinical trials should reflect how a patient **feels, functions and survives**

Most used endpoints in pulmonary studies:

- Lungfunction
- Patient reported outcomes
- 6 minute walk test
- Accelerometry
- Imaging
- Blood biomarkers
- Acute exacerbations/ hospitalisations
- Treatment failure

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Trial design & endpoints

>12 visits in 12 months

Only 6 visits really require presence in the hospital

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	EOT_A[1]	FU[1]
	Screening*		Treatment#												FU
Weeks of treatment			0	2	4	6	12	18	24	30	36	44	52		+4
Day	Before or at the latest at visit 1	≥ 4d before V 2	1	15	29	43	85	127	169	211	253	309	365		+28
Time window				±3	±3	±3	±3	±7	±7	±7	±7	±7	±7		+7
Informed consent	X*														
HRCT sent to central review[2]	X														
Demographics		X													
Medical history		X	X												
Adverse events, concomitant medication		X	X	X	X	X	X		X		X		X	X	X
In-/exclusion criteria		X	X												
Physical examination, vital signs		X	X	X	X	X	X		X		X		X	X	X
Safety Laboratory (blood and urine)		X[3]	X	X	X	X	X	X[4]	X	X[4]	X	X[4]	X	X	
Pregnancy test[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample[6]					X				X						
Serum and plasma biomarker samples[7]			X				X		X		X		X	X	
RNA sample[7]			X						X				X	X	
Serum banking samples[7]			X				X		X		X		X	X	
DNA banking sample (optional)[8]			X												
HCRU assessments			X	X	X	X	X		X		X		X	X	
Non-elective hospitalization				X	X	X	X		X		X		X	X	X
Spirometry (FVC)[9]		X	X	X	X	X	X		X		X		X	X	X
SpO_2 (earlobe or forehead, resting)			X						X				X	X	
DL_{CO}[9]		X	X						X				X	X	
HRCT (optional)[10]			X						X				X	X[11]	
Resting 12-lead ECG[12]			X						X				X	X	
Questionnaires: K-BILD, L-PF Symptoms & Impact, EQ-5D, PF-IQOLS[13]			X				X		X		X		X	X	
Review questionnaires for completeness			X				X		X		X		X	X	
Acute ILD Exacerbations				X	X	X	X		X		X		X	X	X
Randomization			X												
IRT call/notification	X[14]		X		X		X		X		X		X	(X)	
Administer 1st trial medication at the clinic			X												
Dispense trial medication			X		X		X		X		X		X		
Collect trial drug					X		X		X		X		X	X	
Compliance / drug accountability				X	X	X	X		X		X		X	X	
Trial medication termination														X	
Vital status assessment[15]													X		
Conclude subject participation															X[16]

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1908681/suppl_file/nejmoa1908681_protocol.pdf

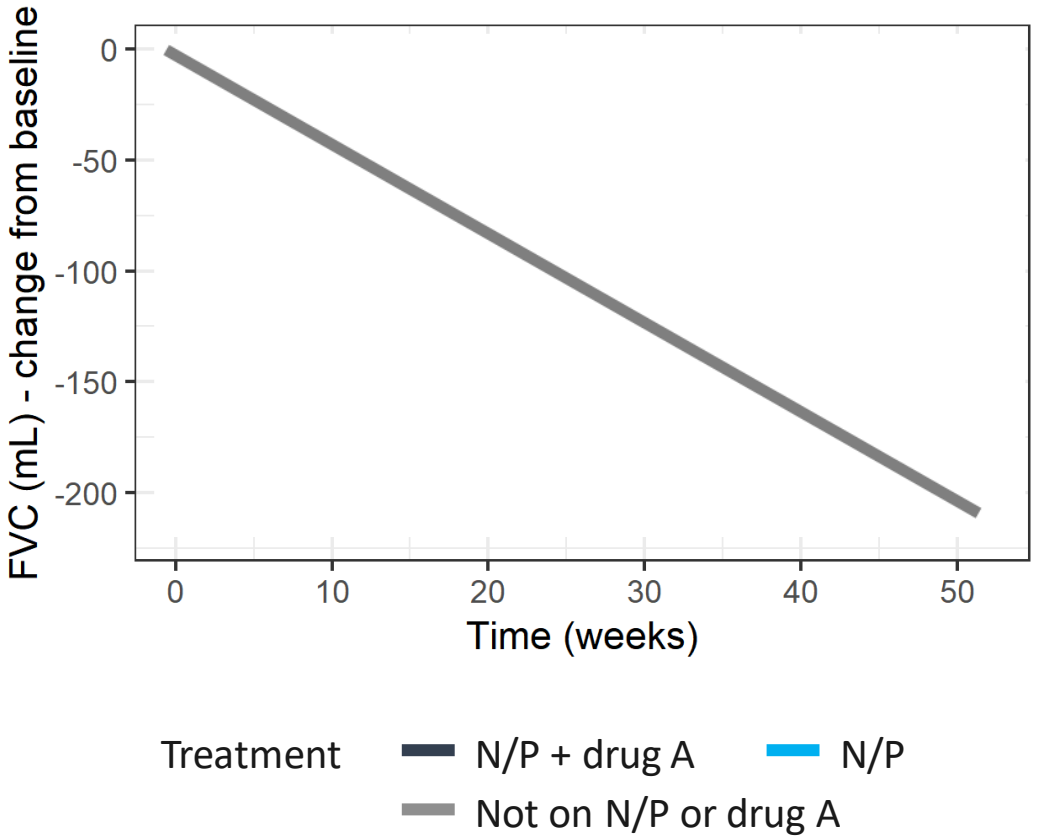
Access to studies to studies may be an issue

Included with permission of patient

- Travel distance to specialised centres
- Dependend on oxygen suppletion
- Energy limitations
- Hesitant to burden family
- COVID-19 impact
- Too much time in the hospital

Another problem: we need more patients or longer trials to find and effect of treatments

Many new trials have smaller margins to detect changes



The example of IPF

The natural decline in FVC in IPF
200 ml/year

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; N, nintedanib; P, pirfenidone

Santermans E *et al. Adv Ther* 2019;36:3059–70; Johannson KA *et al. Eur Respir J* 2017;50:pii1602406

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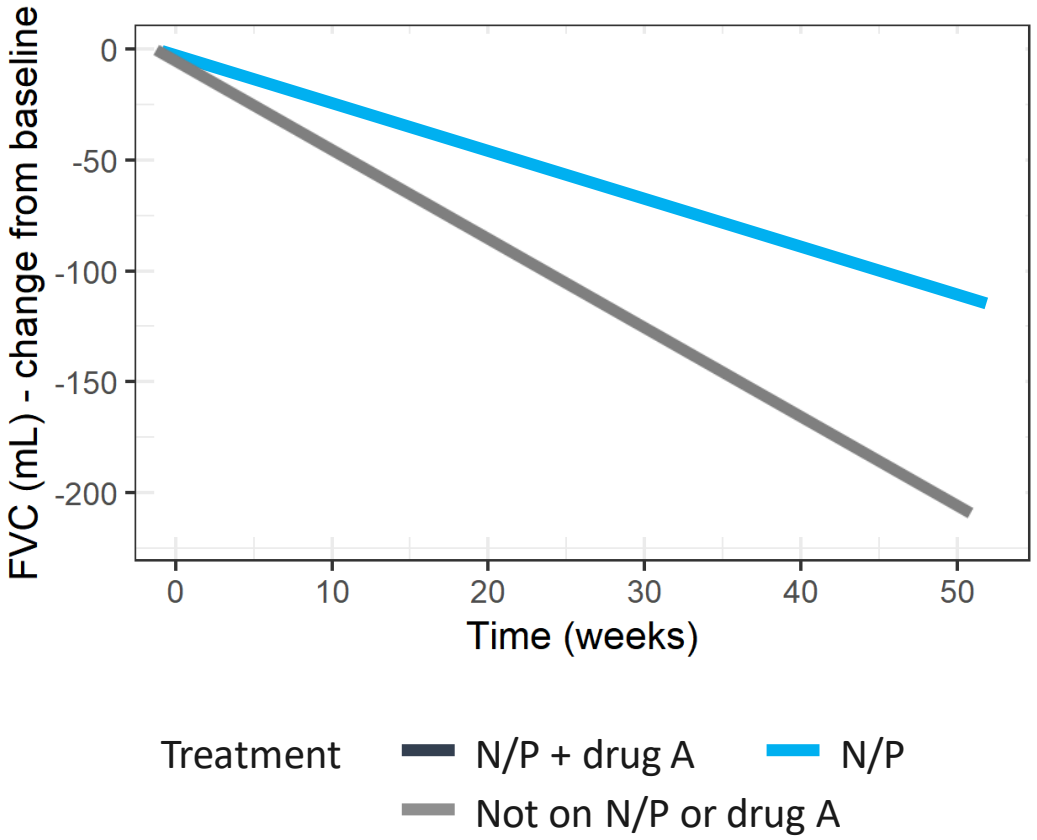

The on ”anti-fibrotics” decline in FVC in IPF 100 ml/year

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; N, nintedanib; P, pirfenidone

Santermans E *et al. Adv Ther* 2019;36:3059–70; Johannson KA *et al. Eur Respir J* 2017;50:pii1602406

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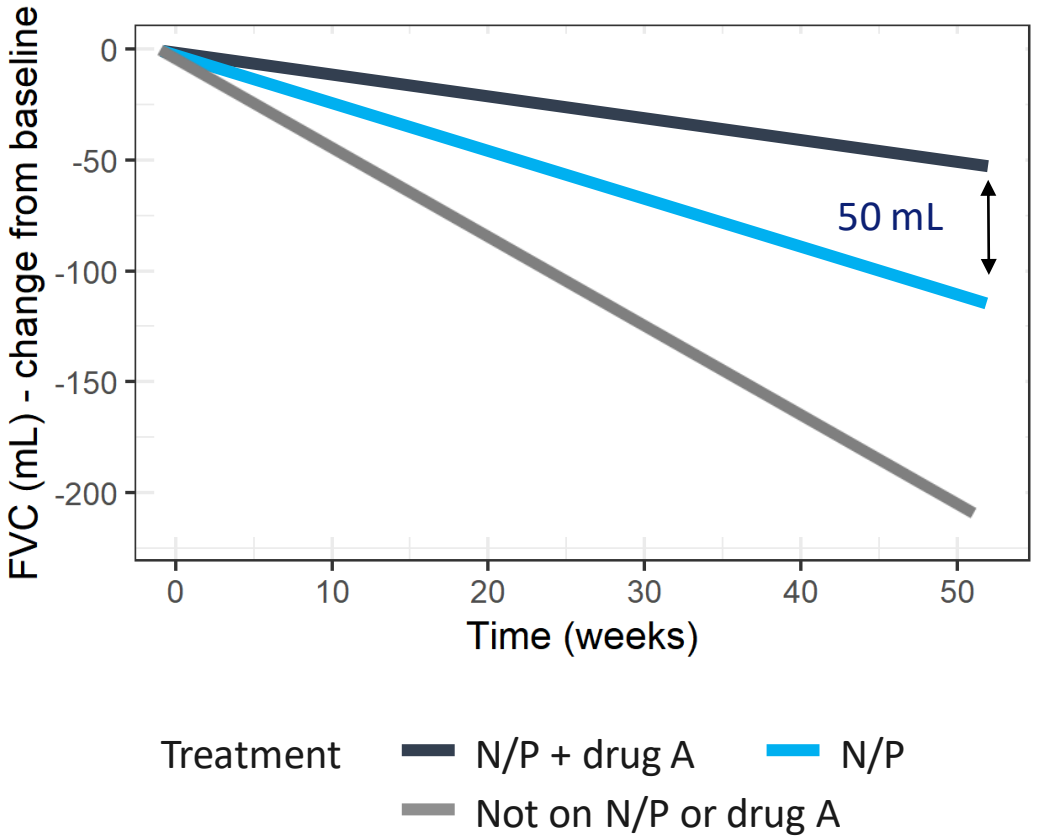


The example of IPF

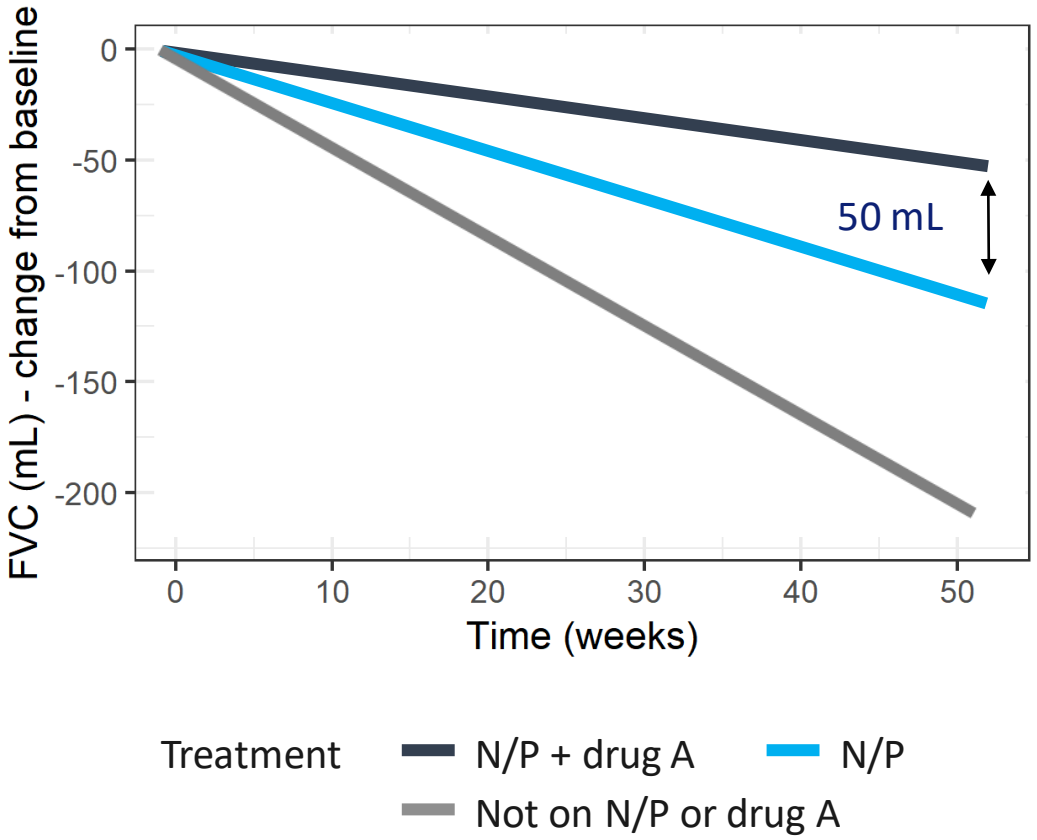
The current margin for a new drug:
50 ml

So to power your study you need
- More patients
- Longer trials
- More measurements

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; N, nintedanib; P, pirfenidone
Santermans E *et al. Adv Ther* 2019;36:3059–70; Johannson KA *et al. Eur Respir J* 2017;50:pii1602406

Home monitoring may improve endpoint efficiency

Many new trials have smaller margins to detect changes



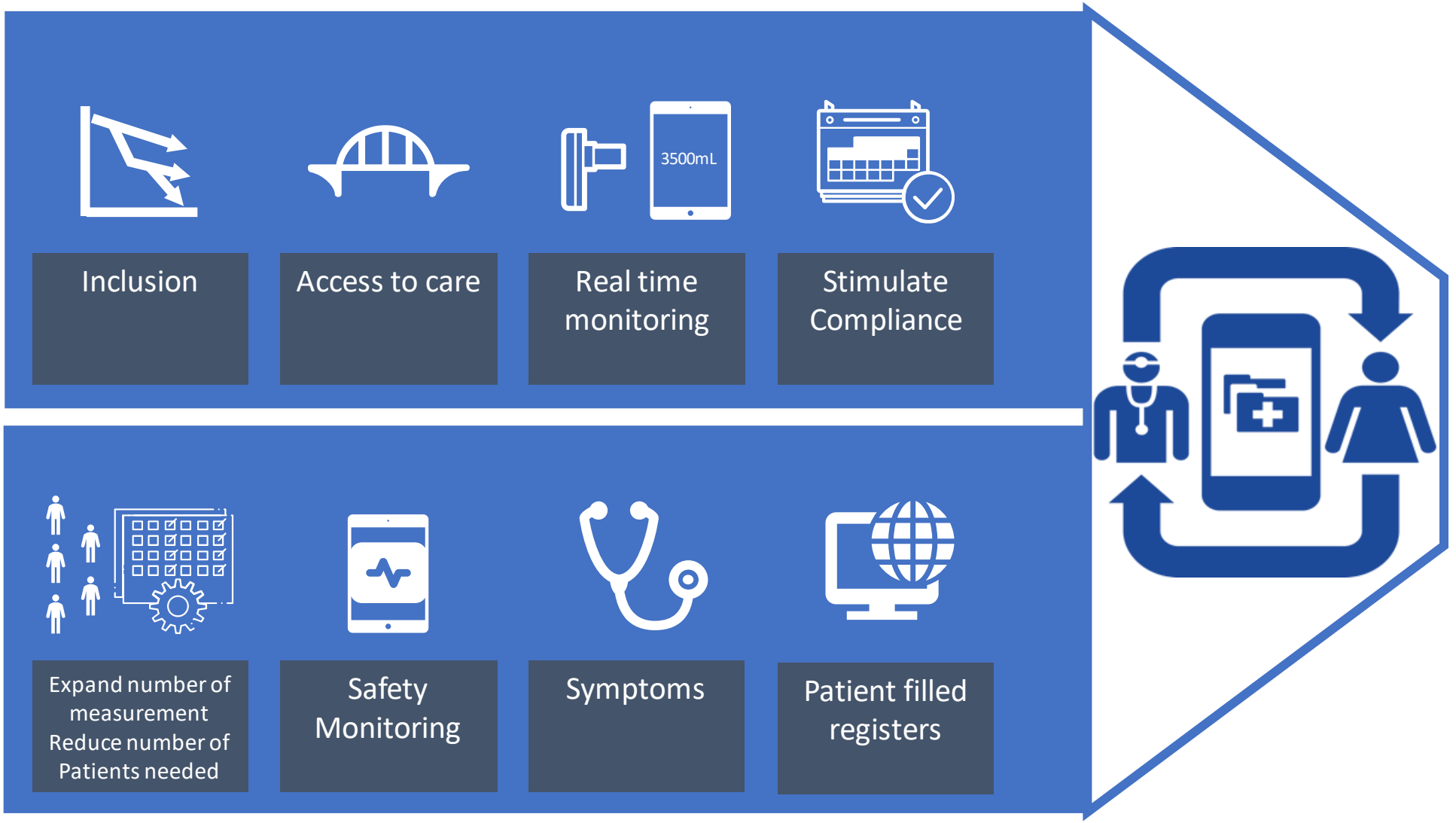
Sample size estimates to achieve 80% power, comparing intermittent and repeated measures

Outcome	Effect size %	Measurement frequency	
		Weekly × 24	Weeks 1 and 24
FVC; assumed control change of -50 mL	20	5946	24002
	35	1942	7837
	50	951	3840

FVC, forced vital capacity; N, nintedanib; P, pirfenidone

Santermans E *et al. Adv Ther* 2019;36:3059–70; Johannson KA *et al. Eur Respir J* 2017;50:pii1602406

Why want home based measurements in trials :



Less burden
COVID-19 proof

Patient as partner in Research

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Digital home resources in clinical trial management
Experiences from the ILD field

- Why do we want home based measurements in trials ?
- What have we learned so far?
- What are the challenges?

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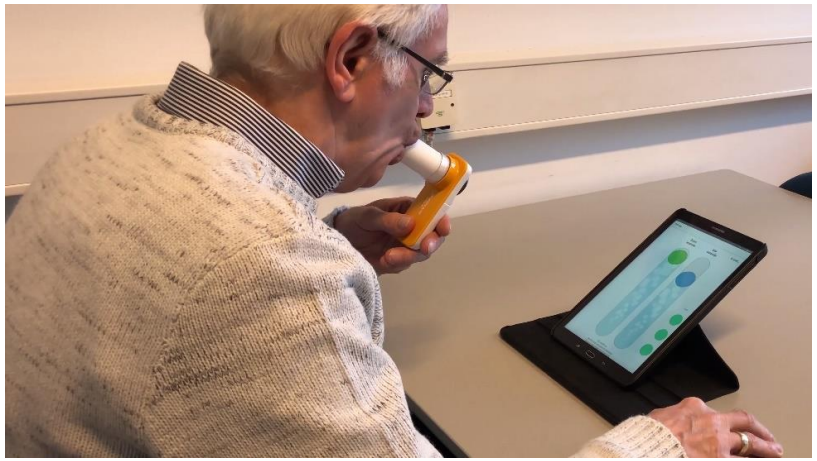
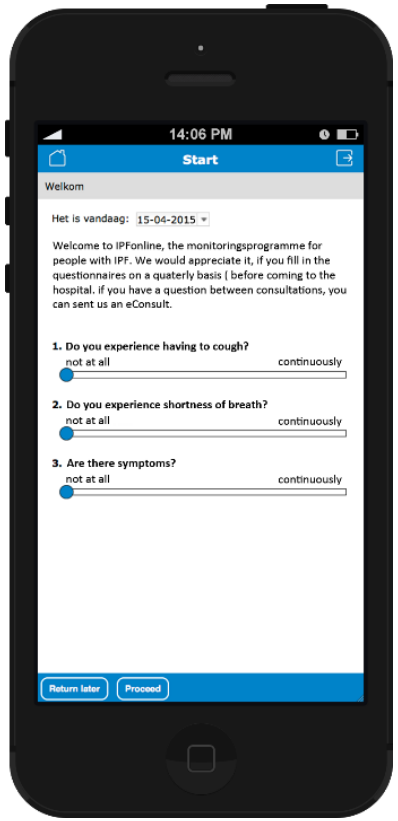
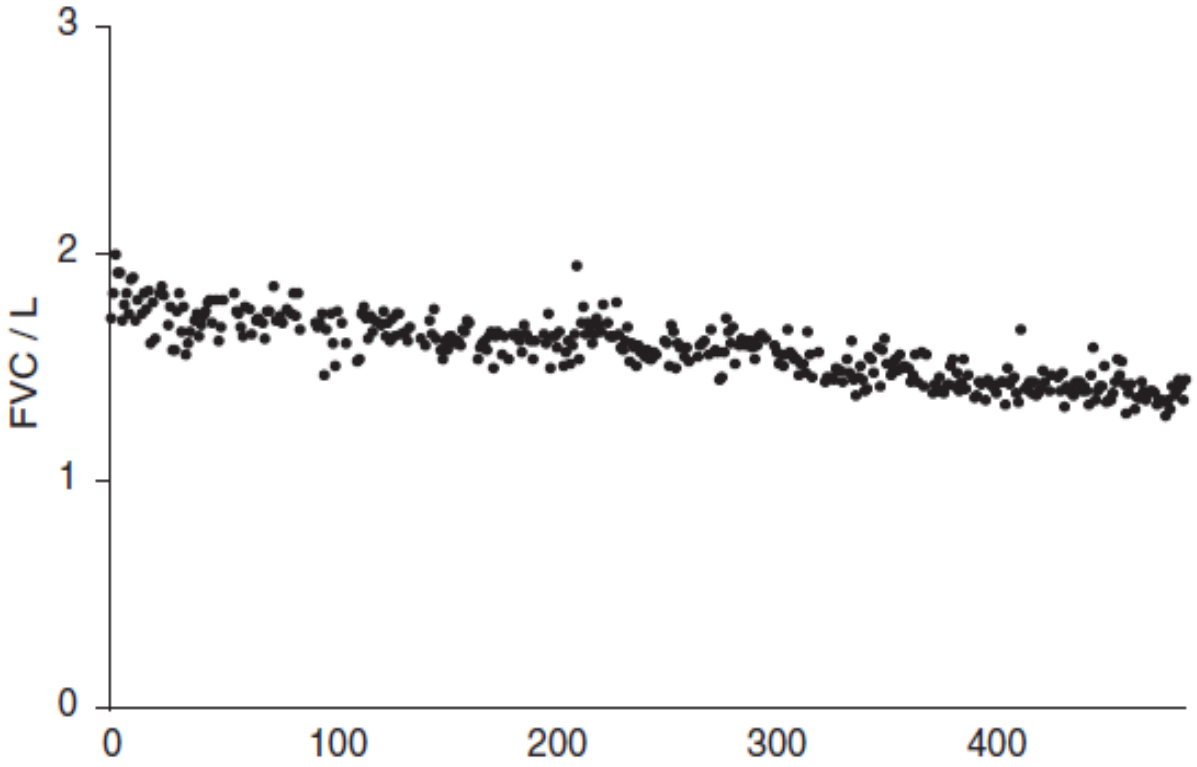
Digital home resources used in clinical trials in ILD

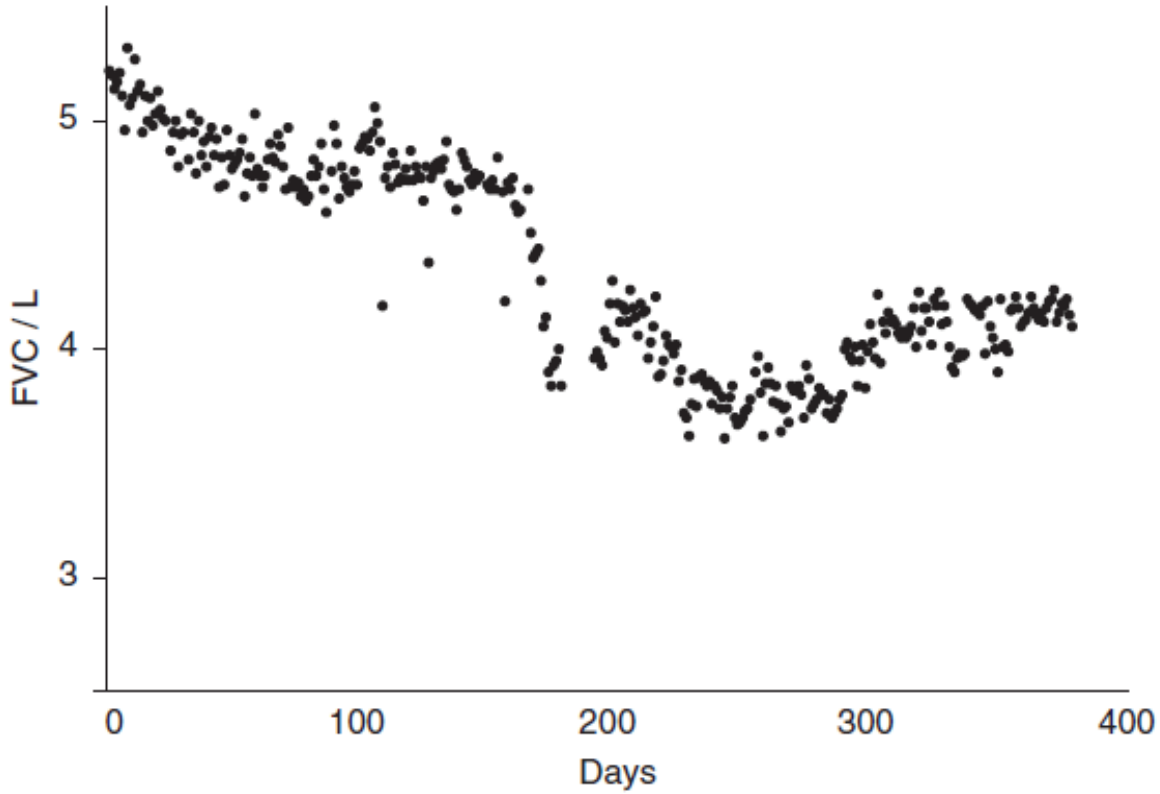




Included with permission of both patients

FVC home monitoring enables patient-tailored detection of decline



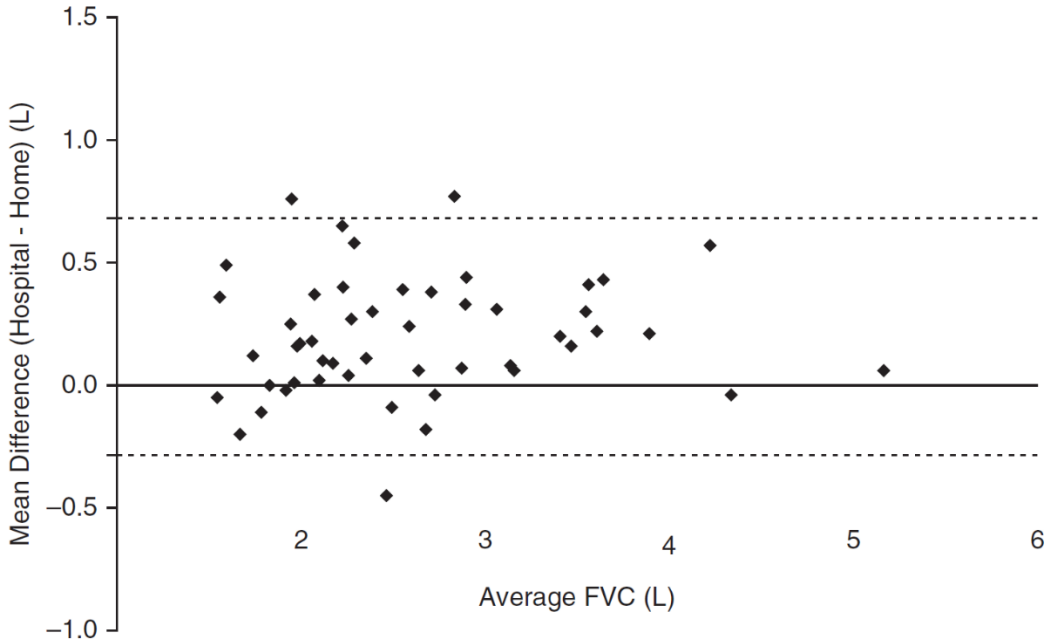


FVC, forced vital capacity

Russell AM *et al. Am J Respir Crit Care Med* 2016;194:989–97

Home spirometry is reliable

Russell *et al*[1]



Marcoux *et al*[2]

	Baseline	Week 4	Week 8	Week 12
Office FVC (L) – mean (SD)	2.77 (0.82)	2.70 (0.77)	2.76 (0.77)	2.70 (0.82)
Home FVC (L) – mean (SD)	2.70 (0.82)	2.63 (0.77)	2.48 (0.55)	2.45 (0.54)
Correlation between office and home-held FVC, r (95% CI)	0.97 (0.92, 0.99)*	0.96 (0.90, 0.98)*	0.93 (0.81, 0.97)*	0.90 (0.75, 0.96)*

Moor *et al*[3]

- Relative variability home FVC: 3.8% (3–12%)
- Median (SD) home FVC: 0.13 L (0.05–0.39 L)
- Home and hospital FVC highly correlated (r=0.94, *P*<0.001)

Home FVC and single-center hospital-based readings show good agreement

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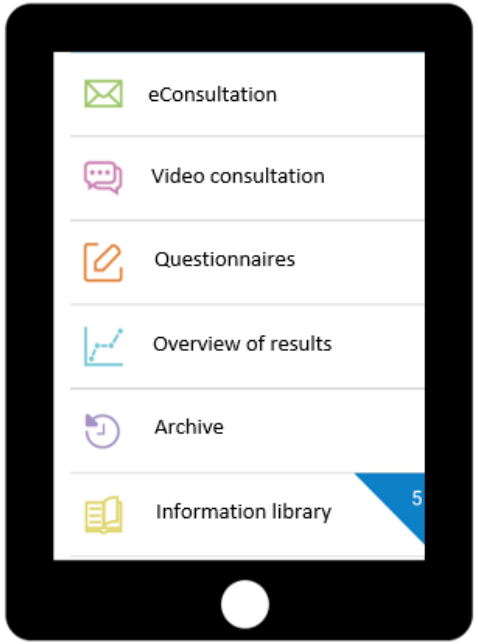
Data presented are Spearman correlations and 95% CI based on Fisher's Z transformation.**P*<0.0001. CI, confidence interval; FVC, forced vital capacity; SD, standard deviation

1. Russell AM *et al. Am J Respir Crit Care Med* 2016;194:989–97; 2. Marcoux V *et al. Ann Am Thorac Soc* 2019;16:1327–9; 3. Moor CC *et al. Respir Res* 2018;19:105

Our experience – home monitoring system developed together with patients

Patient
- Sends real-time data to the platform
- Overview of results
- Information library
- Low threshold communication

Automated email reminders



Automated email alerts

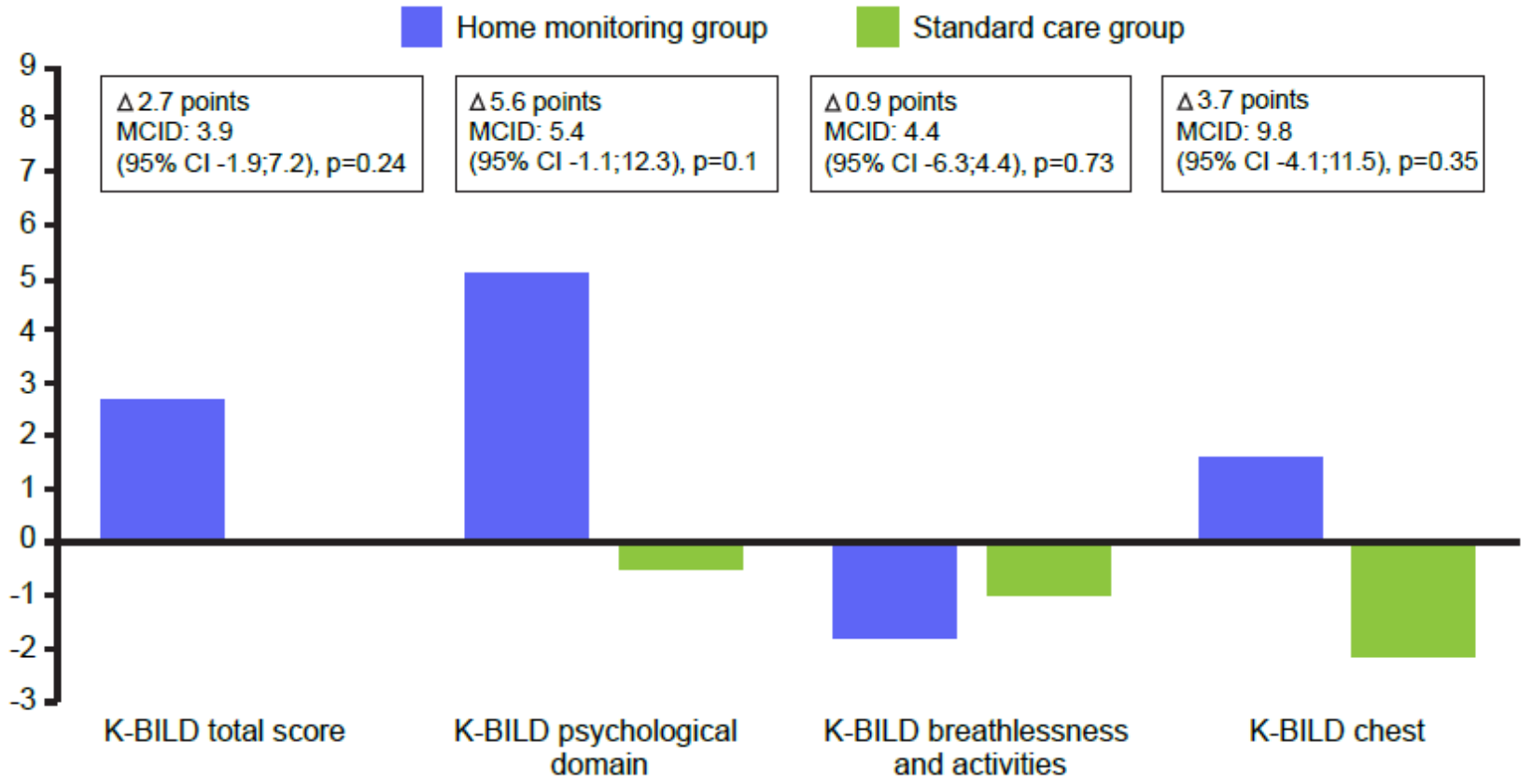
Healthcare provider
Direct access to patient data:
- Enables real-time detection of change in FVC and PROs
- Alarm settings on FVC and adverse effects
- Reduces missing data in trials

FVC, forced vital capacity; PRO, patient-reported outcome

Moor CC *et al. Am J Respir Crit Care Med* 2020;202;393–401

First randomized controlled trial with home monitoring in IPF; endpoint: effect on health related quality of life

Primary endpoint: change in K-BILD total score after 24 weeks

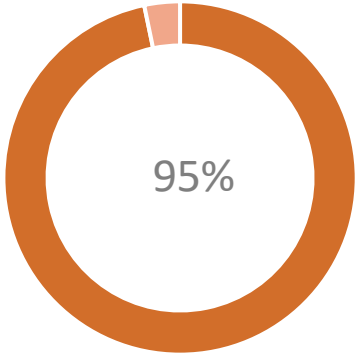


Higher K-BILD total score corresponds with better health-related quality of life. K-BILD, King's Brief Interstitial Lung Disease; MCID, minimal clinically important difference

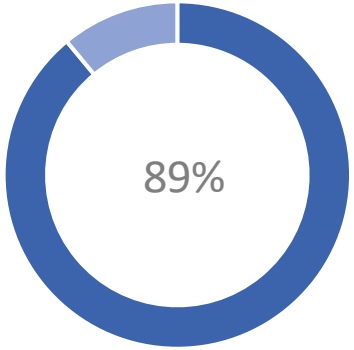
Moor CC *et al. Am J Respir Crit Care Med* 2020;202;393–401

Patient experiences were positive

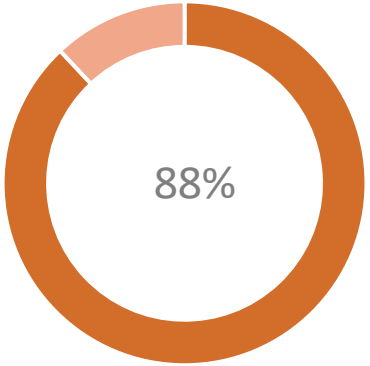
PATIENT EXPERIENCES HOME MONTORING



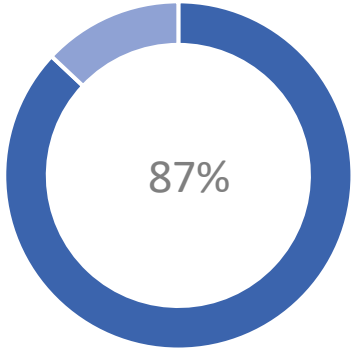
Recommend to others



Better insights disease course



Feels more secure



Lower threshold communication

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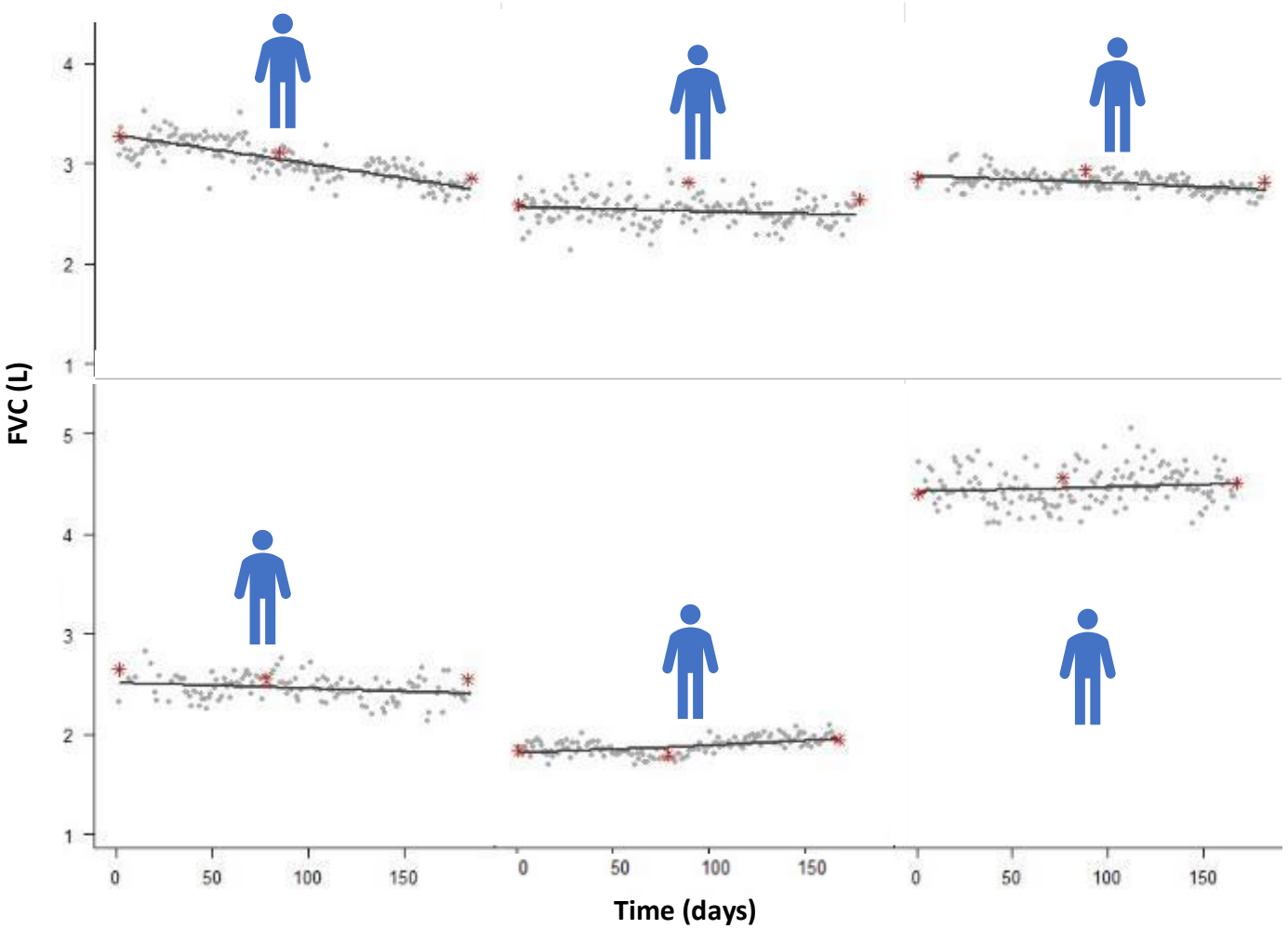
Moor CC *et al. Am J Respir Crit Care Med* 2020;202;393–401

Home monitoring allowed for close and reliable monitoring of disease course

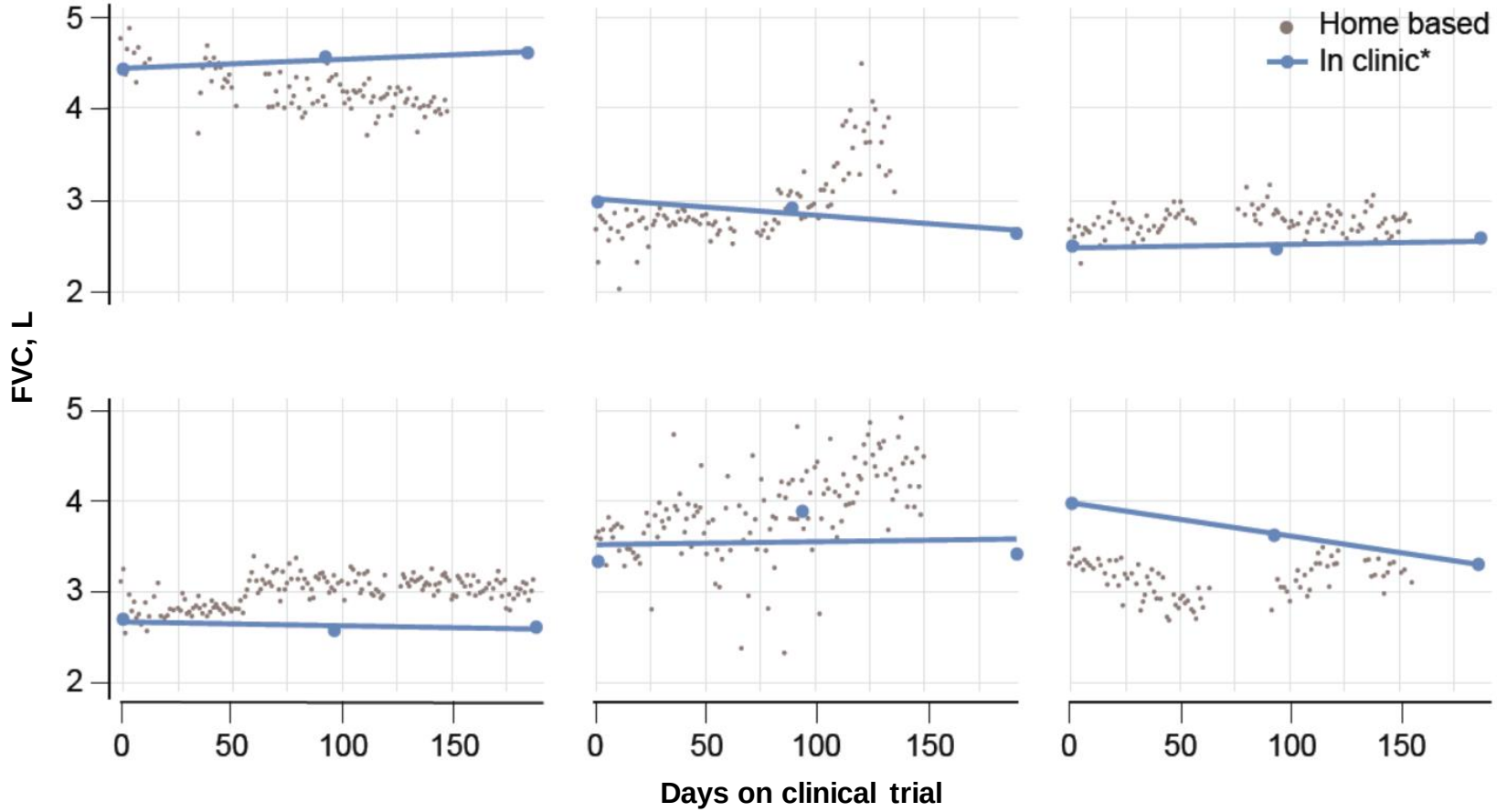


- Mean (SD) within-patient variability of FVC was 5.2% (1.7)
- Strong correlation at all time points
  - (r≥0.96, *P*<0.001)
- Slopes of home and hospital FVC over time were comparable

FVC, forced vital capacity; SD, standard deviation

Moor CC *et al. Am J Respir Crit Care Med* 2020;202;393–401

However: STARMAP study: absence of correlation between slopes of change in home-based and in-clinic FVC

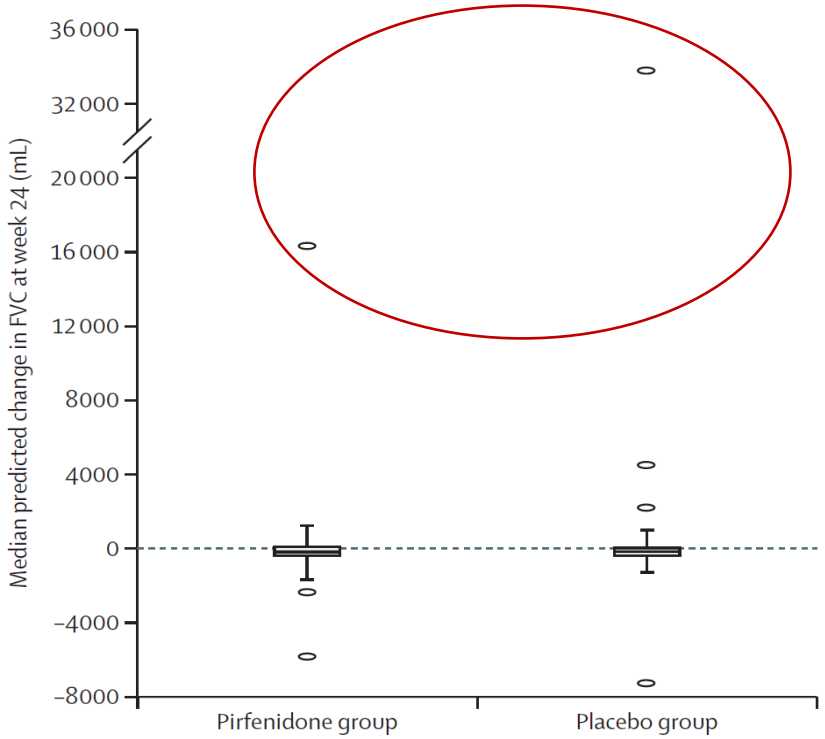


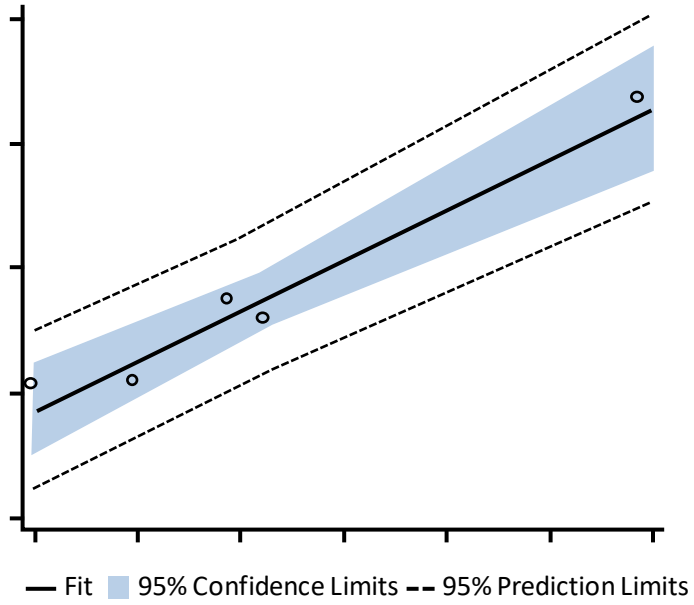
Multicenter studies may experience more FVC variability in individual patients

*Blue lines depict ordinary least squares fit to in-clinic measurements. FVC, forced vital capacity

Swigris JJ *et al. Eur Respir J* 2019;54;PA1333

Pirfenidone in unclassifiable ILD – first time home spirometry as primary outcome: some problems





Median FVC predicted change from baseline at week 24 measured with home spirometry in the ITT analysis set (n=253)

Low number of measures impacts the calculation of individual predictions of 24-week changes; statistical analysis methods impact results

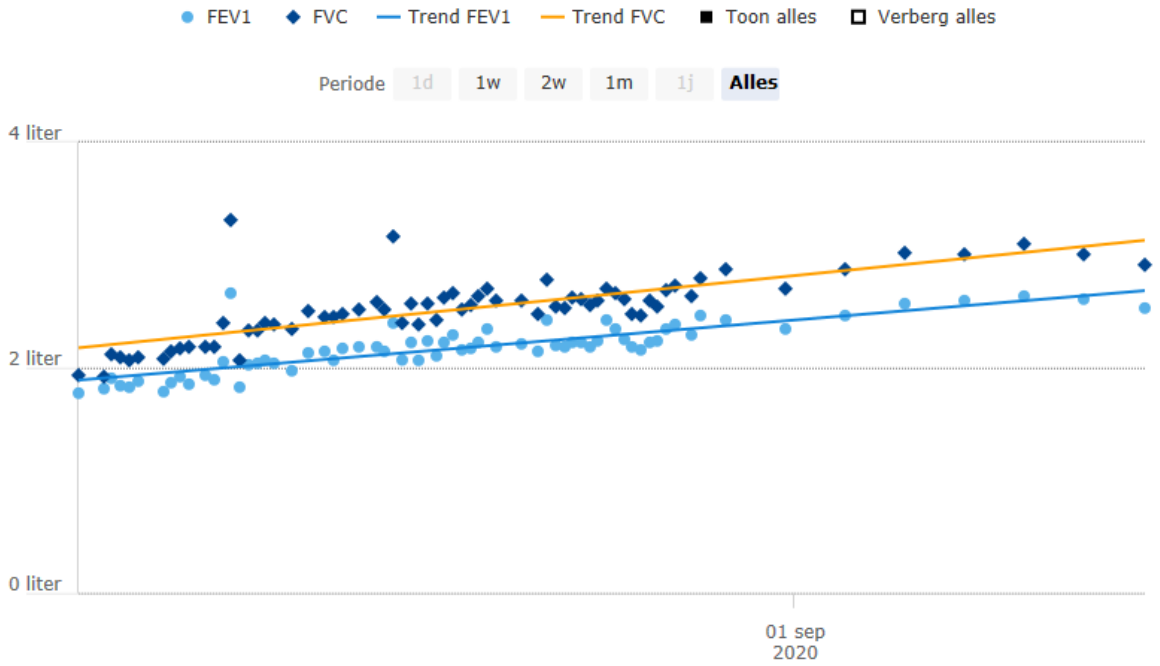
FVC, forced vital capacity; ILD, interstitial lung disease; ITT, intention-to-treat

Maher TM *et al. Lancet Respir Med* 2019;8:147–57;

Pulse-oximetry: use expanded in COVID-19 pandemic

Home monitoring post-SARS-COV-19 infection: HOMECOMIN' project

	09 okt 2020	03 okt 2020	25 sep 2020
Klachten *(0= niet; 10= extreem)*			
Hoesten	2	1.3	9.4
Hoestdrang	0.4	0.9	1.7
Benauwdheid	3.9	3.5	7.4
Moeheid	3.9	3.2	7.9
Klachten	4.4	4.3	2.7
Zelfmetingen			
Saturatie (%)	98	97	84
Hartslag (BPM)	79	85	95
Temperatuur (°C)			
FAS: Vermoeidheid *0-21= geen vermoeidheid* *22-50= vermoeidheid*			

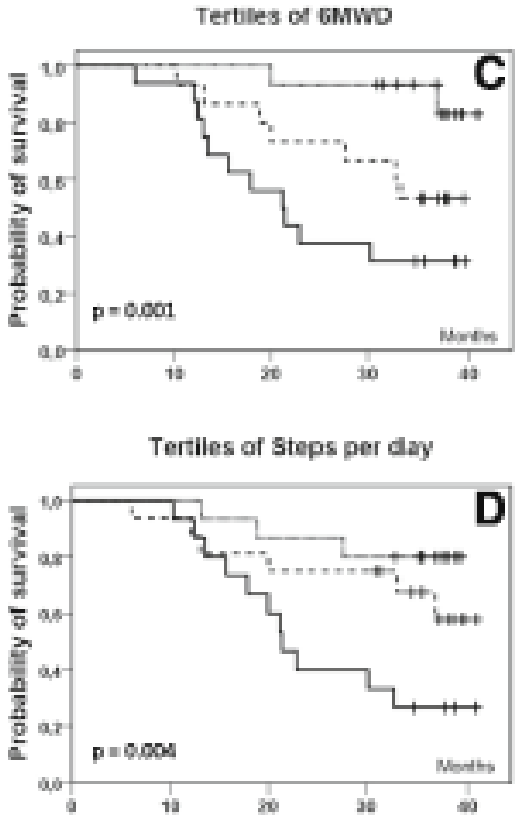


Patient-reported and recorded outcomes

unpublished data

Explorative use of surrogates of the 6 MWT at home

Steps per day predicts mortality similar to 6MWT

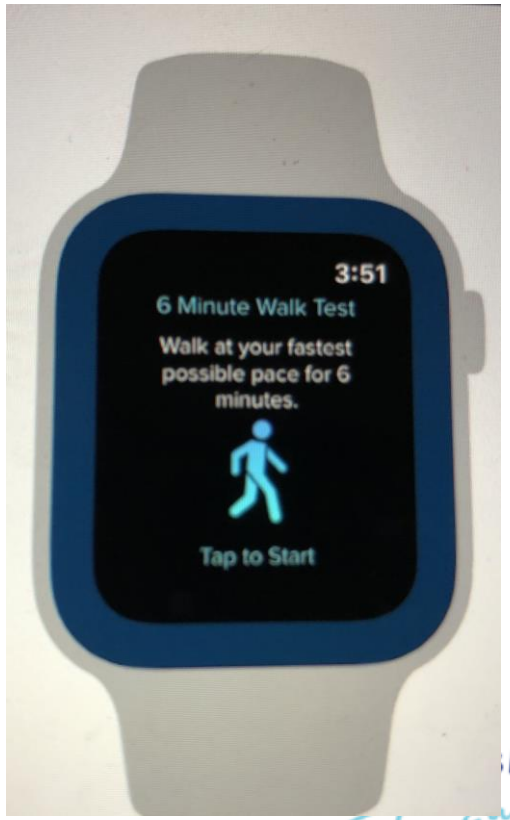


Bahmer T et al. BMC Pulmonary Medicine 2017; 17:104

Sit-to-Stand test correlates well with 6MWT

Fedi A et al. Respiration april 2021

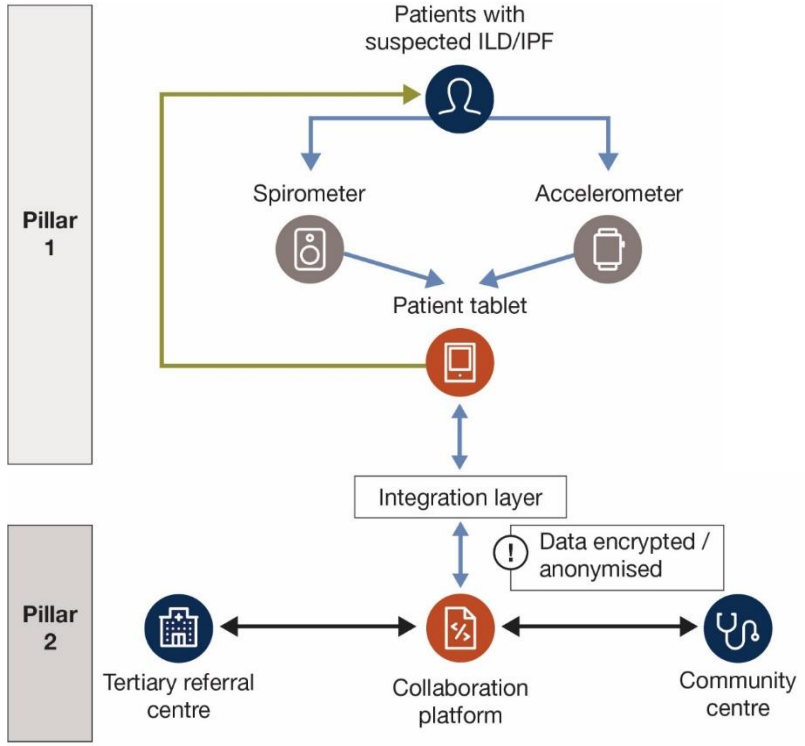
Stanford–Apple collaboration 6 MWT at home

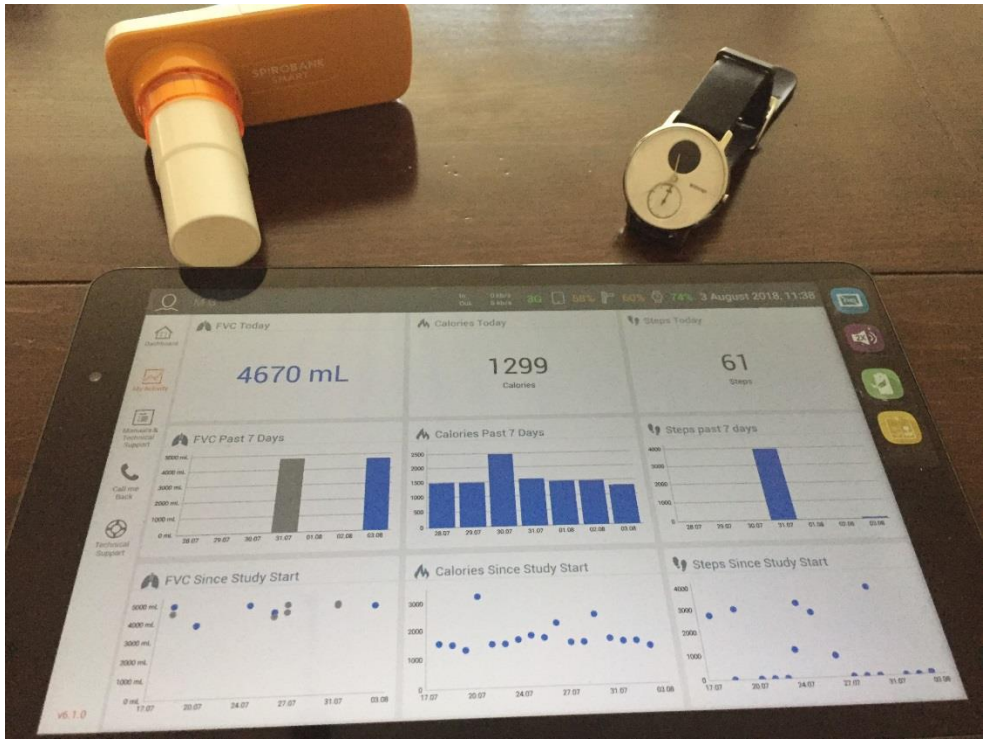


Glinskii V et al. Am J Respir Crit Care Med 2021;203:A1186

STARLINER study

Daily home spirometry and accelerometry during peridiagnostic period





ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Wijsenbeek M *et al. Adv Ther* 2019;36;232–43; Wijsenbeek M *et al. Adv Ther* 2021 in press

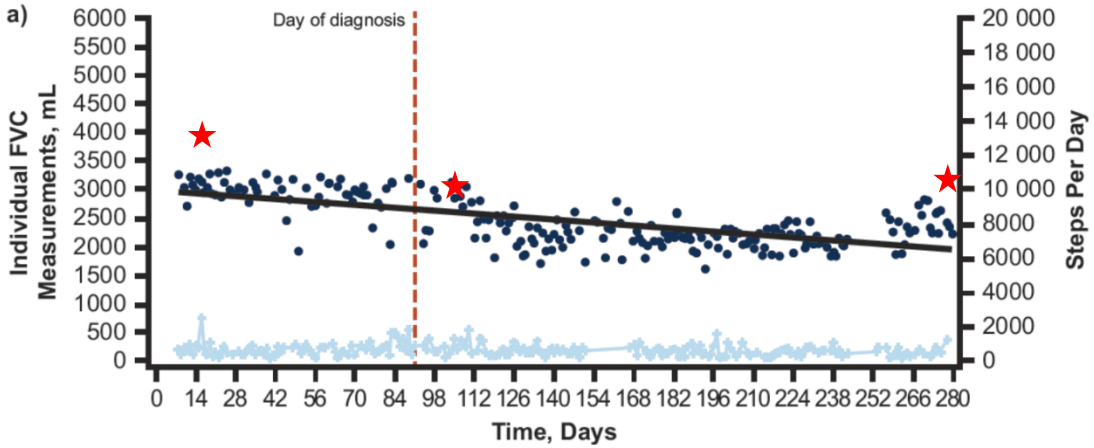
Patients with IPF experienced greater declines in FVC compared with patients with non-IPF ILD

Semi-annual changes in FVC during the peri-diagnostic period*

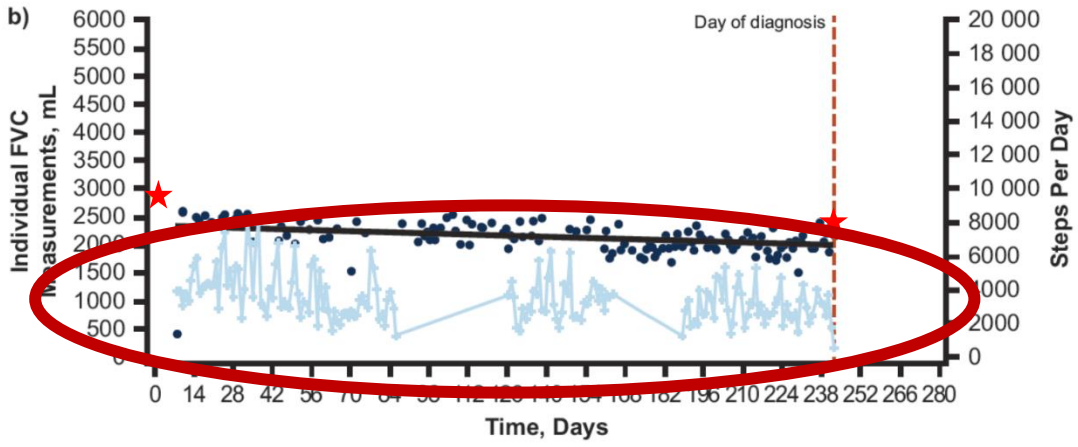
Assessment	Home/site measurement	Statistical analysis model	IPF	Non-IPF ILD
Change in FVC, mL	Home	Linear regression	–167.7 (–441.3, 132.3)**	–25.3 (–272.9, 103.9)†
Change in FVC, mL	Site	Linear regression	–188.2 (–426.1, 85.4)‡	–23.4 (–127.7, 115.5)‡

Individual courses of home spirometry and accelerometry for:

A patient with IPF



A patient with non-IPF ILD



• FVC (home spirometry; good blow) ★ FVC (site spirometry) ◆ Steps per day ▬ Linear regression

*Excluding patients with <30 days of data; **n=42; †n=47; ‡n=46; Interim data. FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Wijsenbeek M *et al. Eur Respir J* 2019;54;PA1335 ; Wijsenbeek M et al . *Adv Ther* 2021 in press

Digital home resources in clinical trial management

Experiences from the ILD field

- Why do we want home based measurements in trials ?
- What have we learned so far?
- What are the challenges?

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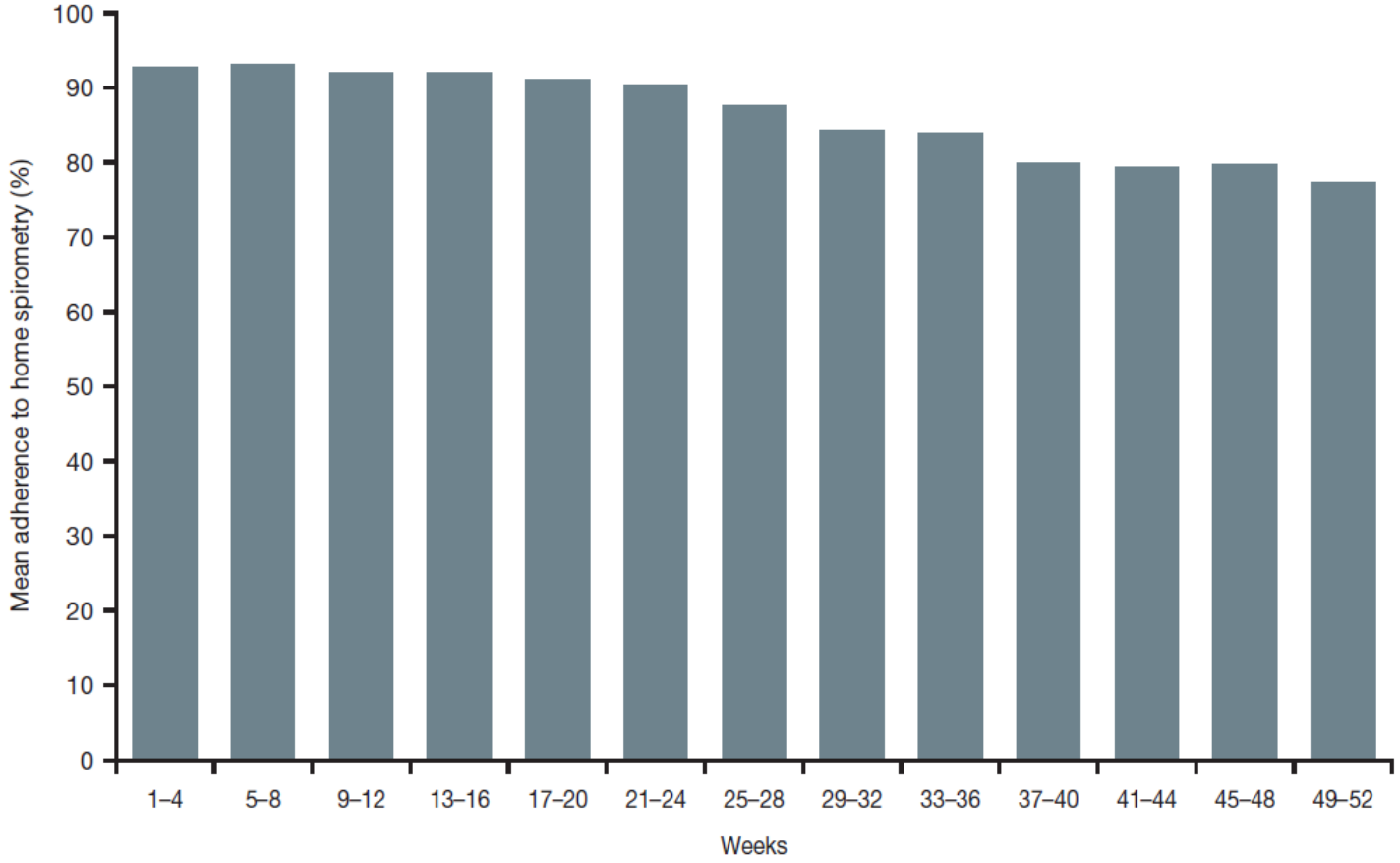
Adherence to home spirometry over time

INMARK® trial; Mean adherence 86% over 52 weeks, median adherence 96%



Adherence was calculated as the number of weeks that a subject provided ≥1 measurement divided by the number of weeks that they were followed in the trial. Analysis was based on the total number of subjects who were still followed in the trial within the time period

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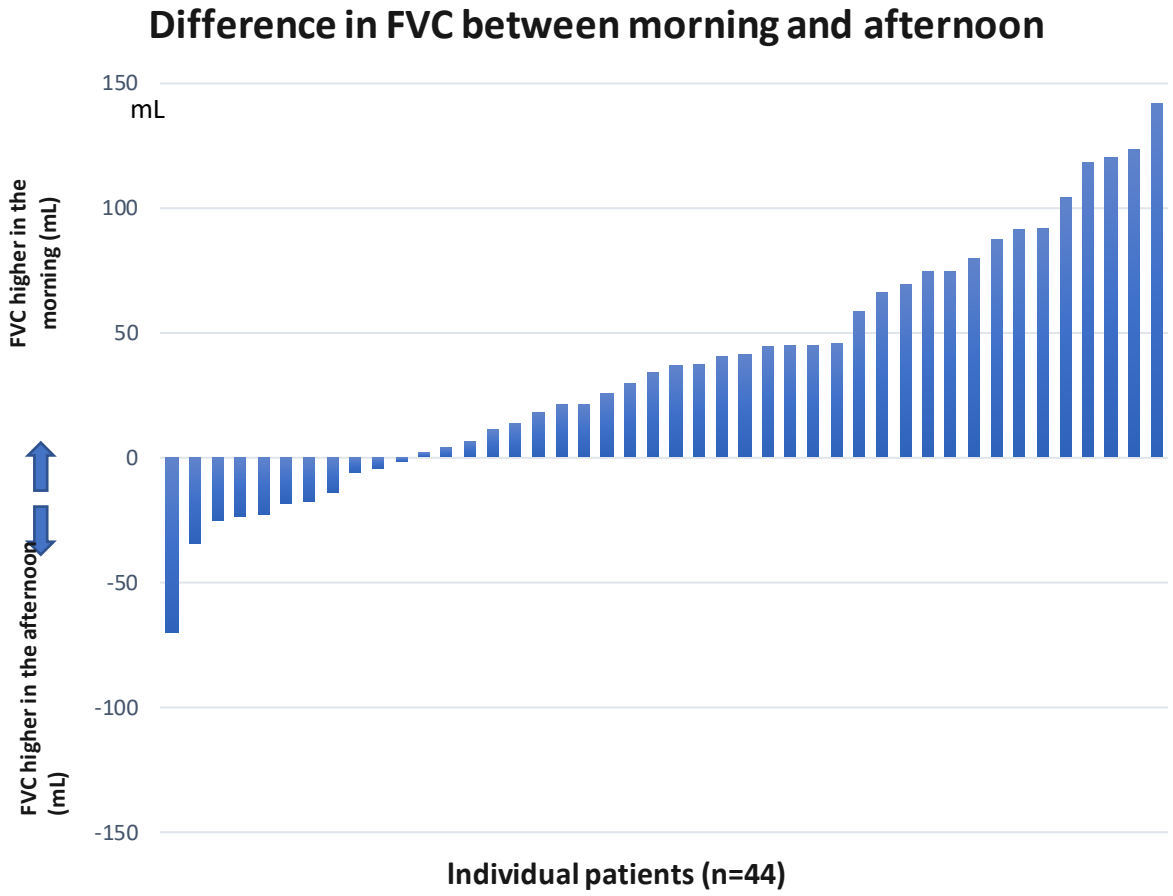
Maher TM *et al. Eur Respir J* 2021

Diurnal variation in FVC



Results of DIVA study

FVC-morning was significantly higher than FVC-afternoon (mean difference: **36 mL, *P*<0.001**)

No diurnal variation was found for FEV1 (7 mL, *P*=0.35)

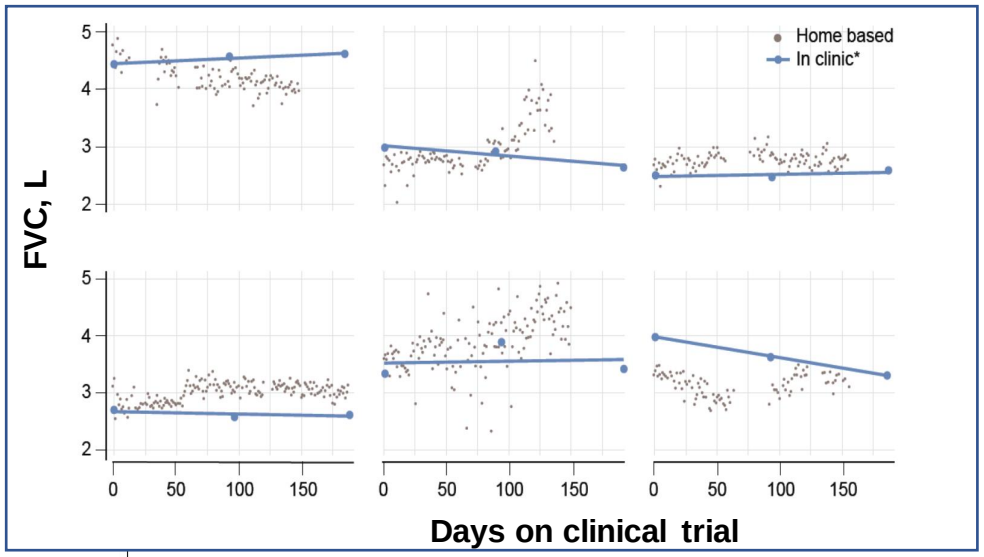
Differences in FVC cannot be fully explained by activity just before the measurement

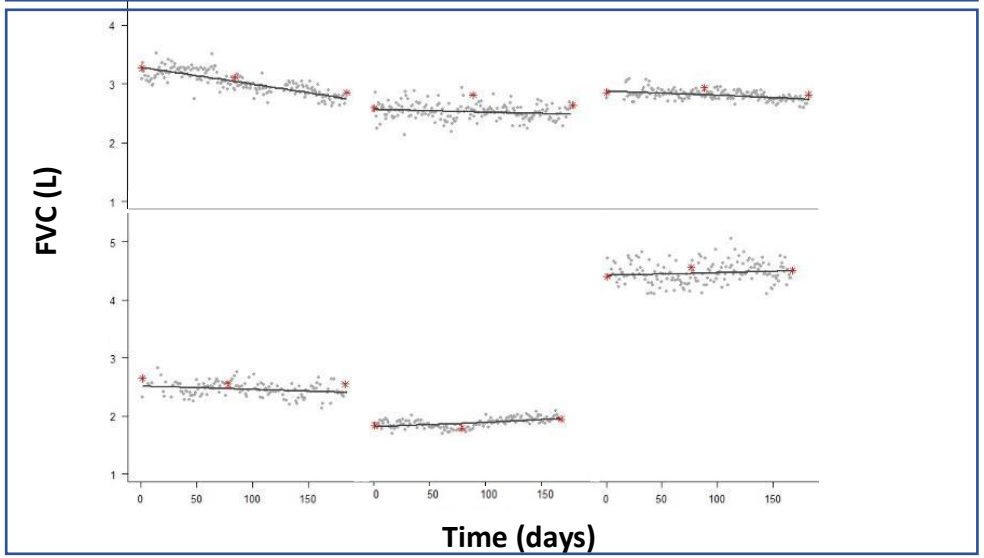
Erasmus MC

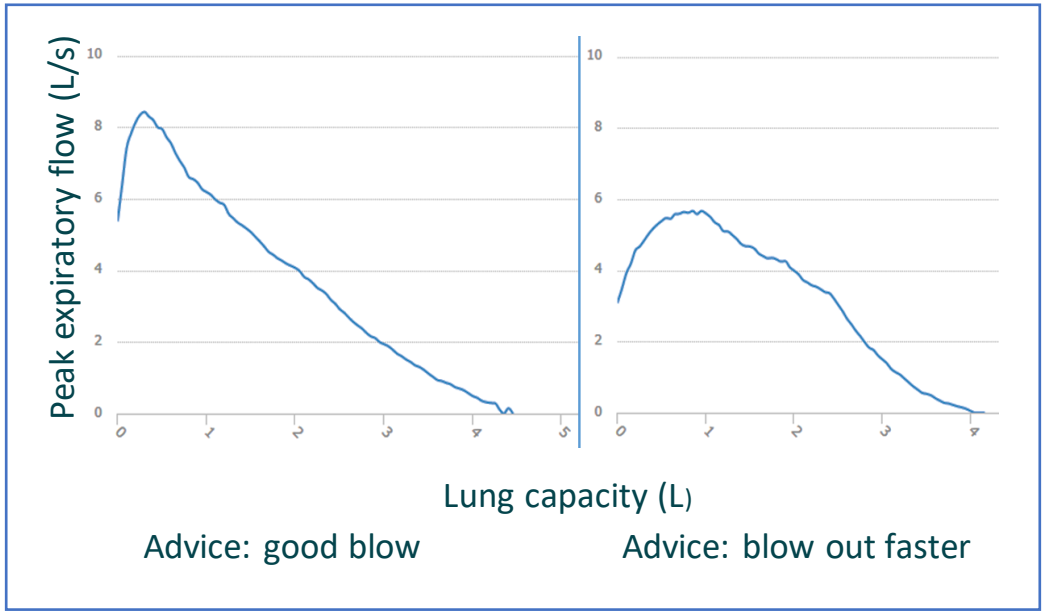
FEV1, forced expiratory volume in one second; FVC, forced vital capacity

Moor CC. *ERJ Open Res* 2020;6:00054-2020

Measurement variability and technical issues
Realtime feedback to center AND patient improves quality







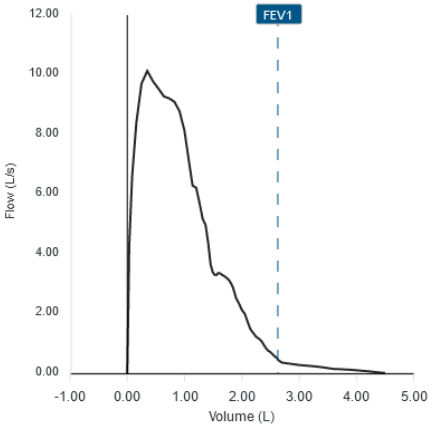
Strong correlation at all time points (r≥0.96, *P*<0.001)

Slopes of home and hospital FVC over time were comparable

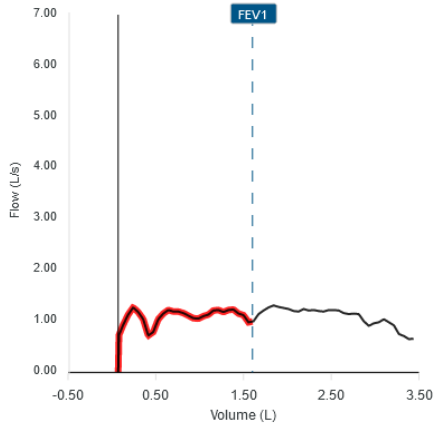
FVC, forced vital capacity. Moor CC *et al. Am J Respir Crit Care Med* 2020;202;393–401. Swigris JJ *et al. Eur Respir J* 2019;54;PA1333

Artificial Intellegence (AI) for Quality Control of Home Spirometry data

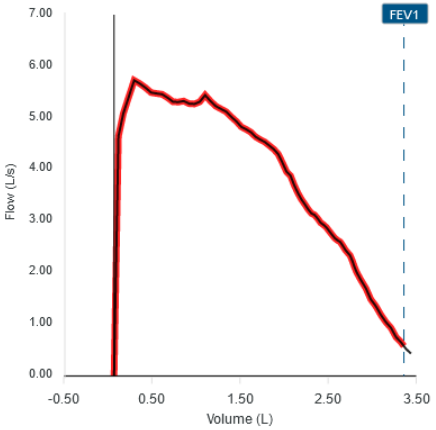
- AI methods[1,2] can perform the artefact detection usually done by trained technicians in centralized clinical trials
- AI methods to provide real-time quality feedback with equivalent accuracy to manual over-reading[3]



ArtiQ.QC Acceptable



ArtiQ.QC Rejected
Sub-maximal effort artefact



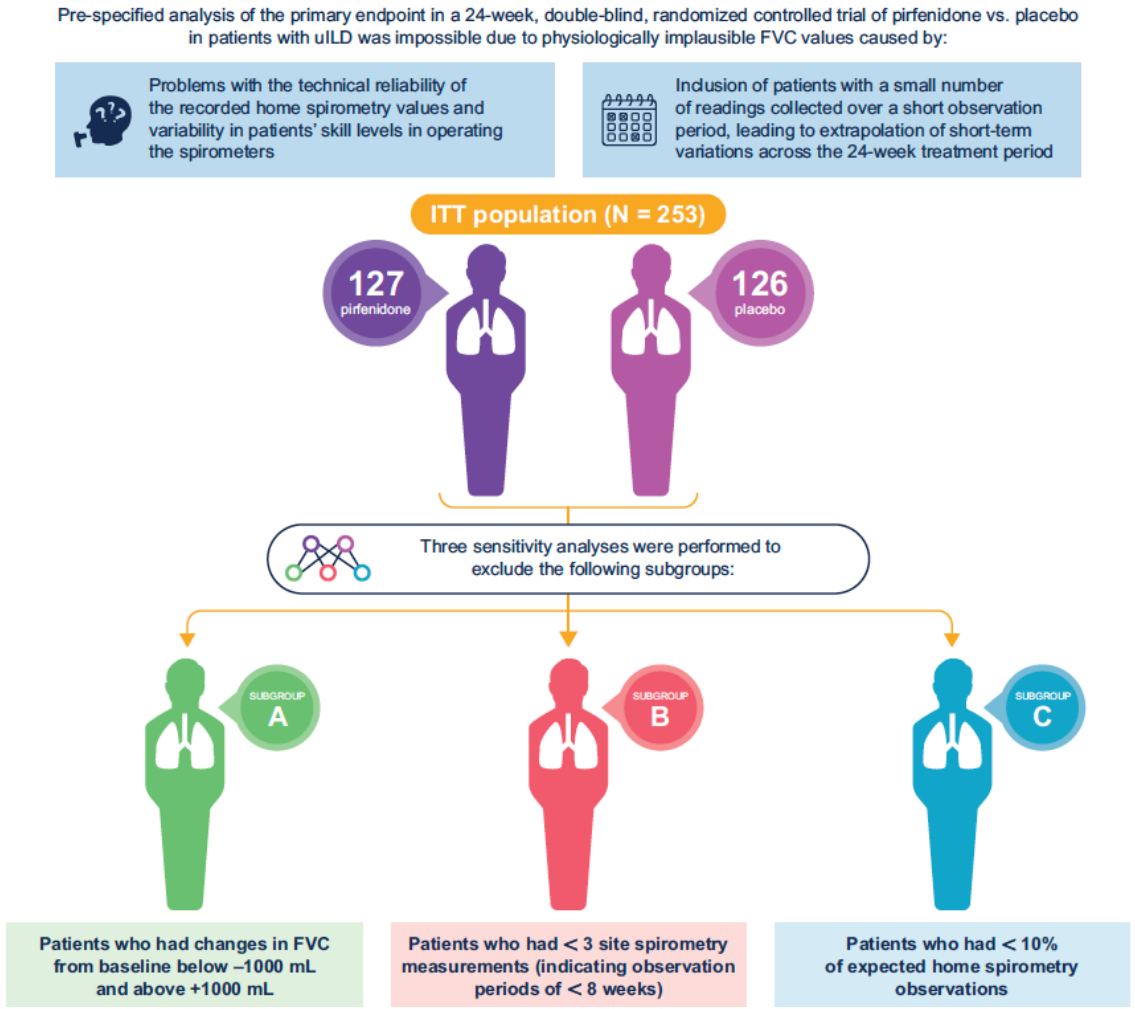
ArtiQ.QC Rejected
Variable effort artefact

- Further validation currently ongoing

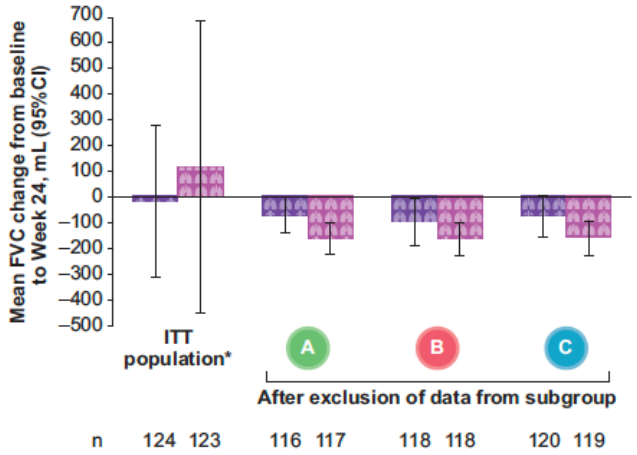
[1] – Das *et. al.*, *ERJ* (2020); 56(6): 2000603. [2] – Das *et. al.*, *ERJ* (2020); 56: Suppl. 64, 3789. [3] - Topole *et. al.*, *ATS* (2021); A4606.

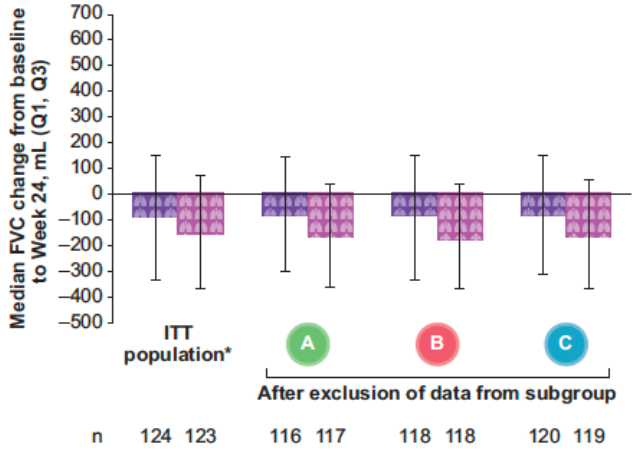
Slide courtesy of ArtiQ

Need for consensus on the method for handling missing data and outliers in the statistical analysis



Sensitivity analyses for mean and median 24-week FVC change measured using home spirometry





CI, confidence interval; FVC, forced vital capacity; ITT, intention-to-treat; uILD, unclassifiable interstitial lung disease

Maher TM *et al. Am J Respir Crit Care Med* 2020;201;A2575

And other challenges

- Optimal frequency of measurements?
- Optimal alarm settings?
- Promoting equal access to trials or not?
- Fit for all patients and doctors?
- How about other wearables / sensors?
- Ready as endpoint ?
- ….

Nakshbandi G *et al. Lancet Respir Med* 2020;

Conclusion:
Digital home resources in clinical trial management

- Why : allows for closer monitoring at lower burden for patients, reduces trial size and makes patients a partner in research

- What we learned: home based spirometry and PRO collection is feasible, reliable and highly appreciated by patients. More data needed also on other outcomes

- Which challenges: technical and analytical, as well as impact on patient and outcomes when longterm used

Erasmus MC

A big thank you

To all the patients that helped us through the years

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Erasmus MC

Thank you!

To learn more about a homemonitoring application and patient experiences scan the QR code