ACtiF: Development and evaluation of an intervention to support Adherence to treatment in adults with Cystic Fibrosis – a randomised controlled trial and parallel process evaluation

WP 3.3 RCT

ISRCTN 55504164

Protocol v3.1 15/02/19

Post hoc analysis report v1.2

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Executive summary

1. No evidence of a difference between randomised groups in exacerbation rates in the second-year follow-up (12 to 21 months) or across the full extended follow-up (baseline to 21 months).
2. No evidence of a difference between randomised groups in severity of exacerbations as measured by the number of Fuchs criteria met for the exacerbation.

Adherence data were not collected prior to consent and randomisation, so 'baseline' adherence was defined and calculated as the average adherence over the first two weeks post-consent. Four baseline adherence subgroups were defined: 0-25%; 26% to 50%; 51% to 75%; 76% to 100%.

3. The largest difference in weekly adherence between randomised groups, in favour of the intervention group, was observed for the subgroup with a baseline adherence of 26% to 50%. All four baseline adherence subgroups observed increases in weekly adherence over the 12-month post-consent period in the intervention group compared to usual care.
4. Excluding the subgroup of 'high' baseline adherers (with adherence of 76% or more) yielded an adjusted between-group estimate of 12.3 (95% CI 11.2, 13.4) percentage points in weekly mean numerator-adjusted normative adherence in favour of the intervention group. This compares to a 9.5 (95% CI 8.6, 10.4) percentage point difference in favour of the intervention group for the whole trial cohort.
5. The largest difference in FEV_1 percent predicted at 12 months post-consent between the randomised groups, in favour of the intervention group, was observed for the subgroup with a baseline adherence of 0% to 25%; a difference in FEV_1 percent predicted of 3.0 (0.1 to 6.0). None of the three other baseline adherence subgroups observed statistically significant differences in weekly adherence over the 12-month post-consent period in the intervention group compared to usual care.
6. The treatment effect for the whole trial cohort was 1.4 (95% CI -0.2, 3.0) percentage points difference in FEV_1 percent predicted at 12 months post-consent between randomised groups, in favour of the intervention group. Exclusion of the 'high baseline adherence' subgroup yielded a treatment effect estimate of 1.9 (95% CI -0.1, 3.9) percentage points, favouring the intervention arm. However, the confidence intervals included zero, consistent with no between-group difference, the same as for the whole trial cohort.
7. No reliable evidence of a difference in monthly FEV_1 percent predicted by group. There was a tendency for higher FEV_1 percent predicted in the intervention arm, 0.63 (95% CI -0.25. 1.51) percentage points, but the confidence interval included zero, consistent with no overall between-group difference.
8. No reliable evidence of a difference in longitudinal FEV_1 percent predicted by randomised group over the extended follow-up period.
9. No reliable evidence of associations between baseline FEV_1 percent predicted and normative adherence levels.
10. Increases in between-group differences in normative adherence were seen when removing data from first two and ten weeks post-baseline.
11. Increased treatment effect in relation to normative adherence in extended follow-up, though a slight decreasing trend in adherence levels over time. Increasing the follow-up time from 12 to 21 months increased the estimated treatment effect from 9.5 to 11.9 percentage points (95% CI 11.1, 12.7) in favour of the intervention arm. The time coefficient was -0.2 (95% CI -0.2, -0.1) percentage points, suggestive of a slight decreasing trend in adherence levels over time.
12. Higher BMI of 0.15 (95% CI 0.04, 0.25) in the intervention group over one year, and 0.32 (95% CI 0.11, 0.52) over the extended follow-up.

List of tables and figures

List of abbreviations

ACtiF	Development and evaluation of an intervention to support Adherence to treatment in adults with Cystic Fibrosis
BMI	Body mass index
CI	Confidence interval
FEV_1	Forced expiratory volume one second
IQR	Interquartile range
IRR	Incidence rate ratio
SAP	Statistical analysis plan
SD	Standard deviation

1 Additional analysis of one-year outcomes

1.1 Severity of exacerbations

The primary clinical outcome was the number of pulmonary exacerbations in the 12-month post-consent follow-up period, defined according to the modified Fuchs criteria. An exacerbation of respiratory symptoms was said to have occurred when a patient was treated with parenteral antibiotics for any one of 12 signs or symptoms.

Overall there were 1008 exacerbations (usual care n=526, intervention n=482) meeting the criteria in the 12-month post-consent follow-up period. The distribution of exacerbation counts by severity (as measured by the number of Fuchs criteria met) is presented by randomised group in Figure 1.

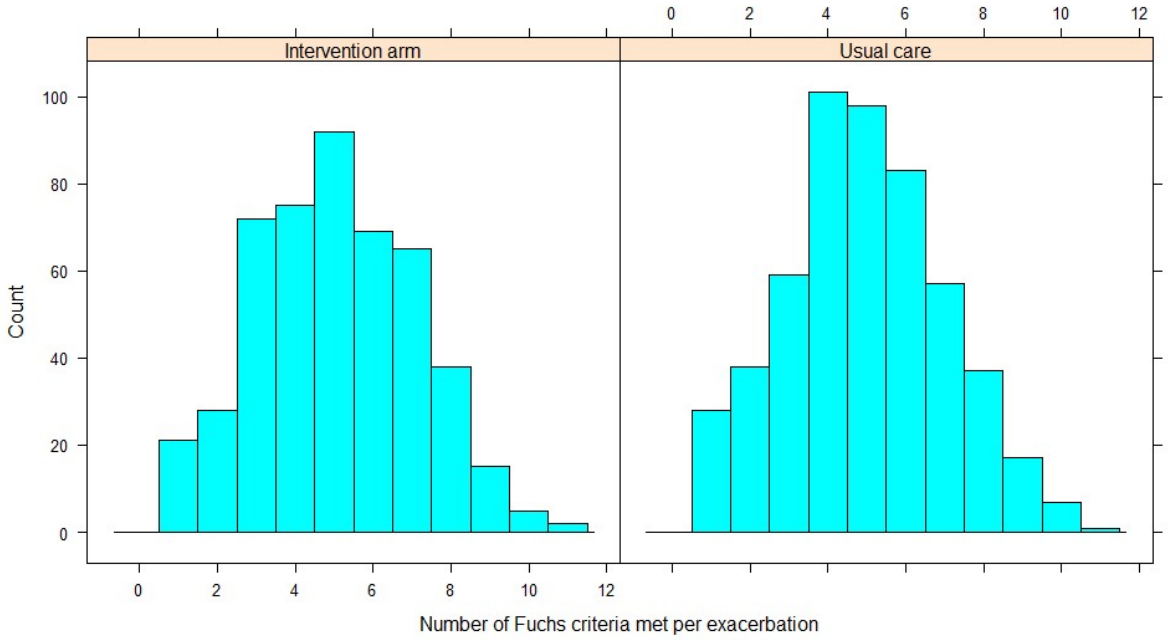

Figure 1 Distribution of exacerbations by severity by randomised group

Summary statistics are provided in Table 1 by three-month period and overall. A linear mixed-effects model was used to examine between-group differences, allowing for non-independence of events (one participant may have multiple exacerbations). The estimated between-group difference in severity was 0.1 (95% CI -0.2 to 0.5). There was no evidence of a difference in severity of exacerbations as measured by the mean Fuchs scores between the randomised groups.

Table 1 Summary of Fuchs criteria met per exacerbation by randomised group

Time period	Statistic	Usual care	Intervention
0-3 months	N exacerbations	116	114
	Mean (SD)	5.1 (2.2)	5.1 (2.0)
	Median (IQR)	5.0 (4.0, 6.0)	5.0 (4.0, 6.8)
>3-6 months	N exacerbations	143	117
	Mean (SD)	4.9 (2.0)	5.1 (2.2)
	Median (IQR)	5.0 (4.0, 6.0)	5.0 (3.0, 7.0)
>6-9 months	N exacerbations	131	125
	Mean (SD)	4.9 (2.0)	4.7 (2.0)
	Median (IQR)	5.0 (3.5, 6.0)	5.0 (3.0, 6.0)
>9-12 months	N exacerbations	136	126
	Mean (SD)	4.9 (2.1)	5.3 (2.0)
	Median (IQR)	5.0 (3.8, 6.0)	5.0 (4.0, 7.0)
Year total	N exacerbations	526	482
	Mean (SD)	4.9 (2.1)	5.0 (2.1)
	Median (IQR)	5.0 (4.0, 6.0)	5.0 (3.3, 7.0)

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1.2 Subgroup analyses of normative adherence and FEV_1 percent predicted

1.2.1 Normative adherence

Adherence for each participant was calculated on a daily basis, capped at the prescribed number of doses if the participant took more than the prescribed dose of medication on that day, and then averaged over the week. Adherence data were not collected prior to consent and randomisation, so 'baseline' adherence was defined and calculated as the average adherence in the first two weeks post-consent. Two definitions of adherence were used: numerator-adjusted and numerator-adjusted normative adherence (full definitions of which can be found in the trial SAP).

The normative adherence model outlined in the trial SAP was repeated including subgroup analysis for the following 'baseline' adherence categories: 0-25%, 26-50%, 51-75% and 76-100%. An additional model was applied excluding the subgroup of participants whose 'baseline' adherence was ≥76% in order to assess whether differences between randomised groups were affected by 'ceiling' effects.

Trends in normative adherence are presented by subgroup in Figure 2 and estimated between-group differences for each subgroup are presented in Table 2. Differences are intervention minus usual care, i.e. positive estimates favour the intervention group. The model excluding the subgroup of 'high' adherers (remaining n=416) yielded an adjusted between-group estimate of 12.3 (95% CI 11.2, 13.4) % in favour of the intervention group. This compares to a 9.5% (95% CI 8.6, 10.4) difference in mean weekly numerator-adjusted normative adherence in favour of the intervention group for the whole trial cohort.

Table 2 Adjusted* estimates for between-group differences in normative adherence for adherence subgroups

Baseline adherence subgroup	Estimated between-group difference (95% CI)
0-25% (n=178)	10.0 (8.4, 11.7) %
26-50% (n=113)	17.6 (15.6, 19.6) %
51-75% (n=125)	14.6 (12.7, 16.5) %
76-100% (n=172)	2.8 (1.1, 4.4) %

*adjusted for previous year's IV days and site

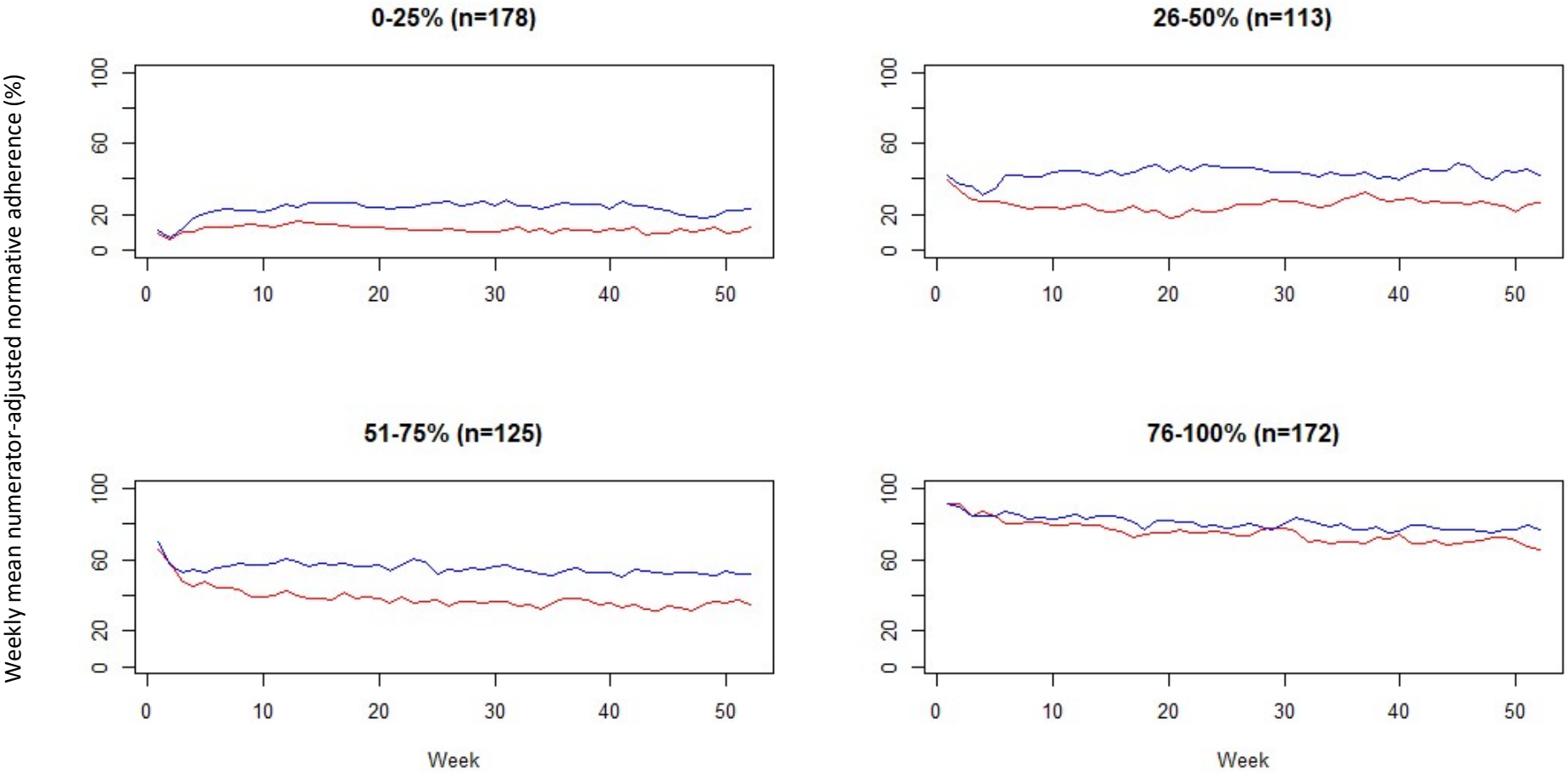

Figure 2 Weekly mean numerator-adjusted normative adherence by baseline adherence subgroup
Red line denotes usual care arm; blue line denotes intervention arm.

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1.2.2 FEV_1 percent predicted

The FEV_1 percent predicted model as outlined in the trial SAP was repeated including subgroup analysis for the following 'baseline' adherence categories: 0-25%, 26-50%, 51-75% and 76-100%. There were 542 participants contributing data to the model. Treatment effects by adherence subgroup are given in Table 3.

Table 3 Adjusted* estimates for between-group differences in FEV_1 percent predicted at 12 months post-consent for adherence subgroups

Baseline adherence subgroup	Estimated between-group difference (95% CI)
0-25% (n=162)	3.0 (0.1, 6.0) %
26-50% (n=107)	0.5 (-3.1, 4.0) %
51-75% (n=115)	2.6 (-0.8, 6.0) %
76-100% (n=158)	-0.4 (-3.3, 2.6) %

*adjusted for baseline FEV_1 percent predicted, previous year's IV days and site

The original model was also repeated without the interaction effect, but excluding the ≥76% adherence subgroup to investigate potential 'ceiling' effects (remaining n=398). The treatment effect for the whole trial cohort was 1.4 (95% CI -0.2, 3.0) percentage points. Exclusion of the 'high adherence' subgroup yielded a treatment effect estimate of 1.9 (95% CI -0.1, 3.9) percentage points, favouring the intervention arm. However, the confidence intervals included zero, consistent with no between-group difference.

FEV_1 percent predicted was available from clinic visits in addition to baseline and 12-month post consent points. Monthly averages were taken and are presented by treatment arm in Figure 3 and by baseline normative adherence subgroup in Figure 4.

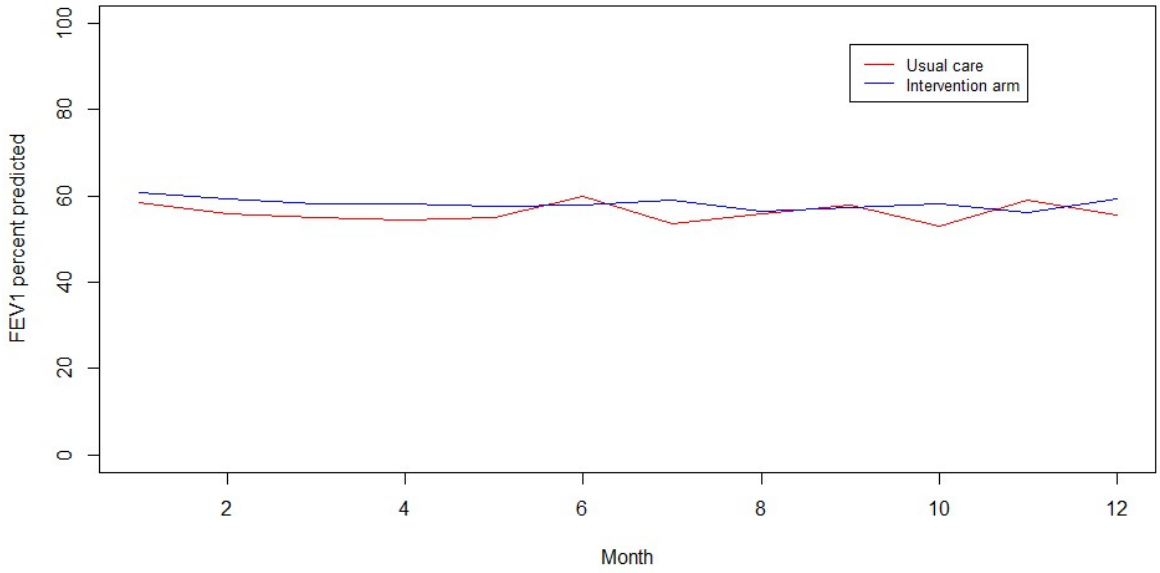

Figure 3 Monthly FEV_1 percent predicted by randomised group

A linear mixed-model with average monthly FEV_1 percent predicted as the outcome and with adjustment for baseline FEV_1 percent predicted, previous year's IV days and participants nested within site yielded a between-group difference of 0.63 (95% CI -0.25. 1.51) percentage points in

average monthly FEV_1 over time in favour of participants randomised to the intervention arm. There were 596 patients with sufficient data for inclusion in the model. There was a tendency for higher FEV_1 percent predicted in the intervention arm, but the confidence interval included zero, consistent with no overall between-group difference. The time coefficient was -0.16 (95% CI -0.26, -0.05), indicating that FEV_1 percent predicted decreased by an average 0.16 percentage points per month or approximately 2 units over a 12-month period in both arms. There was no evidence of a treatment group-by-time interaction (p=0.711).

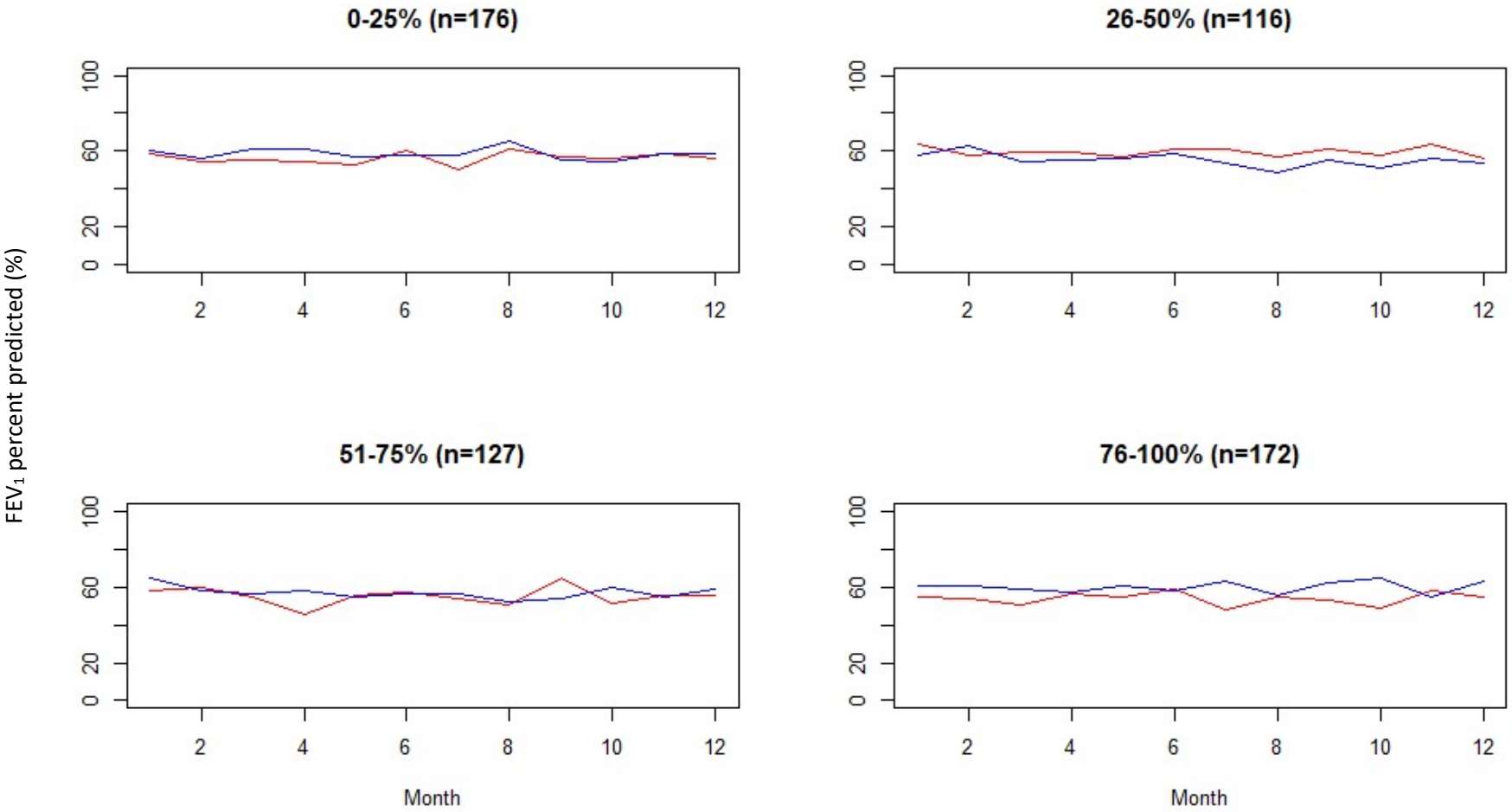

Figure 4 Monthly FEV_1 percent predicted by randomised group and baseline adherence subgroup

Red line denotes usual care arm; blue line denotes intervention arm.

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1.3 Interrelationship between FEV_1 percent predicted and adherence

To investigate interrelationship between pulmonary exacerbations, normative adherence, FEV_1 percent predicted, a correlation matrix is presented in Table 4. The distribution of FEV_1 percent predicted by baseline adherence subgroup is shown for each randomised group in Figure 5.

Table 4 Correlation matrix for exacerbations, normative adherence and FEV_1 percent predicted

		Exacerbation count	FEV_1 pp baseline	FEV_1 pp 12 months	'Baseline' adherence (weeks 1-2)	Six-month adherence (weeks 3-26)	Twelve-month adherence (weeks 27-52)
Exacerbation count	R	1	-0.44	-0.45	-0.08	-0.08	-0.07
	N	607	570	557	591	602	570
FEV_1 percent predicted baseline	R	-0.44	1	0.92	-0.09	-0.09	-0.08
	N	570	570	556	557	568	550
FEV_1 percent predicted 12 months	R	-0.45	0.92	1	-0.05	-0.03	-0.04
	N	557	556	557	544	555	537
'Baseline' adherence (weeks 1-2)	R	-0.08	-0.09	-0.05	1	0.77	0.68
	N	591	557	544	591	588	556
Six-month adherence (weeks 3-26)	r	-0.08	-0.09	-0.03	0.77	1	0.91
	N	602	568	555	588	602	569
Twelve-month adherence (weeks 27-52)	r	-0.07	-0.08	-0.04	0.68	0.91	1
	N	570	550	537	556	569	570

There were moderate correlations between FEV_1 percent predicted values and exacerbations, with higher FEV_1 percent predicted associated with lower exacerbation counts. Relationships between adherence and both FEV_1 percent predicted and exacerbation measures were very weak.

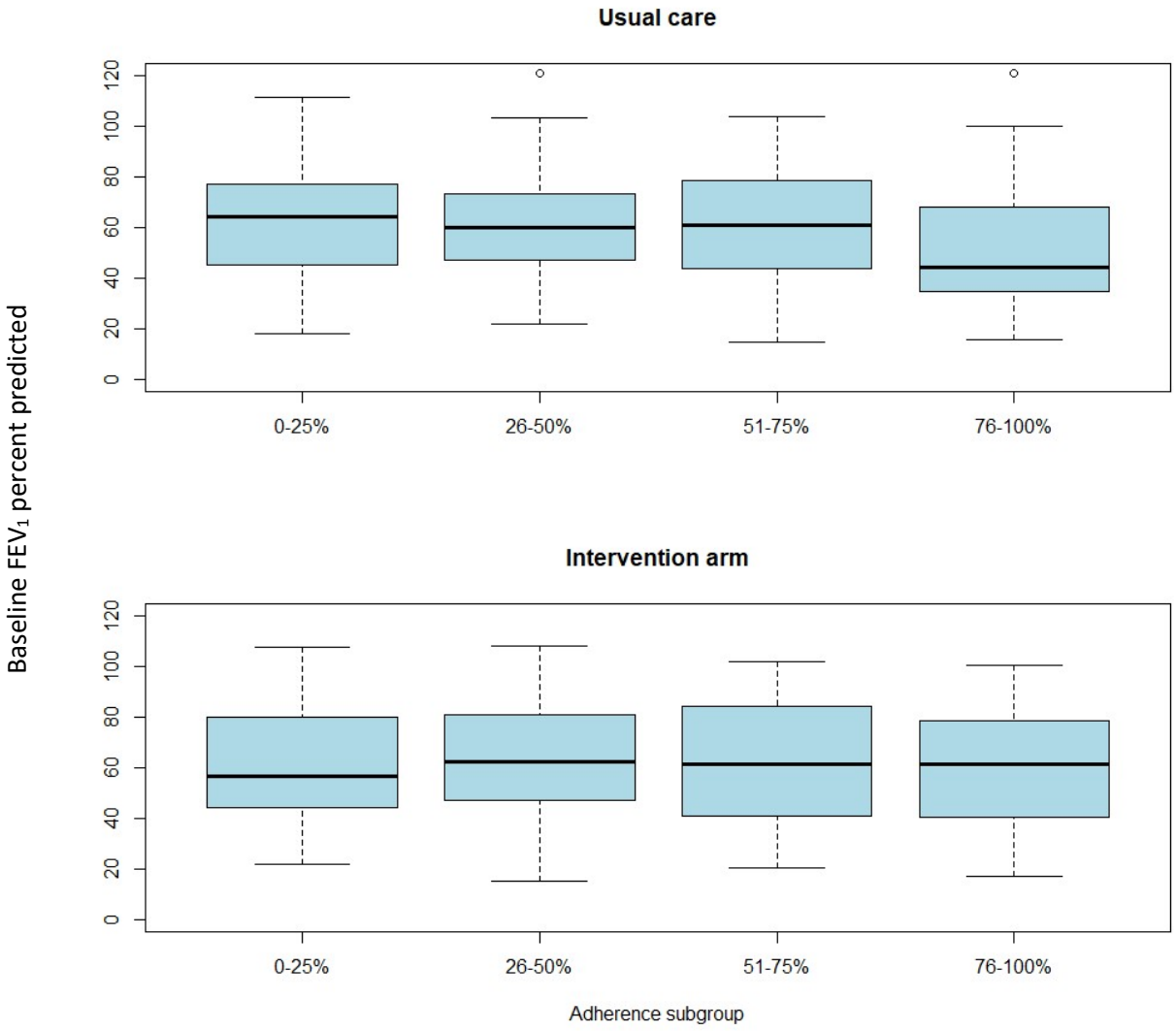

Figure 5 Distribution of baseline FEV_1 percent predicted by baseline adherence subgroup

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1.4 Maintenance/stability of adherence in relation to start of treatment

Of the 305 participants randomised to receive the intervention, 290 had complete session data for at least one session, and 287 had the start date recorded for the first session. The mean (SD) time from randomisation to first intervention visit was 6.7 (3.3) weeks [Med (IQR) 5.9 (4.7, 7.7) weeks]. The distribution is shown in Figure 6.

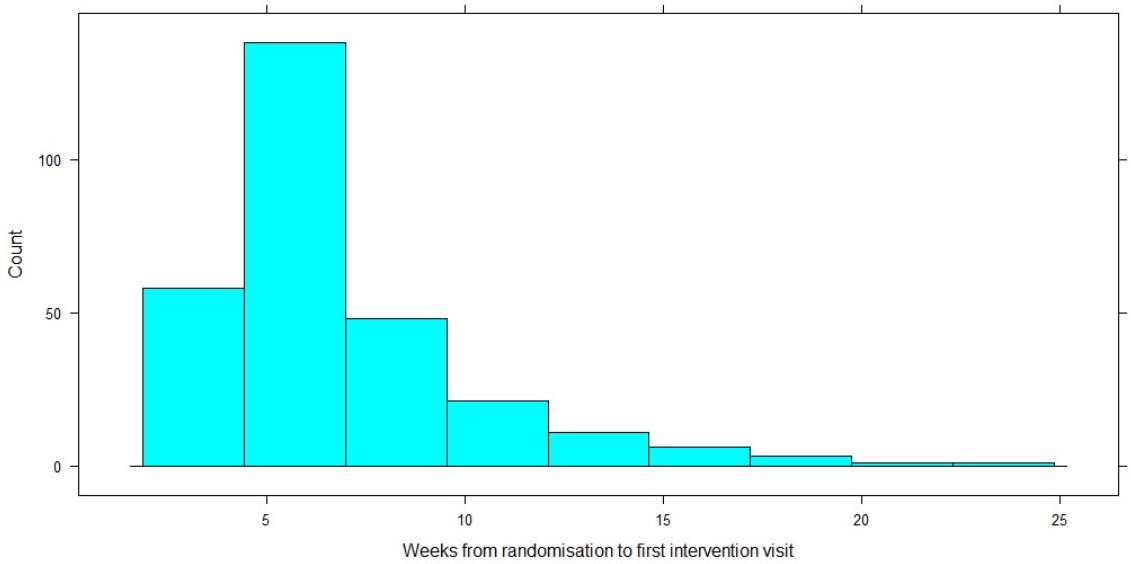

Figure 6 Distribution of time from randomisation to first intervention visit

The longitudinal normative adherence model as described in the trial SAP was repeated in two analyses which excluded adherence data from the early weeks, in order to remove any initial 'spike' that may potentially arise due to participants behaving differently due to them being monitored (known as a "Hawthorne effect"). The first analysis excluded adherence data collected during the first two weeks post 'baseline' (weeks 3 and 4). The estimated treatment effect increased slightly to 10.9 (95% CI 9.9, 11.9) percentage points in favour of the intervention arm. The adherence fell overall during the trial by an average of 0.16 (95% CI -0.22, -0.09) percentage points per week; the change was similar in the two arms and the treatment-by-time interaction was not statistically significant (p=0.203).

The model was repeated excluding the first 10 weeks of follow-up post 'baseline' (weeks 3-12), instead of just the first two, thus beginning at the point by which the intervention should have been delivered. Doing so increased the estimated treatment effect to 13.4 (95% CI 12.1, 14.7) percentage points in favour of the intervention arm. The decline over time was virtually unchanged (-0.16; 95% CI -0.22, -0.10) and again not statistically significantly different between arms (p=0.473).

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2 Two-year outcomes

2.1 Participant characteristics

The ACtiF trial opened to recruitment in October 2017 and 'last patient, last visit' was June 2019, allowing a maximum of 21 months' follow-up. There were 608 participants randomised, one of whom was withdrawn prior to any baseline measurement. There were 571 participants contributing exacerbation, adherence and/or FEV_1 data beyond the 12-month trial window, characteristics for whom are provided in Tables 5-7.

There were 19 sites participating in the trial. All 19 were represented in the extended follow-up group. The 36 participants not contributing second-year data were from 17 different sites.

The relatively small number of patients in the no extended follow-up group meant there was limited scope for comparisons. Nevertheless, the 36 patients appeared generally similar in composition to the 571 that continued beyond 12 months in terms of baseline characteristics. Patients that did not continue were had slightly lower weight (mean 59.5 kg v 63.9 kg) and FEV_1 percent predicted (mean 53.1% v 59.9%) and had more IV days over the past 12 months (medians 27 v 14). Although mean normative adherence was slightly lower amongst those that did not continue (46.7% v 50.0%), self-reported adherence was slightly higher (73.3% v 69.2%).

The 36 patients comprised 21 intervention and 15 usual care. The most notable difference between these groups was in adherence. Baseline normative adherence was higher in the intervention group (mean 56.7%) than usual care (30.4%), compared to 50.0% in patients that continued into the follow-up. The pattern for self-reported baseline adherence was similar, as was adherence during the trial itself. The 21 non- continuing patients in the usual care arm experienced an average rate of 3.1 pulmonary exacerbations per person per year compared to 2.5 in the 15 non-continuing intervention arm and 1.7 among those that continued follow-up.

Table 5 Participant characteristics at baseline for one-year and two-year follow-up cohorts

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
Age (years)						
N	15	21	36	288	283	571
Mean (SD)	27.8 (8)	29.7 (9.7)	28.9 (9)	30.4 (10.9)	31.2 (10.7)	30.8 (10.8)
Median (IQR)	29.7 (20.6, 31.7)	26.4 (21.9, 36.4)	27.5 (21.3, 32.8)	27.7 (22.1, 35.2)	28.9 (23.5, 36.6)	28.2 (22.7, 36.1)
Range	(18.2, 42.7)	(19.4, 52.9)	(18.2, 52.9)	(16.7, 71.4)	(16.1, 71.9)	(16.1, 71.9)
Weight (kg)						
N	15	21	36	288	283	571
Mean (SD)	58.3 (11.8)	60.3 (13.7)	59.5 (12.8)	63.5 (14.3)	64.4 (14.1)	63.9 (14.2)
Median (IQR)	58.2 (47.7, 66.4)	59.6 (50.6, 68.1)	58.8 (49.7, 67.2)	61.9 (52.7, 71.5)	62.5 (54.7, 70.9)	62.4 (53.4, 71.2)
Range	(40.4, 82)	(41.7, 91.4)	(40.4, 91.4)	(37.2, 124.1)	(32.9, 133.8)	(32.9, 133.8)
Height (cm)						
N	15	21	36	288	283	571
Mean (SD)	166.8 (7.3)	169.1 (9.5)	168.2 (8.7)	167.2 (9.3)	167.6 (9.6)	167.4 (9.4)
Median (IQR)	165 (161, 171)	171 (166, 175)	169 (163.5, 174)	166 (161, 174)	167 (161, 175)	166 (161, 174)
Range	(157, 182)	(150, 185)	(150, 185)	(144, 196)	(144, 196)	(144, 196)
BMI						
N	15	21	36	288	283	571
Mean (SD)	20.9 (3.4)	20.9 (3.2)	20.9 (3.2)	22.6 (4.2)	22.8 (4.2)	22.7 (4.2)
Median (IQR)	21 (18, 22)	20 (18, 22)	21 (18, 22)	22 (20, 25)	22 (20, 25)	22 (20, 25)
Range	(15, 27)	(18, 29)	(15, 29)	(13, 41)	(15, 48)	(13, 48)
Gender						
N	15	21	36	288	283	571
Female	11 (73.3%)	7 (33.3%)	18 (50%)	143 (49.7%)	149 (52.7%)	292 (51.1%)
Male	4 (26.7%)	14 (66.7%)	18 (50%)	145 (50.3%)	134 (47.3%)	279 (48.9%)
Deprivation						
N	14	14	35	288	288	569
1st quintile	2 (14.3%)	3 (14.3%)	5 (14.3%)	49 (17%)	47 (16.7%)	96 (16.9%)
2nd quintile	4 (28.6%)	4 (19%)	8 (22.9%)	67 (23.3%)	55 (19.6%)	122 (21.4%)
3rd quintile	3 (21.4%)	6 (28.6%)	9 (25.7%)	63 (21.9%)	57 (20.3%)	120 (21.1%)
4th quintile	4 (28.6%)	1 (4.8%)	5 (14.3%)	63 (21.9%)	62 (22.1%)	125 (22%)
5th quintile	1 (7.1%)	7 (33.3%)	8 (22.9%)	46 (16%)	60 (21.4%)	106 (18.6%)

Table 6 Clinical characteristics at baseline for one-year and two-year follow-up cohorts

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
FEV1 percent predicted						
N	15	21	36	287	283	570
Mean (SD)	52.4 (25.7)	53.6 (26.1)	53.1 (25.5)	58.6 (22.4)	61.2 (23.3)	59.9 (22.9)
Median (IQR)	44.5 (32, 79.1)	45.9 (28.9, 76.2)	45.2 (30.5, 77.7)	56.8 (39.5, 74.9)	61.8 (42.3, 80.9)	60.2 (40.9, 77.9)
Range	(18, 101.3)	(20.4, 98.3)	(18, 101.3)	(14.6, 121.2)	(15, 117.1)	(14.6, 121.2)
IV days in previous 12 months						
N	15	21	36	288	283	571
Mean (SD)	49 (42.4)	27.2 (34.5)	36.3 (39)	26.6 (32.1)	23.9 (27.4)	25.3 (29.9)
Median (IQR)	40 (24, 58)	18 (0, 35)	27 (4, 51)	15 (0, 42)	14 (0, 35)	14 (0, 41)
Range	(0, 147)	(0, 144)	(0, 147)	(0, 184)	(0, 135)	(0, 184)
Normative adherence* (%)						
N	13	21	34	282	275	557
Mean (SD)	30.4 (33.6)	56.7 (37.6)	46.7 (37.9)	46.3 (34.1)	53.8 (32.6)	50 (33.5)
Median (IQR)	17.9 (0, 42.9)	70.5 (17.9, 90)	39.3 (12.2, 85.7)	45.8 (14.3, 77.4)	57.1 (25.6, 83.3)	52.4 (19.1, 81.3)
Range	(0, 91.7)	(0, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)
Subjective adherence (%)						
N	15	21	36	283	279	562
Mean (SD)	65.2 (34.6)	79 (20.6)	73.3 (27.7)	69.2 (30.7)	69.2 (31.6)	69.2 (31.1)
Median (IQR)	85 (50, 90)	90 (70, 90)	85 (60, 90)	75 (50, 95)	80 (50, 95)	80 (50, 95)
Range	(0, 95)	(30, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)
***Pseudomonas* status (consensus definition)**						
N	14	21	35	285	283	568
Chronic	8 (57.1%)	13 (61.9%)	21 (60%)	167 (58.6%)	161 (56.9%)	328 (57.7%)
Not chronic	6 (42.9%)	8 (38.1%)	14 (40%)	118 (41.4%)	122 (43.1%)	240 (42.3%)
***Pseudomonas* status (clinician's judgement)**						
N	14	21	35	287	283	570
Chronic	9 (64.3%)	12 (57.1%)	21 (60%)	154 (53.7%)	149 (52.7%)	303 (53.2%)
Intermittent	0 (0%)	1 (4.8%)	1 (2.9%)	41 (14.3%)	26 (9.2%)	67 (11.8%)
Pseudomonas-free	5 (35.7%)	8 (38.1%)	13 (37.1%)	87 (30.3%)	104 (36.7%)	191 (33.5%)
Unknown	0 (0%)	0 (0%)	0 (0%)	5 (1.7%)	4 (1.4%)	9 (1.6%)

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
***Pseudomonas* status (Leeds criteria)**						
N	14	21	35	288	283	571
Chronic	7 (50%)	12 (57.1%)	19 (54.3%)	120 (41.7%)	117 (41.3%)	237 (41.5%)
Intermittent	1 (7.1%)	2 (9.5%)	3 (8.6%)	66 (22.9%)	47 (16.6%)	113 (19.8%)
Negative	6 (42.9%)	7 (33.3%)	13 (37.1%)	97 (33.7%)	119 (42%)	216 (37.8%)
Unknown	0 (0%)	0 (0%)	0 (0%)	5 (1.7%)	0 (0%)	5 (0.9%)

*Measured during weeks 1 and 2 post-consent

Table 7 Patient-reported outcomes at baseline for one-year and two-year follow-up cohorts

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
EQ-5D-5L						
N	15	21	36	285	282	567
Mean (SD)	0.86 (0.11)	0.83 (0.23)	0.84 (0.19)	0.84 (0.16)	0.86 (0.14)	0.85 (0.15)
Median (IQR)	0.87 (0.79, 0.95)	0.94 (0.74, 1)	0.9 (0.76, 1)	0.87 (0.75, 1)	0.87 (0.77, 1)	0.87 (0.77, 1)
Range	(0.66, 1)	(0.21, 1)	(0.21, 1)	(0.29, 1)	(0.04, 1)	(0.04, 1)
EQ-5D-5L crosswalk						
N	15	21	36	285	282	567
Mean (SD)	0.79 (0.16)	0.77 (0.27)	0.78 (0.23)	0.77 (0.19)	0.79 (0.18)	0.78 (0.19)
Median (IQR)	0.77 (0.7, 0.92)	0.84 (0.66, 1)	0.84 (0.66, 1)	0.78 (0.64, 1)	0.8 (0.68, 1)	0.78 (0.67, 1)
Range	(0.54, 1)	(-0.02, 1)	(-0.02, 1)	(0.2, 1)	(-0.12, 1)	(-0.12, 1)
COM-BMQ concerns						
N	15	21	36	286	283	569
Mean (SD)	2 (0.6)	1.8 (0.4)	1.9 (0.5)	2.1 (0.5)	2.1 (0.6)	2.1 (0.5)
Median (IQR)	2.2 (1.7, 2.4)	1.9 (1.5, 2.1)	2 (1.5, 2.3)	2.1 (1.6, 2.4)	2.1 (1.7, 2.4)	2.1 (1.7, 2.4)
Range	(1.1, 2.8)	(1.1, 2.7)	(1.1, 2.8)	(1, 3.7)	(1, 4.4)	(1, 4.4)
COM-BMQ necessities						
N	15	21	36	286	283	569
Mean (SD)	3.8 (0.7)	3.6 (0.7)	3.7 (0.7)	3.5 (0.8)	3.6 (0.7)	3.6 (0.7)
Median (IQR)	3.6 (3.2, 4.4)	3.6 (3, 4.1)	3.6 (3.1, 4.3)	3.6 (3.1, 4)	3.6 (3.1, 4)	3.6 (3.1, 4)
Range	(2.4, 4.9)	(2.1, 4.7)	(2.1, 4.9)	(1.3, 5)	(1.6, 5)	(1.3, 5)

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
SRBAI (habit)						
N	15	21	36	285	282	567
Mean (SD)	11.3 (4.1)	12.5 (4.8)	12 (4.5)	12 (4.8)	12.1 (5.1)	12.1 (4.9)
Median (IQR)	12 (9, 13.5)	13 (10, 15)	13 (9, 15)	12 (8, 16)	12 (8, 16)	12 (8, 16)
Range	(4, 20)	(4, 20)	(4, 20)	(4, 20)	(4, 20)	(4, 20)
CFQ-R – physical						
N	15	21	36	287	283	570
Mean (SD)	53 (31)	51.2 (32.9)	51.9 (31.7)	53 (30.2)	54.6 (30.4)	53.8 (30.3)
Median (IQR)	50 (29.5, 81)	54 (21, 83)	52 (21, 83)	54 (29, 79)	54 (29, 83)	54 (29, 79)
Range	(4, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)
CFQ-R – emotion						
N	15	21	36	287	283	570
Mean (SD)	64.5 (22.4)	76.9 (16.5)	71.7 (19.9)	66.3 (24.2)	65.8 (21.8)	66 (23)
Median (IQR)	60 (47, 80)	80 (73, 87)	73 (58.2, 87)	67 (47, 87)	67 (47, 80)	67 (47, 87)
Range	(27, 100)	(40, 100)	(27, 100)	(0, 100)	(0, 100)	(0, 100)
CFQ-R – social						
N	15	21	36	287	283	570
Mean (SD)	67.7 (22.3)	64.7 (18.5)	65.9 (19.9)	60.5 (20.8)	61.7 (20.1)	61.1 (20.5)
Median (IQR)	72 (44, 80.5)	61 (50, 78)	67 (50, 79.2)	61 (44, 78)	61 (50, 78)	61 (44, 78)
Range	(33, 100)	(28, 94)	(28, 100)	(6, 100)	(11, 100)	(6, 100)
CFQ-R – eating						
N	15	21	36	287	283	570
Mean (SD)	84.6 (18)	69.9 (31.7)	76 (27.6)	80.3 (24.6)	83 (21.5)	81.7 (23.1)
Median (IQR)	89 (72.5, 100)	78 (44, 100)	83.5 (56, 100)	89 (67, 100)	100 (67, 100)	89 (67, 100)
Range	(56, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)	(0, 100)
CFQ-R – body						
N	15	21	36	287	283	570
Mean (SD)	61.6 (28.2)	57.6 (32.1)	59.3 (30.2)	66.3 (29.4)	66.2 (27.7)	66.2 (28.5)
Median (IQR)	67 (44.5, 83.5)	56 (22, 78)	67 (33, 80.8)	67 (44, 100)	67 (44, 89)	67 (44, 89)
Range	(11, 100)	(11, 100)	(11, 100)	(0, 100)	(0, 100)	(0, 100)
CFQ-R – treatment burden						
N	15	21	36	287	283	570
Mean (SD)	48.8 (16.9)	58.9 (18.5)	54.7 (18.3)	52 (20.4)	54 (19.9)	53 (20.2)
Median (IQR)	44 (44, 56)	56 (44, 67)	56 (44, 67)	56 (44, 67)	56 (44, 67)	56 (44, 67)

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
Range	(22, 78)	(22, 100)	(22, 100)	(0, 100)	(11, 100)	(0, 100)
CFQ-R – respiratory						
N	15	21	36	287	283	570
Mean (SD)	59.7 (20.5)	61 (23)	60.5 (21.7)	56.4 (22)	58 (22.1)	57.2 (22)
Median (IQR)	67 (41.5, 75)	67 (44, 72)	67 (42.8, 73.5)	61 (39, 72)	61 (41.5, 75)	61 (39, 72)
Range	(28, 94)	(17, 100)	(17, 100)	(0, 100)	(6, 100)	(0, 100)
CFQ-R – digestion						
N	15	21	36	287	283	570
Mean (SD)	77.1 (19.1)	84.2 (16.3)	81.3 (17.6)	81.3 (19.4)	79.6 (21.8)	80.5 (20.6)
Median (IQR)	78 (67, 94.5)	89 (78, 100)	89 (67, 100)	89 (67, 100)	89 (67, 100)	89 (67, 100)
Range	(44, 100)	(44, 100)	(44, 100)	(0, 100)	(0, 100)	(0, 100)
MAD-3 (medication adherence)						
N	15	21	36	259	259	518
Mean (SD)	10.7 (2.8)	11.7 (2.7)	11.2 (2.8)	9.9 (3.4)	10.1 (3.4)	10 (3.4)
Median (IQR)	10 (9, 12.5)	12 (9, 14)	12 (9, 14)	10 (7, 12)	10 (8, 13)	10 (8, 13)
Range	(4, 15)	(7, 15)	(4, 15)	(3, 15)	(3, 15)	(3, 15)
Behavioural question (effort)						
N	15	21	36	285	281	566
Mean (SD)	2.9 (1.2)	3.8 (1.2)	3.4 (1.3)	3.1 (1.2)	3 (1.3)	3.1 (1.3)
Median (IQR)	3 (2, 3.5)	4 (3, 5)	3 (2, 5)	3 (2, 4)	3 (2, 4)	3 (2, 4)
Range	(1, 5)	(2, 5)	(1, 5)	(1, 5)	(1, 5)	(1, 5)
CHAOS-6 (routine)						
N	15	21	36	285	282	567
Mean (SD)	10.1 (2.6)	9.9 (3.8)	10 (3.3)	9.5 (2.9)	9.4 (2.8)	9.5 (2.9)
Median (IQR)	10 (8.5, 12)	9 (7, 13)	9.5 (7, 12.2)	9 (7, 12)	9 (7, 11)	9 (7, 11)
Range	(5, 15)	(5, 18)	(5, 18)	(4, 17)	(4, 17)	(4, 17)
PAM-13 (health-style assessment)						
N	15	21	36	287	283	570
Mean (SD)	68.1 (14.4)	69.4 (16.5)	68.8 (15.5)	65.1 (13.3)	65.5 (14.3)	65.3 (13.8)
Median (IQR)	65.5 (55.6, 76.7)	67.8 (55.6, 77.7)	65.5 (55.6, 78.5)	63.1 (55.6, 72.5)	63.1 (54.4, 75)	63.1 (55.6, 72.5)
Range	(53.2, 100)	(47, 100)	(47, 100)	(38.1, 100)	(26.1, 100)	(26.1, 100)
PHQ-8 (depression)						
N	15	21	36	286	283	569
Mean (SD)	6.5 (4)	5.5 (4.9)	5.9 (4.5)	6.4 (5.1)	6.5 (5.3)	6.5 (5.2)

	No second-year follow-up (n=36)			Second-year follow-up (n=571)		
	Usual care	**Intervention**	**Overall**	**Usual care**	**Intervention**	**Overall**
Median (IQR)	7 (3.5, 10.5)	4 (1, 9)	4.5 (2.8, 10)	6 (2, 10)	6 (2, 10)	6 (2, 10)
Range	(0, 12)	(0, 16)	(0, 16)	(0, 23)	(0, 24)	(0, 24)
GAD-7 (anxiety)						
N	15	20	35	287	282	569
Mean (SD)	5 (6)	2.8 (4.3)	3.8 (5.1)	4.7 (4.6)	4.8 (5)	4.7 (4.8)
Median (IQR)	4 (0.5, 8)	0.5 (0, 3.5)	1 (0, 6)	3 (1, 7)	3 (1, 7)	3 (1, 7)
Range	(0, 20)	(0, 16)	(0, 20)	(0, 21)	(0, 21)	(0, 21)

Summaries of 12-month outcomes by follow-up group are presented in Table 8. Exacerbation rates suggest a tendency for drop-out of participants in poorer health. Ten of the 36 cases with no extended follow-up died during the trial (usual care n=4, intervention n=6). FEV_1 percent predicted values in the trial-only group should be interpreted with caution due to high missingness.

Table 8 Twelve-month outcome data for one-year and two-year follow-up cohorts

		No second-year follow-up (n=36)		Second-year follow-up (n=571)	
		Usual care	**Intervention**	**Usual care**	**Intervention**
Pulmonary exacerbations	N	15	21	288	283
	Rate (exacerbations/year)	3.1	2.5	1.7	1.6
Six-month adherence (weeks 3-26)	N	14	19	272	278
	mean (SD)	26.2 (28.8)	57.4 (31.5)	33.9 (31.9)	51.9 (32.6)
Twelve-month adherence (weeks 27-52)	N	10	10	272	278
	mean (SD)	14.3 (18.8)	53.9 (33.3)	33.9 (31.9)	51.9 (32.6)
Twelve-month FEV_1 percent predicted	N	4	3	279	271
	mean (SD)	60 (31.2)	75.8 (6)	56.7 (23)	60.5 (24.3)

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2.2 Primary outcome

2.2.1 Exacerbations (extended follow-up)

Participants in both arms had similar lengths of extended follow-up with regards primary outcome data: 406.7 and 400.7 person-years of follow-up in the usual care and intervention groups, respectively (compared with 297.2 and 294.9 person-years of follow-up in the main trial analysis). The distribution of extended follow-up times is shown in Figure 7. There was a total of 1326 exacerbations (693 usual care, 633 intervention) during that time, the distribution of which is shown by randomised group in Figure 8.

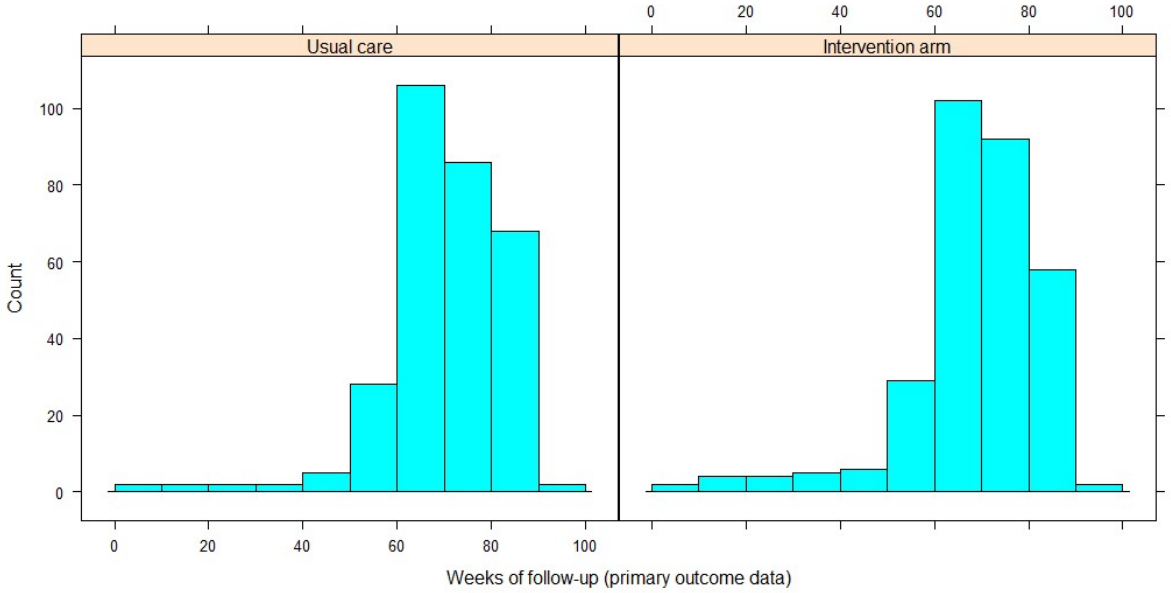

Figure 7 Distribution of extended primary outcome follow-up times by randomised group

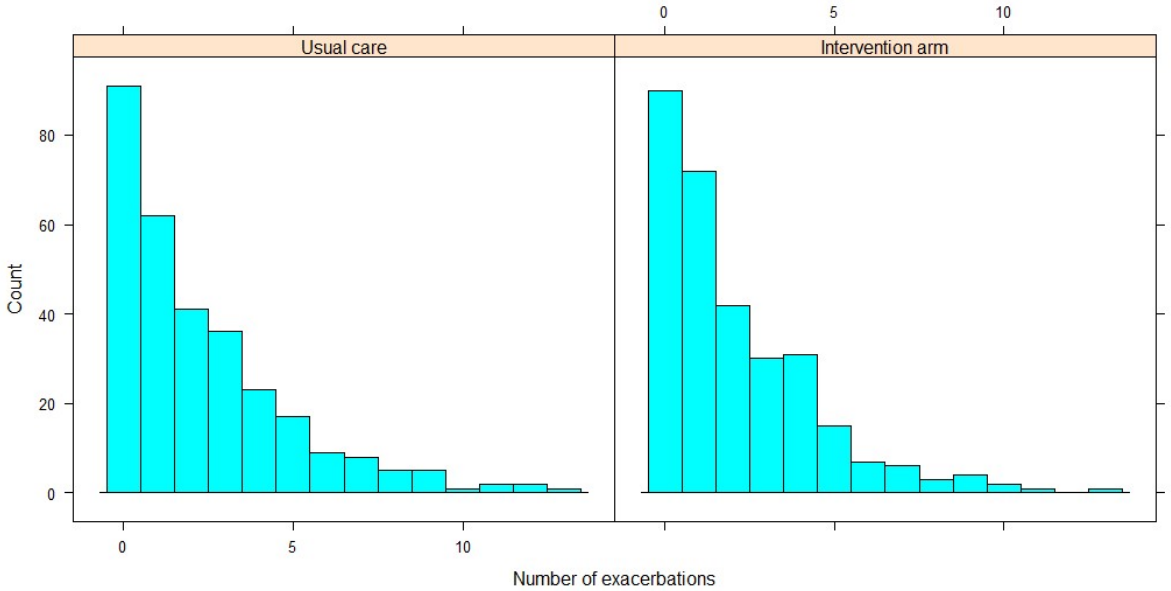

Figure 8 Exacerbation counts over the extended follow-up time by randomised group

Observed exacerbation rates and rate ratios are presented in Table 9. The primary analysis model included adjustments for the previous year's IV days and site, which were stratifying factors in the randomisation schedule. The result from the main trial analysis was an incidence rate ratio (IRR) of 0.96 (95% CI 0.83, 1.12). The ratio is less than one, favouring the intervention arm. However the confidence interval includes one, consistent with no overall difference in exacerbation rates between the two randomised groups.

An analysis of just the second year of follow-up showed lower exacerbation rates than year one, but similar rate ratios when comparing the two groups. The adjusted IRR was less than one, favouring the intervention arm; however, the confidence interval included one, consistent with no overall difference.

The estimated treatment effect for the full longer term follow-up (with just over 100 additional person-years of observations per group compared to the main trial analysis) was very similar to the primary analysis, with an IRR of 0.97 (95% CI 0.84, 1.12).

Table 9 Exacerbation rates over extended follow-up

Model	Usual care				Intervention				IRR (95% CI)	*p* value
	N	Exacerbations	Person-years	Exacerbation rate/year	N	Exacerbations	Person-years	Exacerbation rate/year		
Year one only										
Unadjusted	303	526	297.2	1.77	304	482	294.9	1.63	0.92 (0.77, 1.11)	0.387
Adjusted									0.96 (0.83, 1.12)	0.638
Year two only										
Unadjusted	287	167	109.3	1.53	283	151	106.1	1.42	0.93 (0.73, 1.18)	0.552
Adjusted*									0.95 (0.76, 1.78)	0.630
Complete two-year										
Unadjusted	303	693	406.7	1.70	304	633	400.7	1.58	0.92 (0.77, 1.10)	0.380
Adjusted									0.97 (0.84, 1.12)	0.699

IRR = Incidence Rate Ratio

*Adjusted second-year estimates come from Poisson model as warnings produced by negative binomial model (iteration limit reached). Second-year data do not look overdispersed.

Model definitions:
Unadjusted – unadjusted for any covariates except duration of follow-up
Adjusted – adjusted for stratifying factors (previous year's IV days and site)

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2.2.2 Severity of exacerbations (extended follow-up)

The analysis conducted in section 1.1 was repeated for the extended follow-up data. There were 1326 exacerbations (usual care n=639, intervention n=633) meeting the criteria in the 21-month post-consent follow-up period.

The distribution of exacerbation counts by severity (as measured by the number of Fuchs criteria met) is presented by randomised group in Figure 9.

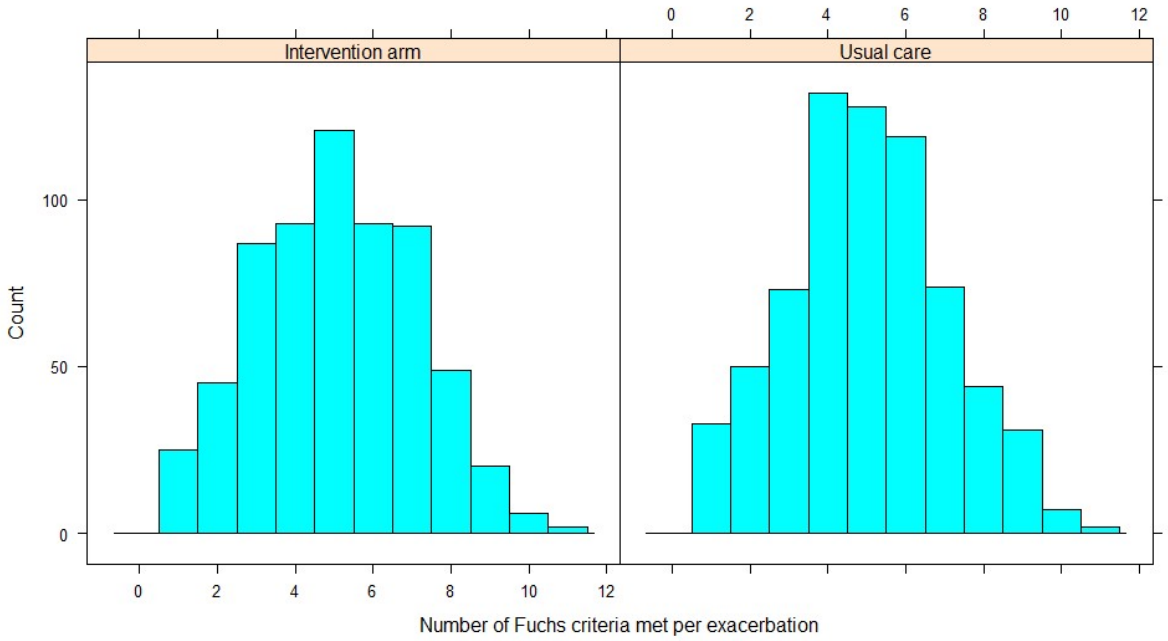

Figure 9 Distribution of exacerbations by severity by randomised group over the extended follow-up

Summary statistics are provided in Table 10. A linear mixed-effects model was used to examine between-group differences, allowing for non-independence of events (one participant may have multiple exacerbations). The estimated between-group difference in severity was 0.08 (95% CI -0.22, 0.38). There was no evidence of a difference in severity of exacerbations as measured by the mean Fuchs scores between the randomised groups.

Table 10 Summary of Fuchs criteria met per exacerbation by randomised group over extended follow-up

Time period	Statistic	Usual care	Intervention
0-21 months	Person-years	406.7	400.7
	N exacerbations	693	633
	Mean (SD)	5.0 (2.1)	5.0 (2.1)
	Median (IQR)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)

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2.3 Key secondary outcomes

2.3.1 Normative adherence (extended follow-up)

Weekly numerator-adjusted normative adherence summaries, for weeks 1 to 91 post-consent, are provided in Table 11. The weekly mean numerator adjusted normative adherence levels are shown by randomised group in Figure 10. Data in Table 11 and Figure 10 towards the end of follow-up should be interpreted cautiously due to the small number of valid observations.

Table 11 Numerator-adjusted normative adherence weekly summaries by randomised group

Week	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
1	289	48 (35)	290	57 (34.2)
2	295	43.7 (35.1)	293	51.4 (34.6)
3	298	39.9 (34.8)	295	49.7 (34.3)
4	297	39.7 (35.4)	297	50.3 (35.1)
5	293	40.5 (34.9)	298	51.4 (34.9)
6	291	38.6 (34.5)	299	54.7 (34.7)
7	291	38.2 (35.1)	298	54.4 (35.2)
8	292	38.1 (35.9)	298	53.8 (36.1)
9	292	37.4 (35.3)	297	54.3 (35)
10	291	36.6 (34.7)	297	54 (35.9)
11	290	36.4 (34.8)	297	54.9 (35.6)
12	290	38 (34.9)	297	56.9 (35.7)
13	290	38.4 (35.6)	296	55.6 (36.4)
14	290	37 (35.2)	294	55.1 (36.9)
15	289	36 (34.9)	293	56.1 (36.8)
16	286	35.8 (34.8)	293	55.1 (36.3)
17	286	36.3 (34.4)	293	55.2 (35.7)
18	285	34.9 (34.6)	293	53.9 (35.6)
19	285	35.5 (34.7)	293	55.2 (35.1)
20	285	34.6 (35.1)	293	54.5 (36)
21	283	34.7 (36.5)	292	54.2 (37.1)
22	283	35.7 (36.6)	292	54.1 (36.3)
23	283	34.2 (35.7)	291	55 (36.4)
24	282	34.5 (34.8)	290	55.3 (35.8)
25	282	34.7 (34)	290	53.2 (35.9)
26	281	34.6 (33.8)	290	54.3 (36)
27	281	34.4 (34.5)	288	53.9 (36.6)
28	279	35.2 (35.9)	288	54.2 (35.7)
29	280	36 (35.8)	287	53.1 (36)
30	276	36 (35.9)	287	54.1 (36.4)
31	275	35.4 (35.5)	285	56.3 (36.5)
32	274	33.7 (34)	285	54.1 (36.7)
33	274	33.3 (34.5)	284	53 (37.2)
34	274	33 (33.5)	283	52.3 (36.8)
35	273	33.9 (34.5)	282	52.3 (36.7)

Week	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
36	273	35.6 (35.1)	281	52.5 (36.4)
37	272	35.6 (34.3)	279	53.3 (35.6)
38	272	35.5 (35.1)	279	52.6 (36.1)
39	272	34.2 (34.8)	279	51.6 (37.2)
40	272	35.5 (35.4)	276	50.6 (37.4)
41	272	33.4 (34.2)	275	52.9 (35.9)
42	272	33.8 (33.9)	274	53.8 (36.2)
43	272	32.7 (35.1)	274	53.1 (36.4)
44	271	32 (34.4)	272	52 (37.3)
45	271	32.7 (34.9)	272	52.6 (36.6)
46	269	33.3 (34.8)	272	52 (36.4)
47	269	32.9 (34.5)	271	50.6 (37.4)
48	269	33.9 (35.7)	271	49.3 (37.1)
49	269	34.7 (35.6)	269	50.8 (36.6)
50	268	32.8 (35.8)	269	52 (36)
51	267	33.1 (35.3)	269	52.7 (35.9)
52	266	33.2 (35)	268	51.4 (36.1)
53	264	33.2 (34.9)	266	51.2 (37.5)
54	262	33 (35.3)	266	51 (36.7)
55	260	33.2 (36)	263	48.6 (36.7)
56	258	32.3 (36)	262	49.1 (36.7)
57	257	33.5 (36.2)	261	48.9 (36.7)
58	249	33.6 (35.4)	257	48.3 (37.1)
59	242	33.3 (35.1)	250	48.4 (38)
60	239	33.3 (34.8)	245	48 (38.3)
61	234	33.4 (34.4)	236	48.5 (38)
62	226	32.8 (34.7)	233	48 (38.2)
63	218	33.3 (35.4)	222	47.2 (38.7)
64	209	34.4 (35.3)	210	48.9 (38.3)
65	196	35.7 (35.9)	197	50 (37.3)
66	186	33.3 (34.9)	185	50.6 (37.6)
67	177	33.3 (35.2)	172	50 (37)
68	169	34.2 (35.2)	165	51.3 (38.6)
69	159	32.5 (35.1)	158	50.2 (38.4)
70	153	31.7 (35.7)	152	50 (37.2)
71	141	32.7 (36.1)	140	53.2 (37)
72	128	33.2 (35.5)	132	52 (36.8)
73	120	31.3 (35)	122	51.3 (36.8)
74	110	30.1 (32.6)	113	50.4 (37.5)
75	98	32.1 (35.4)	101	51.4 (36.2)
76	92	29.9 (34.6)	94	52.1 (35.1)
77	85	31.1 (37)	80	52.1 (37.4)
78	75	30.1 (34.9)	71	53.2 (36.8)
79	73	29.7 (35.7)	63	60.3 (36.3)
80	72	30.5 (36.9)	61	57.1 (36.7)

Week	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
81	64	28.4 (37.6)	53	56.9 (37.6)
82	56	26.1 (36.3)	47	59.1 (35.8)
83	48	25.6 (36.8)	40	60 (36.6)
84	45	28.1 (39)	37	56.6 (36.5)
85	35	27.1 (37.5)	35	54.7 (37.8)
86	27	24.1 (36.8)	29	63.8 (34.5)
87	20	31.1 (42.3)	23	70.3 (31.5)
88	15	41.1 (43.5)	16	65.7 (40.2)
89	10	42.7 (44.6)	11	62.4 (33.6)
90	7	38.2 (43.2)	4	81.8 (17.3)
91	2	58.3 (58.9)	1	83.3 (NA)

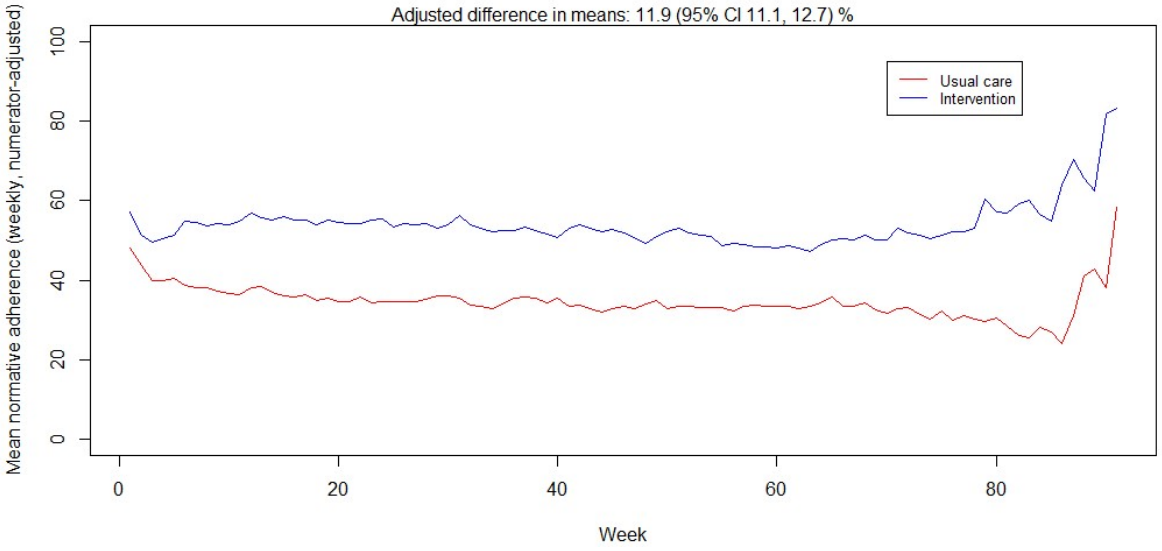

Figure 10 Weekly mean numerator-adjusted normative adherence by randomised group

The original mixed-effects normative adherence model was applied to the extended follow-up data. There were 588 participants contributing data to the model. Increasing the follow-up time from 12 to 21 months increased the estimated treatment effect from 9.5 to 11.9 percentage points (95% CI 11.1, 12.7), in favour of the intervention arm. The time coefficient was -0.2 (95% CI -0.2, -0.1) percentage points, suggestive of a slight decreasing trend in adherence levels over time. There was no evidence of an interaction between randomised group and time (p=0.767).

The same model fit to just the second year of follow-up data (n=517) yielded a between-group estimate of 12.3 (95% CI 9.0, 15.6) percentage points, and a time coefficient of -0.5 (-2.0, 1.0). The intervention arm had significantly higher adherence levels, and there was a tendency for decreasing adherence over time. Again, there was no evidence of interaction between randomised group and time (p=0.968).

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2.3.2 FEV_1 percent predicted (extended follow-up)

Tables 12 and 13 show the mean observed monthly FEV_1 percent predicted summaries by randomised group and baseline adherence strata respectively for months 1 to 21 post-consent. Where participants had more than one FEV_1 measurement in a month, the mean FEV_1 for that month was used. Randomised group means over time are presented in Figure 11. Values in later months should be interpreted with caution due to decreasing N.

Table 12 FEV_1 percent predicted monthly summaries

Month	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
1	302	58.4 (22.6)	304	60.7 (23.2)
2	100	56 (23.4)	93	59.5 (22.6)
3	148	55.1 (21.1)	136	58 (24.6)
4	120	54.4 (22.2)	109	58.2 (23.5)
5	108	55 (23)	114	57.6 (23.9)
6	117	59.9 (23)	125	58 (23.1)
7	119	53.5 (20.9)	118	59 (22.3)
8	110	56 (21.5)	112	56.6 (22.7)
9	121	57.8 (23.2)	117	57.2 (23.4)
10	120	53.1 (20.8)	107	58.3 (24)
11	117	59 (20.6)	115	56.1 (23.4)
12	171	55.5 (23.3)	186	59.4 (24)
13	155	56.6 (22)	150	57.8 (23.3)
14	95	54.5 (21.8)	78	60.4 (23.4)
15	77	57.5 (22.8)	80	61.6 (21.7)
16	58	55.6 (20.5)	60	60.6 (26.2)
17	36	51.4 (21.4)	33	61.9 (23.8)
18	30	55.4 (21.5)	26	59 (25.4)
19	19	54.3 (22.7)	21	51.9 (20.3)
20	8	50.8 (23.1)	7	48.2 (23.6)
21	1	81.9 (NA)	0	NaN (NA)

Table 13 FEV_1 percent-predicted monthly summaries by baseline normative adherence subgroup

	0-25%				26-50%				51-75%				76-100%			
	Usual care		Intervention		Usual care		Intervention		Usual care		Intervention		Usual care		Intervention	
Month	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
1	93	58.3 (19.6)	76	60.3 (24.8)	59	63.3 (22.6)	56	57.6 (23.8)	68	57.9 (25.9)	59	64.5 (23)	82	55.3 (22.6)	113	60.5 (21.9)
2	34	54.3 (22)	24	56.1 (23.7)	22	57.8 (20.9)	14	62.7 (22.2)	20	59.5 (29.1)	19	58.2 (22)	24	53.7 (23.2)	36	61 (22.9)
3	48	55.6 (19.8)	30	60.8 (29.6)	30	59.8 (24.5)	19	54.3 (25)	32	55 (20.5)	34	56.6 (24.6)	38	50.9 (20.1)	53	58.8 (21.7)
4	37	54.1 (20)	35	60.9 (24.2)	25	59.5 (22.8)	16	55.6 (22.8)	23	45.8 (17.9)	20	58.1 (21)	35	56.6 (25.6)	38	57 (24.9)
5	24	52.4 (18.5)	31	57 (26.5)	23	56.6 (21.1)	19	56.1 (26.8)	30	56 (26.9)	23	54.5 (21.1)	31	54.9 (24.2)	41	60.4 (22.5)
6	43	60.6 (20.5)	31	58.2 (25.6)	22	61.4 (23.5)	24	58.4 (26)	20	57.6 (24.7)	21	56.4 (20.8)	32	59.4 (25.5)	49	58.5 (21.6)
7	29	50.5 (23.2)	29	57.6 (24.5)	31	61.4 (20.4)	21	53.8 (22.1)	28	53.9 (18.3)	22	56.8 (21.2)	31	48.2 (19.6)	46	63.2 (21.3)
8	29	60.9 (19.4)	29	65.1 (24.4)	22	56.9 (23.2)	20	48.9 (26.1)	26	50.6 (20.6)	15	52.6 (16.7)	33	55.2 (22.8)	48	55.9 (20.6)
9	36	57 (22.8)	31	55.2 (24.7)	27	60.9 (22)	26	55.6 (27)	20	64.7 (25.7)	24	53.8 (22.4)	38	52.9 (22.6)	36	62.4 (20.2)
10	26	56 (21.8)	29	54 (25.1)	25	57.4 (22.4)	21	51.4 (17.7)	31	51.8 (21)	20	59.5 (25.4)	38	49.3 (18.9)	37	65 (24.6)
11	32	59 (19.6)	37	58.3 (26.2)	24	63.8 (21.4)	23	55.9 (25.5)	26	55.5 (20.1)	16	54.9 (22.1)	35	58.3 (21.5)	39	54.6 (20.4)
12	40	55.8 (22.6)	52	58.9 (26.9)	36	55.8 (21.1)	30	53.6 (22.8)	35	55.8 (27.2)	41	58.7 (21.5)	60	55 (23.2)	63	63.1 (23.4)
13	42	63.7 (22.6)	40	57.8 (23.5)	26	57.7 (22.5)	31	56.1 (24.3)	38	56.4 (22.1)	39	60.3 (23.3)	49	50.2 (19.7)	40	56.6 (23.1)
14	34	54.7 (19)	17	70.4 (25.7)	13	53 (19.3)	18	54.5 (24.9)	20	52.2 (24.8)	19	64.2 (20.6)	28	56.5 (24.5)	24	54.8 (20.9)
15	19	61.3 (22.7)	25	57.5 (27.2)	16	47.3 (17.6)	17	63.2 (21)	20	59.3 (23.7)	19	65.5 (20)	22	60.1 (24.5)	19	61.6 (16)
16	25	52 (21.6)	19	61 (30.1)	10	61.4 (17.7)	10	51.1 (20.7)	14	55.7 (20.6)	13	65.2 (26.5)	9	59.4 (21.7)	18	62.2 (24.9)
17	9	48 (22)	7	53.5 (26.5)	9	63 (24.3)	8	54.3 (20.3)	10	48.3 (22.1)	10	70.7 (24)	8	45.9 (13.8)	8	65.8 (23.9)
18	4	57 (19.9)	10	57.9 (31.1)	7	70.4 (25.4)	1	55.2 (NA)	8	43.5 (14.9)	6	63 (27.3)	11	54 (20.1)	9	58.1 (20.9)
19	4	58.2 (12.8)	8	51.5 (26.2)	1	97.2 (NA)	4	52.2 (17.5)	7	53.4 (23.8)	3	59 (24.4)	7	46.9 (22.8)	6	48.7 (15.2)
20	1	67.2 (NA)	2	26.4 (9.6)	2	71.9 (20.3)	1	61.1 (NA)	2	57.4 (18.7)	2	74.6 (4.9)	3	26.9 (3.9)	2	37.3 (21.5)
21	0	NaN (NA)	0	NaN (NA)	1	81.9 (NA)	0	NaN (NA)	0	NaN (NA)	0	NaN (NA)	0	NaN (NA)	0	NaN (NA)

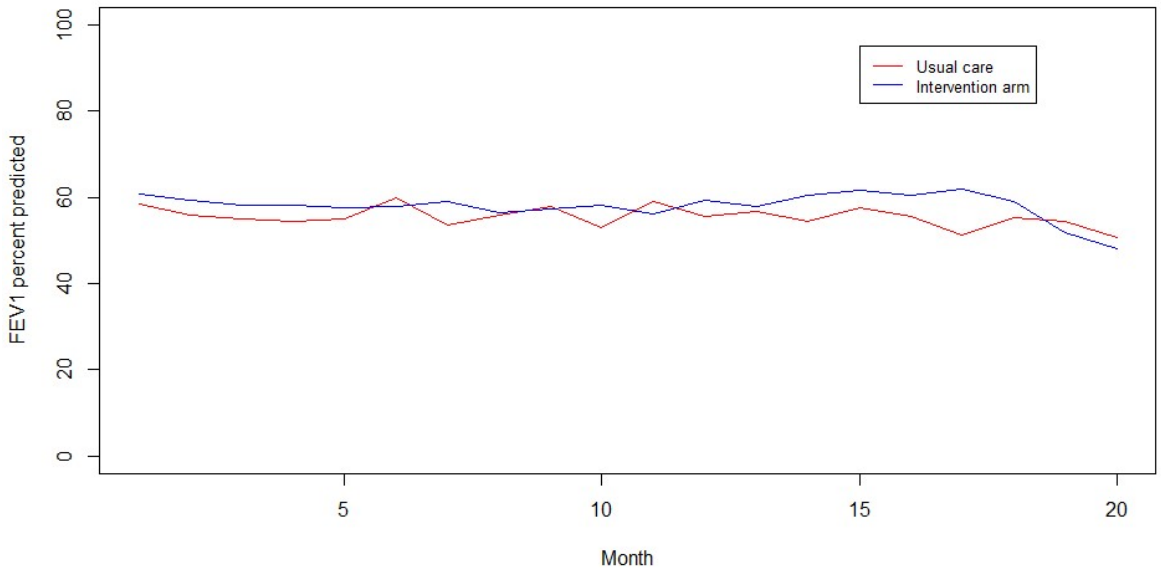

Figure 11 Longitudinal FEV_1 percent predicted by randomised group

Longitudinal data were analysed using a random slopes and intercepts model with adjustment for baseline FEV_1 percent predicted and the previous year's IV days, and participants nested within site. There were 599 participants contributing data to the model. The estimated treatment effect was 0.61 (95% CI -0.18, 1.40) percentage points and the time effect was -0.09 (-0.17, -0.02) percentage points decline in FEV_1 per month. The direction of effect favoured the intervention arm, but the confidence interval included zero, consistent with there being no difference between randomised groups. There was a small trend for decreasing FEV_1 percent predicted over time and no significant interaction between randomised treatment group and time (p=0.736).

The model was repeated using just the second year of follow-up data; data were available from 460 participants. The estimated treatment effect was 1.28 (95% CI -0.07, 2.63). The direction of effect favoured the intervention arm, but the confidence interval included zero, consistent with there being no difference between randomised groups. There was no significant interaction between randomised group and time (p=0.286).

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2.3.3 Body mass index (extended follow-up)

Longitudinal body mass index (BMI) data over the 21-month follow-up period are plotted in Figure 12. Data were aggregated by month post-consent and the mean taken if more than one value was provided in a given month period. Later months should be interpreted cautiously due to the small number of observations in the final months of follow-up.

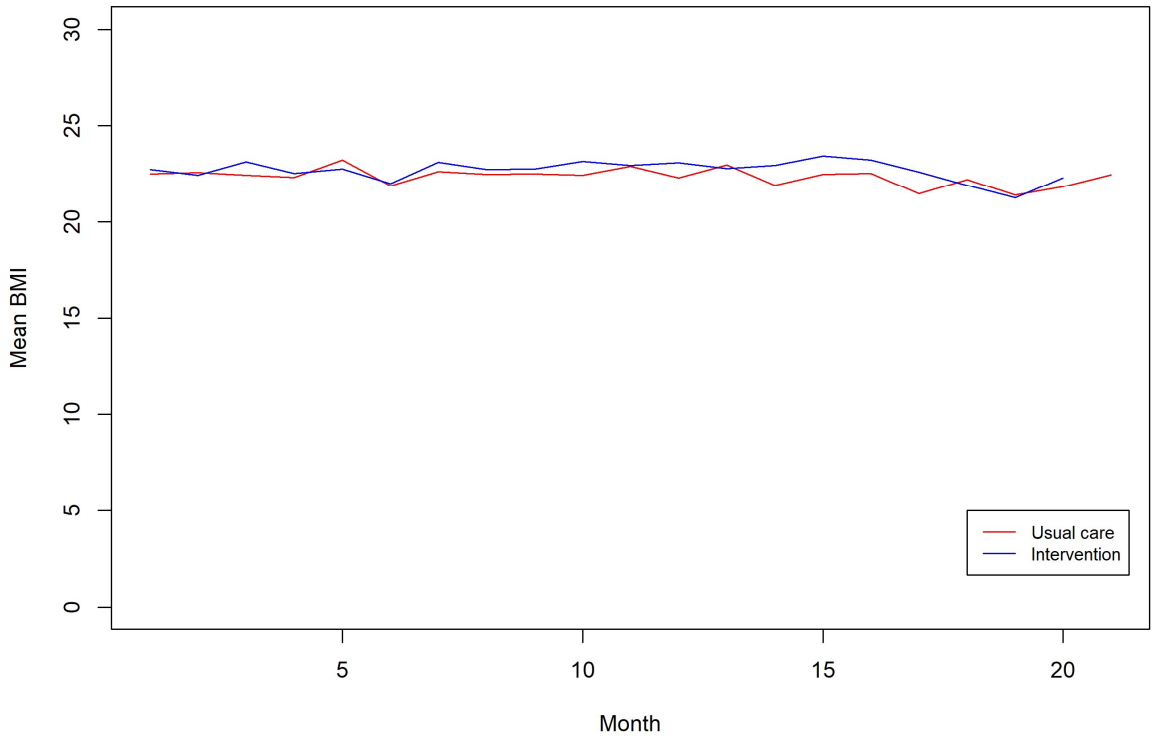

Figure 12 Longitudinal BMI by randomised group

Data were modelled using a linear mixed-effects model controlling for baseline BMI, previous year's IV days and site. The random effects structure consisted of participants nested within site with random slopes and intercepts, allowing for varying trajectories over time (months post-baseline). An exchangeable correlation structure was applied, which assumes equal correlation between repeated measures for each successive month of observation.

Data were included from 600 participants. A treatment group-by-time interaction effect was included, but dropped as p=0.877. The estimated between-group difference was 0.15 (95% CI 0.04, 0.25), indicative of higher BMI values in the intervention arm.

The model was repeated using just the second year of follow-up data; data were available from 455 participants. The between-group estimate was 0.32 (95% CI 0.11, 0.52), indicative of higher BMI values in the intervention arm. There was no evidence of a treatment group-by-time interaction (p=0.203).

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2.4 CFHealthHub interaction

Of the 305 participants randomised to receive intervention, there were 38 participants prematurely discontinuing the intervention during the ACtiF trial due to withdrawal or death, and a further 19 discontinuing during the extended follow-up period. Participants prematurely discontinuing the intervention could still contribute clinical data, unless fully withdrawn from the trial. Summaries of interaction with the CFHealthHub platform are presented for the 248 participants not formally discontinuing intervention.

There were 151 participants (60.9%) with at least one recorded interaction with an interventionist after the 12-month trial window. Participants were based across all 19 trial sites. Session summaries are presented in Table 14.

Table 14 Interventionist session delivery post-trial

	Face-to-face	Telephone	All*
Sessions per participant			
N participants	130	50	248
Mean (SD)	1.9 (1.1)	1.4 (0.8)	1.3 (1.4)
Med (IQR)	2 (1, 2)	1 (1, 1)	1 (0, 2)
Min, max	(1, 7)	(1, 4)	(0, 7)
Participants with at least…			
1 session	130 (52.4%)	50 (20.2%)	151 (60.9%)
3 sessions	29 (11.7%)	7 (2.8%)	47 (19%)
5 sessions	4 (1.6%)	0 (0%)	7 (2.8%)

*Includes sessions with unknown mode of delivery and session count of 0 for participants not formally withdrawing from intervention but having no interventionist session data

Of the 248 participants with no formal intervention discontinuation recorded, 108 (43.5%) interacted with the CFHealthHub platform at least once during the extended follow-up period. Participants were based across all 19 trial sites. Participant interaction outside of intervention sessions is presented by module in Table 15.

Table 15 Participant CFHealthHub interactions outside of intervention sessions post-trial

Module	Total clicks in module (n=4908)	Participants with at least 1 click in module (n=248)	Number of sessions with at least 1 click in module (n=1291)
About	8 (0.2%)	6 (2.4%)	7 (0.5%)
Action Plan	33 (0.7%)	7 (2.8%)	7 (0.5%)
Coping Plan	14 (0.3%)	5 (2%)	5 (0.4%)
Home	1822 (37.1%)	108 (43.5%)	1290 (99.9%)
How am I Doing	2423 (49.4%)	103 (41.5%)	1274 (98.7%)
Planner	7 (0.1%)	1 (0.4%)	2 (0.2%)
Prescription	5 (0.1%)	4 (1.6%)	4 (0.3%)
Problem Solving	23 (0.5%)	8 (3.2%)	10 (0.8%)
Reward	356 (7.3%)	75 (30.2%)	342 (26.5%)
Toolkit	73 (1.5%)	17 (6.9%)	25 (1.9%)
Treatment	117 (2.4%)	32 (12.9%)	42 (3.3%)
Videos	27 (0.6%)	16 (6.5%)	18 (1.4%)

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3 Mapping report contents to Additional Analysis SAP

Additional analysis plan v2.0 (10/02/2020)	Additional analysis report section	Table(s)	Figures(s)
2.1.1 Severity of exacerbations	1.1	Table 1 Summary of Fuchs criteria met per exacerbation by randomised group	Figure 1 Distribution of exacerbations by severity by randomised group
2.1.2 Subgroup analyses of FEV_1 and adherence	1.2	Table 2 Adjusted estimates for between-group differences in normative adherence for adherence subgroups Table 3 Adjusted estimates for between-group differences in FEV_1 percent predicted for adherence subgroups	Figure 2 Weekly mean numerator-adjusted normative adherence by baseline adherence subgroup Figure 3 Monthly FEV_1 percent predicted by randomised group Figure 4 Monthly FEV_1 percent predicted by randomised group and baseline adherence subgroup
2.1.3 Interrelationship between FEV_1 and adherence	1.3	Table 4 Correlation matrix for exacerbations, normative adherence and FEV_1 percent predicted	Figure 5 Distribution of baseline FEV_1 percent predicted by baseline adherence subgroup
2.1.4 Maintenance/stability of adherence in relation to start of treatment	1.4	-	Figure 6 Distribution of time from randomisation to first intervention visit
2.2.1 Characteristics of participants who continue follow-up beyond one year	2.1	Table 5 Participant characteristics at baseline for one-year and two-year follow-up cohorts Table 6 Clinical characteristics at baseline for one-year and two-year follow-up cohorts Table 7 Patient-reported outcomes at baseline for one-year and two-year follow-up cohorts Table 8 Twelve-month outcome data for one-year and two-year follow-up cohorts	-

Additional analysis plan v2.0 (10/02/2020)	Additional analysis report section	Table(s)	Figures(s)
2.2.2 Use of system	2.4	Table 14 Interventionist session delivery post-trial Table 15 Participant CFHealthHub interactions outside of intervention sessions post- trial	-
2.2.3 Long term outcomes	2.2	Table 9 Exacerbation rates over extended follow-up Table 11 Numerator-adjusted normative adherence weekly summaries by randomised group Table 12 FEV_1 percent predicted monthly summaries Table 13 FEV_1 percent-predicted monthly summaries by baseline normative adherence subgroup	Figure 7 Distribution of extended primary outcome follow-up times by randomised group Figure 8 Exacerbation counts over the extended follow-up time by randomised group Figure 10 Weekly mean numerator-adjusted normative adherence by randomised group Figure 11 Longitudinal FEV_1 percent predicted by randomised group Figure 12 Longitudinal BMI by randomised group
2.2.3 Severity of exacerbations	2.2.2	Table 10 Summary of Fuchs criteria met per exacerbation by randomised group over extended follow-up	Figure 9 Distribution of exacerbations by severity by randomised group over the extended follow-up