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

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Statistical analysis report v1.3

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List of abbreviations

ACtiF	Development and evaluation of an intervention to support Adherence to treatment in adults with Cystic Fibrosis
AE	Adverse event
BMI	Body mass index
CACE	Complier average causal effect
CF	Cystic Fibrosis
CFHH	CFHealthHub
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
FEV1	Forced expiratory volume one second
HR	Hazard ratio
IRR	Incidence rate ratio
MICE	Multiple imputation using chained equations
SAE	Serious adverse event
SAP	Statistical analysis plan

1 Recruitment

1.1 Recruitment graph

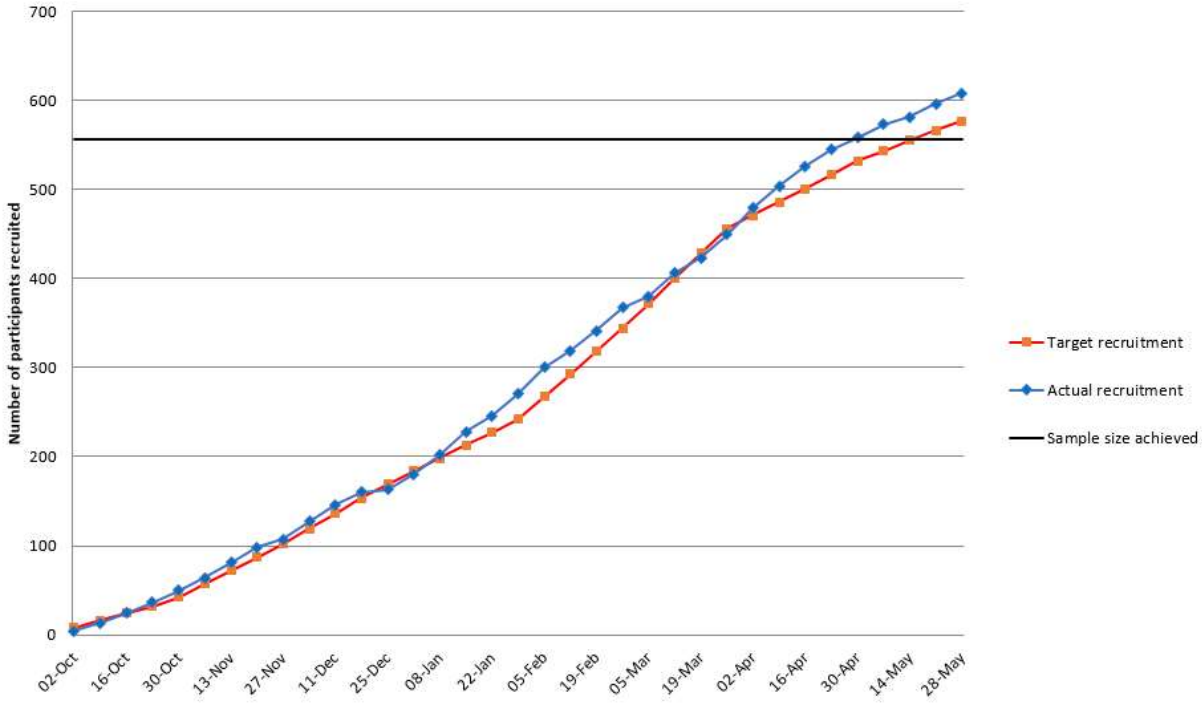

Figure 1 Planned and actual recruitment for the ACtiF trial

Figure 1 shows recruitment to the ACtiF trial and Figure 2 shows participant disposition throughout the trial. There were 608 participants randomised, but one participant randomised to the intervention arm withdrew on the day of consent prior to baseline data collection, giving a maximum n=607 for baseline summaries.

1.2 Participant flow

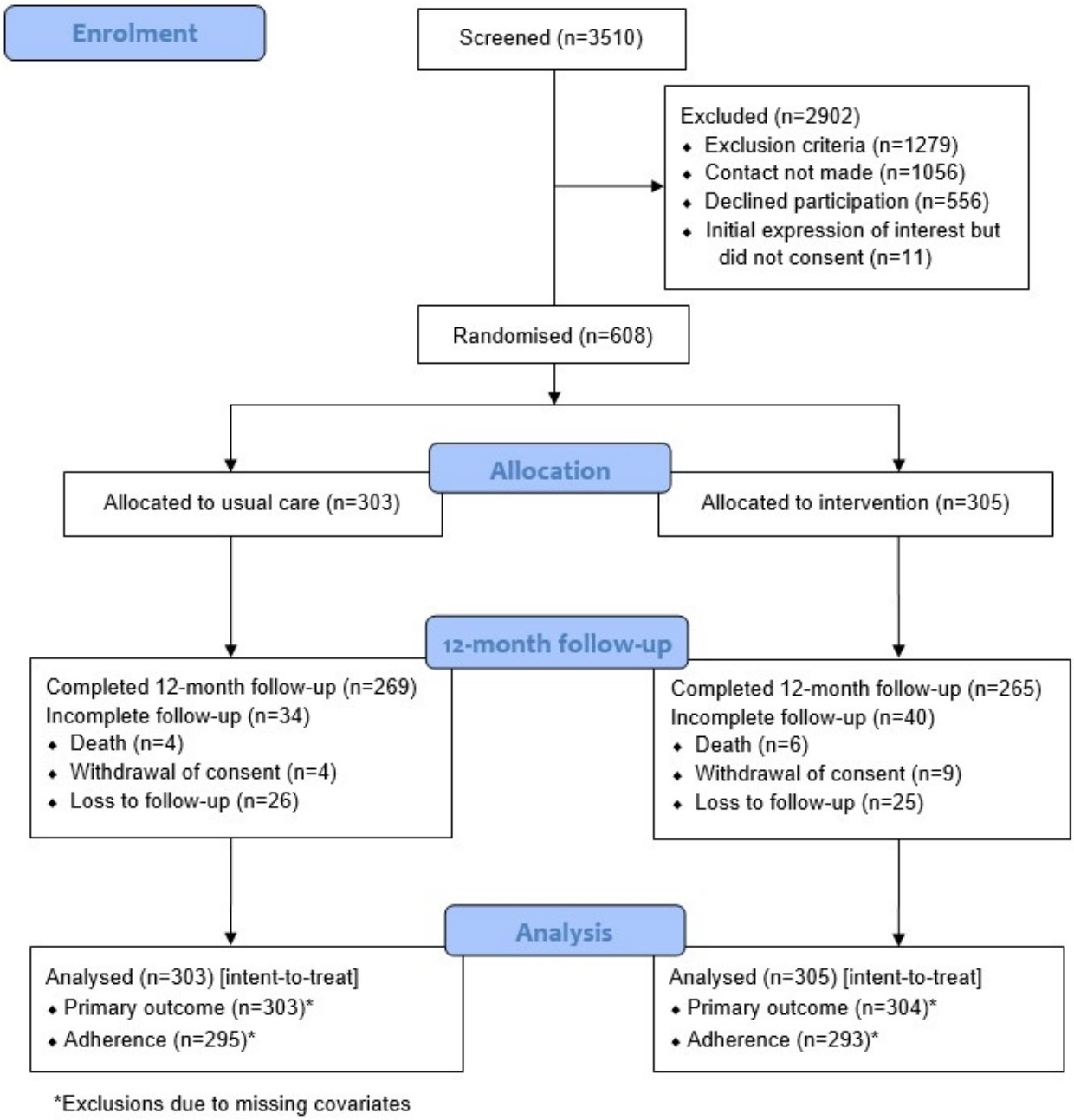

Figure 2 CONSORT flow diagram

Table 1 Reasons for declining trial participation (n=556)

Reason	N (%)
Unwilling to change nebuliser	125 (22.5%)
Not stated	123 (22.1%)
Too time consuming/too much effort	118 (21.2%)
Does not want to be involved in any trials	39 (7%)
Does not see benefit of trial	16 (2.9%)
Technology issues	7 (1.3%)
Didn't want to be randomly assigned	2 (0.4%)
Other*/missing	126 (22.7%)

*See appendix for line listings

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1.3 Reasons for premature discontinuation/withdrawal

Participants could withdraw from any of the following aspects of the trial during the follow-up period: primary outcome data collection; adherence data collection; intervention receipt; entire trial. Tables 2-4 give reasons for premature discontinuation where known. Participants may be included in more than one table.

There were 33 participants (usual care n=13, intervention n=20) with fewer than 365 days' primary outcome follow-up. Ten cases (usual care n=4, intervention n=6) were due to death during the 12-month follow-up period.

Table 2 Reasons for premature discontinuation of primary outcome data collection

ID	Allocation	Time from consent (weeks)	Reason	Reason if 'other' (verbatim text)
B158282	Usual care	28.3	Investigator decision	
B160667	Usual care	42.9	Investigator decision	
B158770	Usual care	11.9	Participant died	
B160013	Usual care	33.4	Participant died	
B167363	Usual care	44.9	Participant died	
B156633	Usual care	50.4	Participant died	
B157507	Usual care	22.7	Participant withdrew consent	
B159842	Usual care	32.9	Participant withdrew consent	
B158808	Usual care	35.9	Participant withdrew consent	
B160471	Usual care	45	Participant withdrew consent	
B157897	Usual care	0	Other	Ineligible
B157615	Usual care	8.1	Other	Participant found to be ineligible
B159861	Usual care	16.9	Other	patient could not recall consenting to the study and did not wish to be involved
B158638	Intervention arm	19.4	Participant died	
B164846	Intervention arm	26.3	Participant died	
B157363	Intervention arm	32.6	Participant died	
B156588	Intervention arm	36.9	Participant died	
B156565	Intervention arm	42.1	Participant died	
B167534	Intervention arm	43.9	Participant died	
B159594	Intervention arm	0	Participant withdrew consent	
B159340	Intervention arm	7.7	Participant withdrew consent	
B164970	Intervention arm	12.7	Participant withdrew consent	
B157699	Intervention arm	25.4	Participant withdrew consent	
B167683	Intervention arm	31.9	Participant withdrew consent	
B167468	Intervention arm	33.9	Participant withdrew consent	
B164462	Intervention arm	39.1	Participant withdrew consent	
B157667	Intervention arm	50	Participant withdrew consent	
B159423	Intervention arm	3	Other	Participant wants to go back to using Ineb
B160096	Intervention arm	10.6	Other	Depression
B164976	Intervention arm	13.9	Other	has insufficient time to nebulise each morning on top of work/ family life. Has returned to dry powder inhaler
B159875	Intervention arm	20.1	Other	moved to another centre that is not in the study
B157685	Intervention arm	27.3	Other	Participant's care has been transferred to Glasgow.
B158408	Intervention arm	40.7	Other	Wishes to take part in parma study

Tables 3 and 4 give reasons for premature discontinuation of other specific aspects of the trial within 12 months of consent for reasons other than death. There were 54 premature discontinuations of adherence data collection (usual care n=29, intervention n=25) and 32 premature discontinuations of intervention delivery.

Table 3 Reasons for premature discontinuation of adherence data collection

ID	Allocation	Time from consent (weeks)	Reason	Reason if 'other' (verbatim text)
B160081	Usual care	3.6	Prefers previous device	
B164705	Usual care	4.4	Prefers previous device	
B158166	Usual care	7.1	Prefers previous device	
B161067	Usual care	11.9	Prefers previous device	
B163325	Usual care	14.9	Prefers previous device	
B164728	Usual care	15	Prefers previous device	
B162598	Usual care	19.1	Prefers previous device	
B156857	Usual care	24.3	Prefers previous device	
B164858	Usual care	27.3	Prefers previous device	
B170303	Usual care	28.4	Prefers previous device	
B158330	Usual care	30.6	Prefers previous device	
B162685	Usual care	31	Prefers previous device	
B158808	Usual care	35.9	Prefers previous device	
B156896	Usual care	36	Prefers previous device	
B168087	Usual care	37.9	Prefers previous device	
B161250	Usual care	19.6	Unhappy sharing adherence data	
B158151	Usual care	4.1	Unhappy with device	
B171666	Usual care	28.6	Unhappy with device	
B157897	Usual care	0	Other	Protocol deviation, not eligible for study
B157615	Usual care	8.1	Other	Protocol non compliance
B169597	Usual care	14.7	Other	Participant suffers OCD and anxiety and found using the completely new device too overwhelming so has reverted back to turbo pari.
B159861	Usual care	16.9	Other	does not wish to be involved in trial at all- too busy
B157507	Usual care	22.7	Other	Participation in other clinical trial
B165852	Usual care	26.4	Other	wants to use two devices, to have one at boyfriends house or upstairs and one downstairs.
B158282	Usual care	28.3	Other	Patient too unwell to continue participation in the study.
B159842	Usual care	32.9	Other	device reported as broken/ vandalized by cleaner whilst in care of the patient. PI / interventionist decision not to replace and patient issued with standard eflow
B168954	Usual care	37.6	Other	Not taking nebulised treatments
B160667	Usual care	42.9	Other	Recruited into Vertex triple therapy trial
B160471	Usual care	45	Other	To take part in another trial

ID	Allocation	Time from consent (weeks)	Reason	Reason if 'other' (verbatim text)
B159423	Intervention arm	3	Prefers previous device	
B158488	Intervention arm	6.4	Prefers previous device	
B160096	Intervention arm	10.6	Prefers previous device	
B164970	Intervention arm	12.7	Prefers previous device	
B157374	Intervention arm	27.9	Prefers previous device	
B160001	Intervention arm	35.9	Prefers previous device	
B158095	Intervention arm	39	Prefers previous device	
B159340	Intervention arm	7.7	Unhappy sharing adherence data	
B167807	Intervention arm	12.1	Unhappy with device	
B164976	Intervention arm	13.9	Unhappy with device	
B157699	Intervention arm	25.4	Unhappy with device	
B164961	Intervention arm	39	Unhappy with device	
B166361	Intervention arm	43	Unhappy with device	
B159594	Intervention arm	0	Other	Changed mind about participation
B159974	Intervention arm	14	Other	not ready to commit to time for research
B166902	Intervention arm	14	Other	wanted to go back to using ineb
B159875	Intervention arm	20.1	Other	moved to another centre that is not in the study
B162708	Intervention arm	21.4	Other	No information available - no separate space on CRF for this.
B157685	Intervention arm	27.3	Other	Transferred to care under a different NHS location
B157667	Intervention arm	30.6	Other	In hospital long-term during pregnancy and does not have white plug with her to transfer. Feels it easier to just withdraw from this aspect of the trial too.
B167683	Intervention arm	31.9	Other	Not for them. Too much for them
B167468	Intervention arm	33.9	Other	Personal / family issues
B165433	Intervention arm	37.9	Other	Nebulisers stopped by consultant
B164462	Intervention arm	39.1	Other	personal/social issues, not a priority
B158408	Intervention arm	40.7	Other	Patient wishes to take part in pharma trial therefore must withdraw totally from CFHH study

Table 4 Reasons for premature discontinuation of trial intervention

ID	Time from consent (weeks)	Reason	Reason if 'other' (verbatim text)
B164976	13.9	No longer has enough time	
B162708	21.4	No longer has enough time	
B159496	22.1	No longer has enough time	
B157374	27.9	No longer has enough time	
B165085	40.6	No longer has enough time	
B160096	10.6	Personal / family issues	
B156999	13	Personal / family issues	
B164660	22.9	Personal / family issues	
B162636	33.3	Personal / family issues	
B167468	33.9	Personal / family issues	
B164462	39.1	Personal / family issues	
B159340	7.7	Unhappy with intervention	
B157699	25.4	Unhappy with intervention	
B159594	0	Other	changed miond about participation
B159423	3	Other	Wants to go back to Ineb
B158488	6.4	Other	prefers ineb
B167807	12.1	Other	didn't give the e-flow a chance long enough to permit any interventions. withdrew before first intervention could be completed
B164970	12.7	Other	feels less stable with e-track
B159974	14	Other	not ready to commit to time for research
B166902	14	Other	Wanted to go back to using I-neb
B159875	20.1	Other	patient has moved to a CF centre that is not participating in the study
B160693	20.3	Other	Nothing on form completed by [REDACTED] to indicate participants withdrawal reasons.
B158495	23.7	Other	longstanding depression but consistently refusing psychology / medication. Intervention felt to be negatively affecting mood- joint decision with patient to withdraw
B157685	27.3	Other	Transferred to care under a different NHS location
B157667	30.6	Other	Fell pregnant, overwhelmed with this and feels intervention etc are just too much at this time.
B167683	31.9	Other	Not for them. Too much for them
B162838	34.9	Other	finds no benefit of intervention
B160001	35.9	Other	wants to concentrate on other things
B165433	37.9	Other	Nebulisers stopped by consultant
B164961	39	Other	didn't want to continue using the e-flow due to length of time to nebulise, inconsistency. switched back to I-neb
B158408	40.7	Other	Wishes to take part in pharma trial
B166361	43	Other	Unhappy with device

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2 Baseline characteristics

2.1 Demographic details

Table 5 Participant characteristics at baseline

	Usual care	Intervention	Overall
Age (years)			
N	303	304	607
Mean (SD)	30.3 (10.8)	31.1 (10.6)	30.7 (10.7)
Median (IQR)	27.7 (22, 34.8)	28.9 (23.4, 36.5)	28.1 (22.5, 36.1)
Range	(16.7, 71.4)	(16.1, 71.9)	(16.1, 71.9)
Weight (kg)			
N	303	304	607
Mean (SD)	63.2 (14.2)	64.1 (14.1)	63.7 (14.1)
Median (IQR)	61.6 (52.6, 71.2)	62.4 (54.2, 70.5)	62.2 (53.3, 71.1)
Range	(37.2, 124.1)	(32.9, 133.8)	(32.9, 133.8)
Height (cm)			
N	303	304	607
Mean (SD)	167.2 (9.2)	167.7 (9.5)	167.5 (9.4)
Median (IQR)	166 (161, 174)	167.5 (161, 175)	167 (161, 174)
Range	(144, 196)	(144, 196)	(144, 196)
BMI			
N	303	304	607
Mean (SD)	22.5 (4.2)	22.7 (4.2)	22.6 (4.2)
Median (IQR)	22 (20, 25)	22 (20, 24)	22 (20, 24)
Range	(13, 41)	(15, 48)	(13, 48)
Gender			
N	303	304	607
Female	154 (50.8%)	156 (51.3%)	310 (51.1%)
Male	149 (49.2%)	148 (48.7%)	297 (48.9%)
Deprivation			
N	302	302	604
1st quintile	51 (16.9%)	50 (16.6%)	101 (16.7%)
2nd quintile	71 (23.5%)	59 (19.5%)	130 (21.5%)
3rd quintile	66 (21.9%)	63 (20.9%)	129 (21.4%)
4th quintile	67 (22.2%)	63 (20.9%)	130 (21.5%)
5th quintile	47 (15.6%)	67 (22.2%)	114 (18.9%)

2.2 Clinical characteristics at baseline

Table 6 Clinical characteristics at baseline

	Usual care	Intervention	Overall
FEV1 percent predicted			
N	302	304	606
Mean (SD)	58.3 (22.6)	60.7 (23.5)	59.5 (23.1)
Median (IQR)	56.4 (39.1, 74.9)	61.3 (41.1, 80.5)	59.1 (40, 77.9)
Range	(14.6, 121.2)	(15, 117.1)	(14.6, 121.2)
IV days in previous 12 months			
N	303	304	607
Mean (SD)	27.7 (33)	24.2 (27.9)	25.9 (30.6)
Median (IQR)	17 (0, 42)	14 (0, 35)	14 (0, 41)
Range	(0, 184)	(0, 144)	(0, 184)
Normative adherence* (%)			
N	295	296	591
Mean (SD)	45.6 (34.2)	54 (32.9)	49.8 (33.8)
Median (IQR)	42.9 (10.7, 76.4)	57.2 (25, 84.2)	52.4 (17.9, 81.4)
Range	(0, 100)	(0, 100)	(0, 100)
Subjective adherence (%)			
N	298	300	598
Mean (SD)	69 (30.8)	69.9 (31)	69.4 (30.9)
Median (IQR)	77 (50, 95)	80 (50, 95)	80 (50, 95)
Range	(0, 100)	(0, 100)	(0, 100)
***Pseudomonas* status (consensus definition)**			
N	299	304	603
Chronic	175 (58.5%)	174 (57.2%)	349 (57.9%)
Not chronic	124 (41.5%)	130 (42.8%)	254 (42.1%)
***Pseudomonas* status (clinician's judgement)**			
N	301	304	605
Chronic	163 (54.2%)	161 (53%)	324 (53.6%)
Intermittent	41 (13.6%)	27 (8.9%)	68 (11.2%)
Pseudomonas-free	92 (30.6%)	112 (36.8%)	204 (33.7%)
Unknown	5 (1.7%)	4 (1.3%)	9 (1.5%)
***Pseudomonas* status (Leeds criteria)**			
N	302	304	606
Chronic	127 (42.1%)	129 (42.4%)	256 (42.2%)
Intermittent	67 (22.2%)	49 (16.1%)	116 (19.1%)
Negative	103 (34.1%)	126 (41.4%)	229 (37.8%)
Unknown	5 (1.7%)	0 (0%)	5 (0.8%)

*Measured during weeks 1 and 2 post-consent

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2.3 Patient-reported outcomes at baseline

Table 7 Patient-reported outcome measures at baseline

	Usual care	Intervention	Overall
EQ-5D-5L			
N	300	303	603
Mean (SD)	0.84 (0.16)	0.85 (0.15)	0.85 (0.15)
Median (IQR)	0.87 (0.75, 1)	0.89 (0.77, 1)	0.87 (0.77, 1)
Range	(0.29, 1)	(0.04, 1)	(0.04, 1)
EQ-5D-5L crosswalk			
N	300	303	603
Mean (SD)	0.78 (0.19)	0.79 (0.19)	0.78 (0.19)
Median (IQR)	0.78 (0.65, 1)	0.8 (0.68, 1)	0.79 (0.66, 1)
Range	(0.2, 1)	(-0.12, 1)	(-0.12, 1)
COM-BMQ concerns			
N	301	304	605
Mean (SD)	2.1 (0.5)	2.1 (0.6)	2.1 (0.5)
Median (IQR)	2.1 (1.6, 2.4)	2.1 (1.7, 2.4)	2.1 (1.7, 2.4)
Range	(1, 3.7)	(1, 4.4)	(1, 4.4)
COM-BMQ necessities			
N	301	304	605
Mean (SD)	3.6 (0.8)	3.6 (0.7)	3.6 (0.7)
Median (IQR)	3.6 (3.1, 4)	3.6 (3.1, 4)	3.6 (3.1, 4)
Range	(1.3, 5)	(1.6, 5)	(1.3, 5)
SRBAI (habit)			
N	300	303	603
Mean (SD)	12 (4.7)	12.1 (5)	12 (4.9)
Median (IQR)	12 (8, 16)	12 (8, 16)	12 (8, 16)
Range	(4, 20)	(4, 20)	(4, 20)
CFQ-R – physical			
N	302	304	606
Mean (SD)	53 (30.2)	54.3 (30.6)	53.7 (30.4)
Median (IQR)	54 (29, 79)	54 (29, 83)	54 (29, 80.5)
Range	(0, 100)	(0, 100)	(0, 100)
CFQ-R – emotion			
N	302	304	606
Mean (SD)	66.2 (24.1)	66.5 (21.6)	66.4 (22.9)
Median (IQR)	67 (47, 87)	70 (51.5, 87)	67 (47, 87)
Range	(0, 100)	(0, 100)	(0, 100)
CFQ-R – social			
N	302	304	606
Mean (SD)	60.9 (20.9)	61.9 (20)	61.4 (20.5)
Median (IQR)	61 (44, 78)	61 (50, 78)	61 (44, 78)
Range	(6, 100)	(11, 100)	(6, 100)
CFQ-R – eating			
N	302	304	606
Mean (SD)	80.5 (24.3)	82.1 (22.5)	81.3 (23.4)
Median (IQR)	89 (67, 100)	89 (67, 100)	89 (67, 100)
Range	(0, 100)	(0, 100)	(0, 100)

	Usual care	Intervention	Overall
CFQ-R – body			
N	302	304	606
Mean (SD)	66.1 (29.3)	65.6 (28)	65.8 (28.6)
Median (IQR)	67 (44, 89)	67 (44, 89)	67 (44, 89)
Range	(0, 100)	(0, 100)	(0, 100)
CFQ-R – treatment burden			
N	302	304	606
Mean (SD)	51.8 (20.2)	54.4 (19.8)	53.1 (20)
Median (IQR)	56 (44, 67)	56 (44, 67)	56 (44, 67)
Range	(0, 100)	(11, 100)	(0, 100)
CFQ-R – respiratory			
N	302	304	606
Mean (SD)	56.6 (21.9)	58.2 (22.1)	57.4 (22)
Median (IQR)	61 (39, 72)	61 (42.8, 73.5)	61 (39, 72)
Range	(0, 100)	(6, 100)	(0, 100)
CFQ-R – digestion			
N	302	304	606
Mean (SD)	81.1 (19.4)	79.9 (21.5)	80.5 (20.5)
Median (IQR)	89 (67, 100)	89 (67, 100)	89 (67, 100)
Range	(0, 100)	(0, 100)	(0, 100)
MAD-3 (medication adherence)			
N	274	280	554
Mean (SD)	9.9 (3.4)	10.2 (3.4)	10.1 (3.4)
Median (IQR)	10 (7, 12)	10 (8, 13)	10 (8, 13)
Range	(3, 15)	(3, 15)	(3, 15)
Behavioural question (effort)			
N	300	302	602
Mean (SD)	3.1 (1.2)	3.1 (1.3)	3.1 (1.3)
Median (IQR)	3 (2, 4)	3 (2, 4)	3 (2, 4)
Range	(1, 5)	(1, 5)	(1, 5)
CHAOS-6 (routine)			
N	300	303	603
Mean (SD)	9.5 (2.9)	9.5 (2.9)	9.5 (2.9)
Median (IQR)	9 (7, 12)	9 (7, 11)	9 (7, 11)
Range	(4, 17)	(4, 18)	(4, 18)
PAM-13 (health-style assessment)			
N	302	304	606
Mean (SD)	65.3 (13.3)	65.8 (14.5)	65.5 (13.9)
Median (IQR)	63.1 (55.6, 72.5)	63.1 (55.6, 75)	63.1 (55.6, 72.5)
Range	(38.1, 100)	(26.1, 100)	(26.1, 100)
PHQ-8 (depression)			
N	301	304	605
Mean (SD)	6.4 (5.1)	6.4 (5.2)	6.4 (5.2)
Median (IQR)	6 (2, 10)	6 (2, 10)	6 (2, 10)
Range	(0, 23)	(0, 24)	(0, 24)
GAD-7 (anxiety)			
N	302	302	604
Mean (SD)	4.7 (4.7)	4.6 (4.9)	4.7 (4.8)
Median (IQR)	3.5 (1, 7)	3 (1, 7)	3 (1, 7)
Range	(0, 21)	(0, 21)	(0, 21)

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3 Intervention fidelity

3.1 Interventionist fidelity

There were 32 interventionists and a total of 213 quality assessments conducted (Table 8).

Table 8 Interventionists and assessments at each stage

Review type	Assessment	Interventionists assessed	Interventionists reassessed	Total number of assessments	Reassessments
First visit	Fidelity	27	1	28	1
	Drift	23	0	29	0
Review visit	Fidelity	30	8	39	9
	Drift	26	0	47	0
Phase review	Fidelity	30	5	36	6
	Drift	26	0	34	0

At the first intervention visit, all but one of the interventionists were assessed once before becoming certified; one interventionist required a second session to achieve certification. At the review visit, seven interventionists required a second session and one required a third. At phase review, four interventionists required a second session and one required a third session. Fidelity scores are summarised for each type of assessment in Table 9.

Table 9 Fidelity score summaries by session type

Review type	Assessment	N	Mean (SD)	Median (IQR)	Min, max
First visit	First fidelity	27	96.0 (3.8)	97.2 (92.3, 100.0)	88.9, 100.0
	Fidelity reassessments	1	98.6 (-)	98.6 (98.6, 98.6)	98.6, 98.6
	Drift	29	94.1 (8.1)	95.8 (93.1, 97.2)	54.2, 100.0
Review visit	First fidelity	30	89.8 (12.3)	92.6 (87, 98.1)	48.1, 100.0
	Fidelity reassessments	9	94.6 (4.0)	96.3 (94.4, 96.3)	85.2, 98.1
	Drift	47	91.5 (8.7)	92.6 (90.2, 96.3)	48.1, 100.0
Phase review	First fidelity	30	92.7 (9.1)	94.4 (91.7, 97.2)	63.9, 100.0
	Fidelity reassessments	6	93.2 (10.3)	97.2 (93.1, 99.3)	73.0, 100.0
	Drift	34	92.7 (7.9)	94.4 (91.7, 97.2)	68.2, 100.0

Reasons for assessment:

- 97 for certification
- 36 for interventionists who failed certification at any point
- 18 targeted for high withdrawal rates
- 37 for insufficient audio recordings
- 82 for having fewer visits or action/coping plans created than expected
- 9 at random to ensure total assessment sample at least 20% of all interventionist visits

N.B. Each assessment could be conducted for multiple reasons, so number of reasons exceed number of sessions.

The maximum number of reassessments per stage was two. All reassessed interventionists received a 'booster' training session. There was just one interventionist who did not achieve at least 80% fidelity in drift assessment at least once. Consensus quality scores over the course of the trial are

presented in Figure 3.

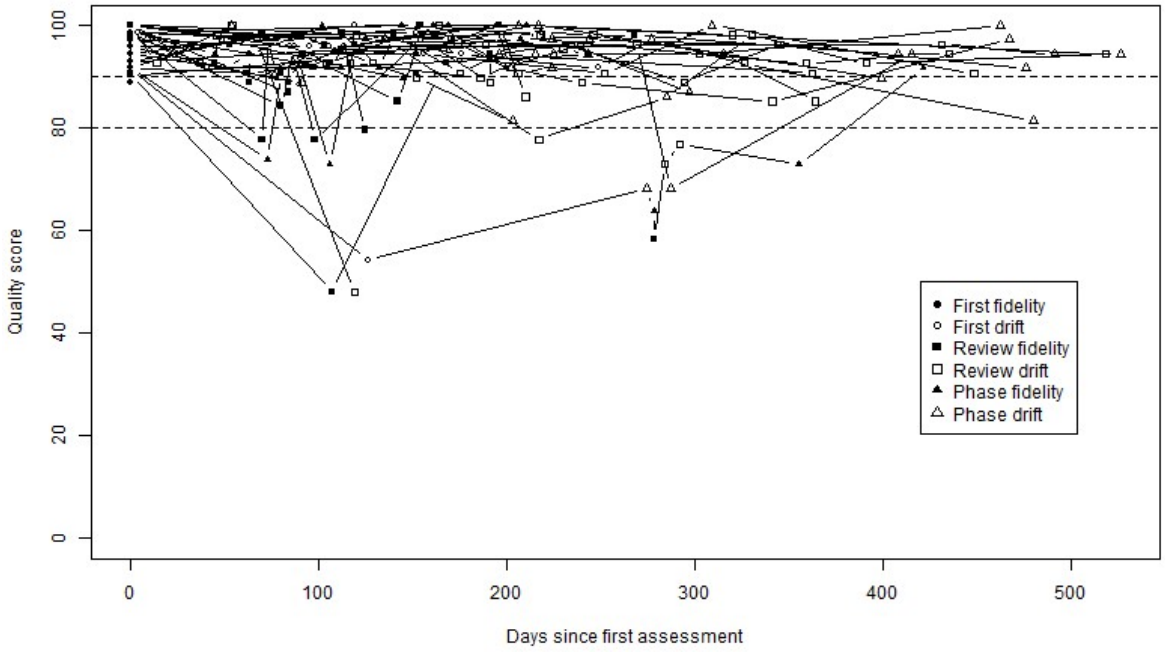

Figure 3 Interventionist fidelity scores over time during which intervention delivered

Each assessment score was weighted by the time for which it was valid and means calculated by interventionist, then aggregated by site. Overall fidelity scores are provided in Table 10.

Table 10 Overall intervention fidelity scores by site

Site	Fidelity score (%)
1	92.4
2	93.2
3	96.6
4	89.9
5	78.7
6	94.0
7	89.3
8	86.6
9	98.3
10	90.5
11	93.2
12	92.4
13	94.8
14	94.9
15	87.4
16	92.8
17	94.3
18	94.7
19	95.0

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3.2 Inter-rater agreement

Scoring for each assessment was conducted by two of three assessors. Inter-rater agreement plots for each of the three assessor pairings are given in Figures 4-6. Intra-class correlation coefficients (95% CI) were as follows:

Assessors 1 & 2: 0.93 (0.87, 0.96)

Assessors 1 & 3: 0.84 (0.76, 0.89)

Assessors 2 & 3: 0.90 (0.85, 0.94)

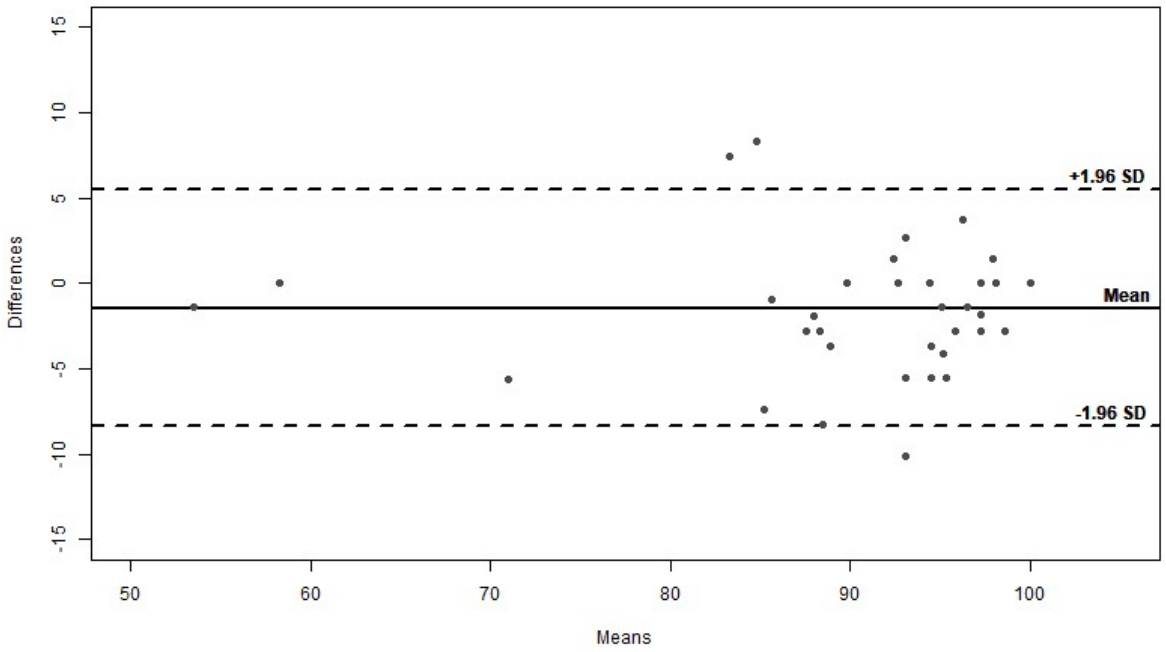

Figure 4 Inter-rater agreement for assessors 1 & 2 (95% limits of agreement; n=47)

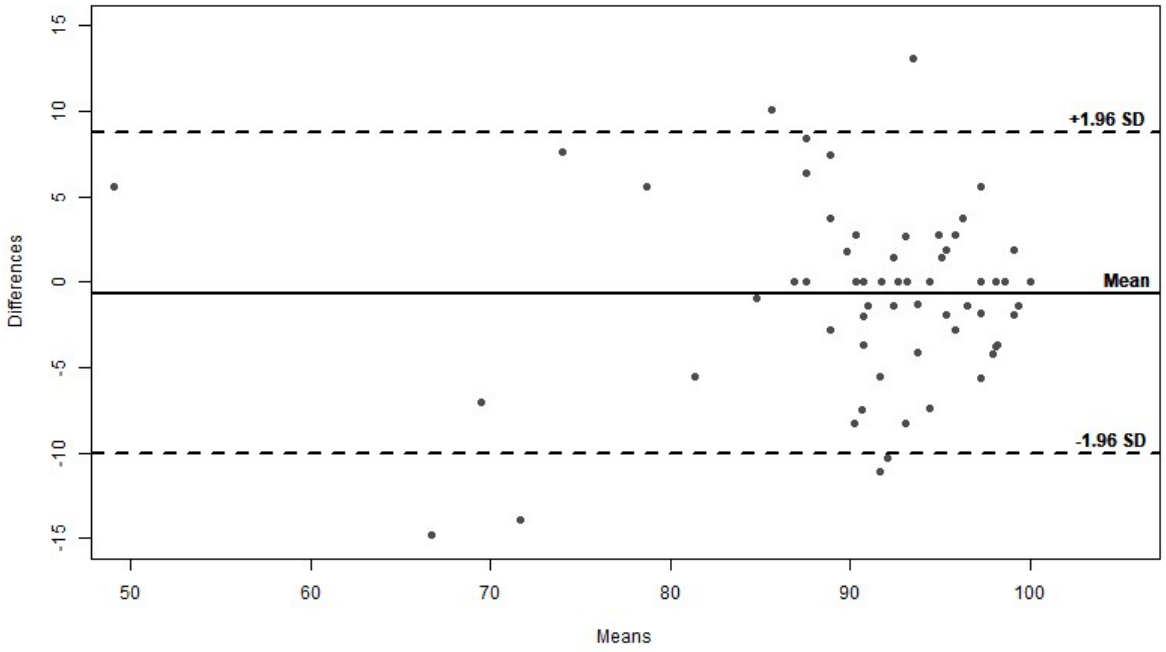

Figure 5 Inter-rater agreement for assessors 1 & 3 (95% limits of agreement; n=83)

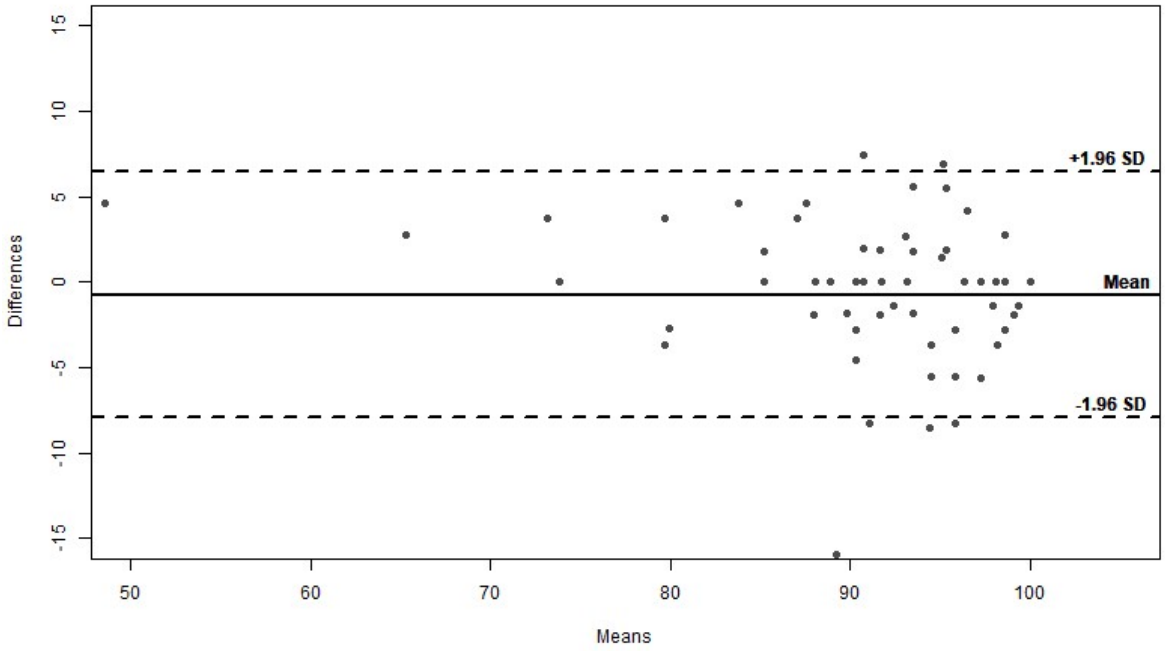

Figure 6 Inter-rater agreement for assessors 2 & 3 (95% limits of agreement; n=83)

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4 Compliance with the intervention

The number of interventionist sessions by mode of delivery are presented in Table 11. Sessions were included if they fell within the primary outcome window and the participant did not formally withdraw from the intervention during that time.

Table 11 Interventionist session delivery

	Face-to-face	Telephone	All*
Sessions per participant			
N participants	263	227	268
Mean (SD)	5.6 (2.9)	2.7 (1.9)	7.9 (3.8)
Med (IQR)	5.0 (4.0, 7.0)	2.0 (1.0, 4.0)	7.0 (6.0, 10.0)
Min, max	1.0, 15.0	1.0, 11.0	0.0, 22.0
Participants with at least…			
1 session	263 (98.1%)	227 (84.7%)	263 (98.1%)
3 sessions	228 (85.1%)	98 (36.6%)	252 (94.0%)
5 sessions	162 (60.4%)	37 (13.8%)	227 (84.7%)

*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

A summary of time spent on session delivery by site is provided in Table 12.

Table 12 Interventionist session delivery time per participant by site

Site	N participants	Total session time per participant (min)		
		Mean (SD)	Median (IQR)	Min, max
1	15	183.3 (44.8)	180.0 (140.0, 217.5)	115.0, 250.0
2	16	329.4 (172.1)	297.5 (203.8, 373.8)	130.0, 750.0
3	14	198.2 (95.9)	187.5 (142.5, 256.3)	50.0, 355.0
4	20	138.4 (97.6)	155.0 (93.8, 185.0)	0.0, 415.0
5	10	92.7 (30.9)	89.0 (75.3, 114.8)	35.0, 135.0
6	14	100.3 (25.9)	107.5 (83.8, 113.0)	57.0, 144.0
7	14	247.3 (148.9)	260.0 (140.3, 343.8)	25.0, 515.0
8	7	316.4 (65.0)	350.0 (270.0, 365.0)	215.0, 380.0
9	15	331.9 (185.9)	277.0 (195.0, 467.5)	123.0, 703.0
10	18	147.0 (59.5)	148.0 (89.5, 195.0)	65.0, 239.0
11	7	197.0 (60.6)	180.0 (155.0, 233.5)	126.0, 296.0
12	18	214.6 (94.6)	190.0 (152.5, 243.0)	75.0, 446.0
13	3	232.0 (133.8)	166.0 (155.0, 276.0)	144.0, 386.0
14	12	277.8 (109.1)	283.0 (203.5, 330.8)	94.0, 483.0
15	17	133.1 (63.1)	133.0 (102.0, 178.0)	0.0, 232.0
16	19	206.4 (69.5)	211.0 (160.5, 259.5)	81.0, 326.0
17	17	338.2 (155.2)	288.0 (238.0, 450.0)	130.0, 699.0
18	15	133.8 (64.5)	130.0 (80.0, 187.5)	45.0, 250.0
19	17	233.7 (144.1)	173.0 (142.0, 340.0)	40.0, 539.0

Interventionist CFHH interaction

Click analytic data at the interventionist/session level are provided in Table 13.

Table 13 Interventionist interactions with CFHH with and without participant present

	Participant within interventionist session/interventionist in participant view	**Interventionist outside of interventionist session**
Interactions with CFHH per participant		
N participants	268	268
Mean (SD)	8.4 (6.1)	67.6 (42.6)
Median (IQR)	7.0 (4.0, 11.5)	58.0 (41.0, 84.0)
Min, max	(0.0, 34.0)	(13.0, 330.0)
Total duration of interactions (min) per participant		
N participants	268	268
Mean (SD)	105.2 (73.4)	163.5 (132.4)
Median (IQR)	88.0 (52.0, 139.0)	130.0 (81.0, 204.5)
Min, max	(0.0, 398.0)	(8.0, 938.0)
Mean duration of interactions (min) per participant		
N participants	268	268
Mean (SD)	14.8 (8.4)	2.5 (1.2)
Median (IQR)	13.1 (9.4, 19.3)	2.2 (1.5, 3.2)
Min, max	(0.0, 56.0)	(0.2, 6.4)
Days with interactions per participant		
N participants	268	268
Mean (SD)	5.5 (3.4)	50.8 (26.8)
Median (IQR)	5.0 (3.0, 7.5)	44.5 (33.0, 63.0)
Min, max	(0.0, 19.0)	(10.0, 197.0)
Duration of interactions (min)		
N interactions	2243	18113
Mean (SD)	12.6 (14.7)	2.4 (5.5)
Median (IQR)	6.8 (0.8, 20.2)	0.2 (0.0, 1.8)
Min, max	(0.0, 85.5)	(0.0, 84.8)
Participants with at least…		
1 session	263 (98.1%)	268 (100.0%)
5 sessions	184 (68.7%)	268 (100.0%)
10 sessions	98 (36.6%)	268 (100.0%)
15 sessions	37 (13.8%)	267 (99.6%)
25 sessions	9 (3.4%)	257 (95.9%)

Participant CFHH interaction

During the primary outcome window there were 10453 notifications successfully sent to 195 participants via the mobile application (app). The mean (SD) number of notifications per participant was 53.6 (14.9) [med (IQR) 53.0 (44.0, 65.0); min 2.0, max 88.0]. Of the 216 participants who interacted with CFHH outside of interventionist sessions, 185 (85.6%) did so at some point via the app. Click analytic data are provided for both web and app in Table 14. Summaries include interactions during the primary outcome window by participants not formally withdrawing from the intervention during that time.

Table 14 Participant interactions with CFHH outside intervention sessions

	Participant outside of interventionist session
Interactions with CFHH per participant	
N participants	268
Mean (SD)	31.2 (58.9)
Median (IQR)	8.0 (1.0, 36.5)
Min, max	(0.0, 599.0)
Total duration of interactions (min) per participant	
N participants	268
Mean (SD)	37.5 (107.7)
Median (IQR)	12.0 (1.0, 42.0)
Min, max	(0.0, 1637.0)
Mean duration of interactions (min) per participant	
N participants	268
Mean (SD)	1.8 (4.2)
Median (IQR)	0.9 (0.3, 1.8)
Min, max	(0.0, 48.3)
Days with interactions per participant	
N participants	268
Mean (SD)	23.2 (35.5)
Median (IQR)	7.0 (1.0, 31.0)
Min, max	(0.0, 254.0)
Duration of interactions (min)	
N interactions	8362
Mean (SD)	1.2 (3.7)
Median (IQR)	0.1 (0.0, 0.6)
Min, max	(0.0, 93.8)
Participants with at least…	
1 session	216 (80.6%)
5 sessions	158 (59.0%)
10 sessions	125 (46.6%)
15 sessions	110 (41.0%)
25 sessions	85 (31.7%)

Participant interactions with the CFHH system outside of interventionist sessions are presented by module in Table 15.

Table 15 Participant interactions by CFHH module outside intervention sessions

Module	Total clicks in module (n=36605)	Participants with at least 1 click in module (n=268)	Number of sessions with at least 1 click in module (n=8362)
About	141 (0.4%)	67 (25.0%)	125 (1.5%)
Action Plan	186 (0.5%)	42 (15.7%)	64 (0.8%)
Coping Plan	72 (0.2%)	28 (10.4%)	40 (0.5%)
Home	12977 (35.5%)	216 (80.6%)	8355 (99.9%)
How am I Doing	17029 (46.5%)	210 (78.4%)	8205 (98.1%)
Planner	159 (0.4%)	26 (9.7%)	46 (0.6%)
Prescription	31 (0.1%)	18 (6.7%)	26 (0.3%)
Problem Solving	1042 (2.8%)	97 (36.2%)	208 (2.5%)
Reward	1851 (5.1%)	168 (62.7%)	1707 (20.4%)
Toolkit	1230 (3.4%)	147 (54.9%)	378 (4.5%)
Treatment	1497 (4.1%)	161 (60.1%)	456 (5.5%)
Videos	390 (1.1%)	105 (39.2%)	242 (2.9%)

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5 Primary outcome

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 treatment group is shown in Figure 7.

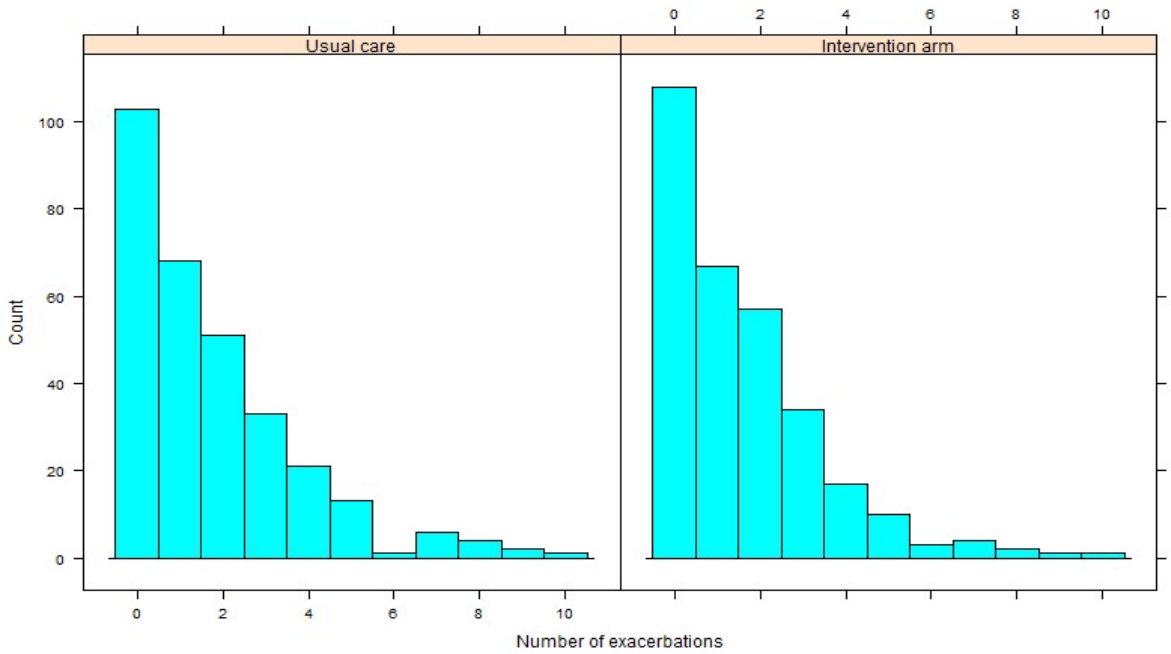

Figure 7 Exacerbation counts by treatment group

The statistical analysis plan (SAP) specified the use of a Poisson model, or negative binomial model should there be evidence of overdispersion (high variance in the count outcome relative to the mean). The variance was more than twice the mean, therefore, as per SAP, the primary outcome was analysed using a mixed-effects negative binomial model. The model included duration of follow-up for each individual participant (in days) as an offset, the number of IV days in previous 12 months (≤14 days and >14 days) and treatment arm as fixed effects, and site as a random effect. The estimated treatment effect from the negative binomial model was exponentiated to give the incidence-rate ratio (IRR). The total number of person-years and exacerbations was also presented by treatment arm to aid interpretation.

Participants in both arms had similar lengths of follow-up: 297.2 and 294.9 person-years in the usual care and intervention groups, respectively. The observed exacerbation rate in the year post-consent (i.e. the annual rate) was 1.77 in the usual care arm and 1.63 in the intervention arm. The main analysis unadjusted for any covariate (except length of follow-up) gave an estimated IRR of 0.92 (95% CI 0.77 to 1.11). The point estimate of the IRR is less than one, which favours the intervention arm. However, the 95% CI for the treatment effect included one, which is consistent with no overall difference in exacerbation rates between the two randomised groups.

The primary analysis model included adjustments for the previous year's IV days and site, which were stratifying factors in the randomisation schedule. The estimated treatment effect for this analysis, the IRR, was 0.96 (95% CI 0.83 to 1.12) which is less than one, favouring the intervention arm. However, the 95% CI for the treatment effect includes one, which is consistent with no overall difference in exacerbation rates between the two randomised groups.

A number of sensitivity analyses for the primary outcome were conducted. The results were broadly similar to the primary analysis, with point estimates for the IRR less than one (favouring the intervention) for all sensitivity analyses except the per-protocol analysis. However, for all sensitivity analyses of the primary outcome the 95% CI for the treatment effect included one, which is consistent with no overall difference in exacerbation rates between the two randomised groups.

Table 16 Primary and sensitivity analysis results

Model	Usual care				Intervention				IRR (95% CI)	*p* value
	N	Exacerbations	Person-years	Exacerbation rate	N	Exacerbations	Person-years	Exacerbation rate		
Main - unadjusted	303	526	297.2	1.77	304	482	294.9	1.63	0.92 (0.77, 1.11)	0.387
Main - adjusted	303	526	297.2	1.77	304	482	294.9	1.63	0.96 (0.83, 1.12)	0.638
All exacerbations	303	558	297.2	1.88	304	504	294.9	1.71	0.95 (0.82, 1.1)	0.511
Per protocol	303	526	297.2	1.77	195	343	192.6	1.78	1.01 (0.85, 1.2)	0.902
CACE	303	526	297.2	1.77	195	343	192.6	1.78	0.99 (0.82, 1.19)	0.908
MICE	303	-	-	-	304	-	-	-	0.98 (0.84, 1.15)	0.821
Best case imputation	303	526	297.2	1.77	304	482	301.9	1.60	0.94 (0.81, 1.1)	0.444
									HR (95% CI)	
Recurrent event survival	303	526	-	-	304	482	-	-	0.95 (0.8, 1.13)	0.567

IRR = Incidence Rate Ratio; HR = Hazard Ratio

Model definitions:

Main – unadjusted for any covariates except duration of post-consent follow-up.

Main – adjusted for stratifying factors (previous year's IV days and site).

All exacerbations – main model including additional exacerbations meeting Fuchs criteria but not treated with parenteral antibiotics.

Per protocol – just intervention participants with both a first intervention visit and a review visit during which access to the CFHH 'How am I doing?' page was recorded in participant click analytic data.

CACE – complier average causal effect – per protocol subset with probability of compliance in usual care arm predicted from baseline age, gender, FEV1 percent predicted, BMI, concern, necessity, habit, effort, EQ-5D-5L, subjective adherence, previous year's IV days and site.

MICE – multiple imputation using chained equations – missing count data imputed (where missingness not due to death) using randomisation group, site, previous year's IV days, age, gender, FEV1 percent predicted, *Pseudomonas* status, exacerbation count.

Best case imputation – missing intervention arm follow-up time imputed (where missingness not due to death) assuming no further exacerbations.

Recurrent event survival – extension of proportional hazards time-to-event model allowing for repeat events (exacerbations) with no assumption of constant event rate.

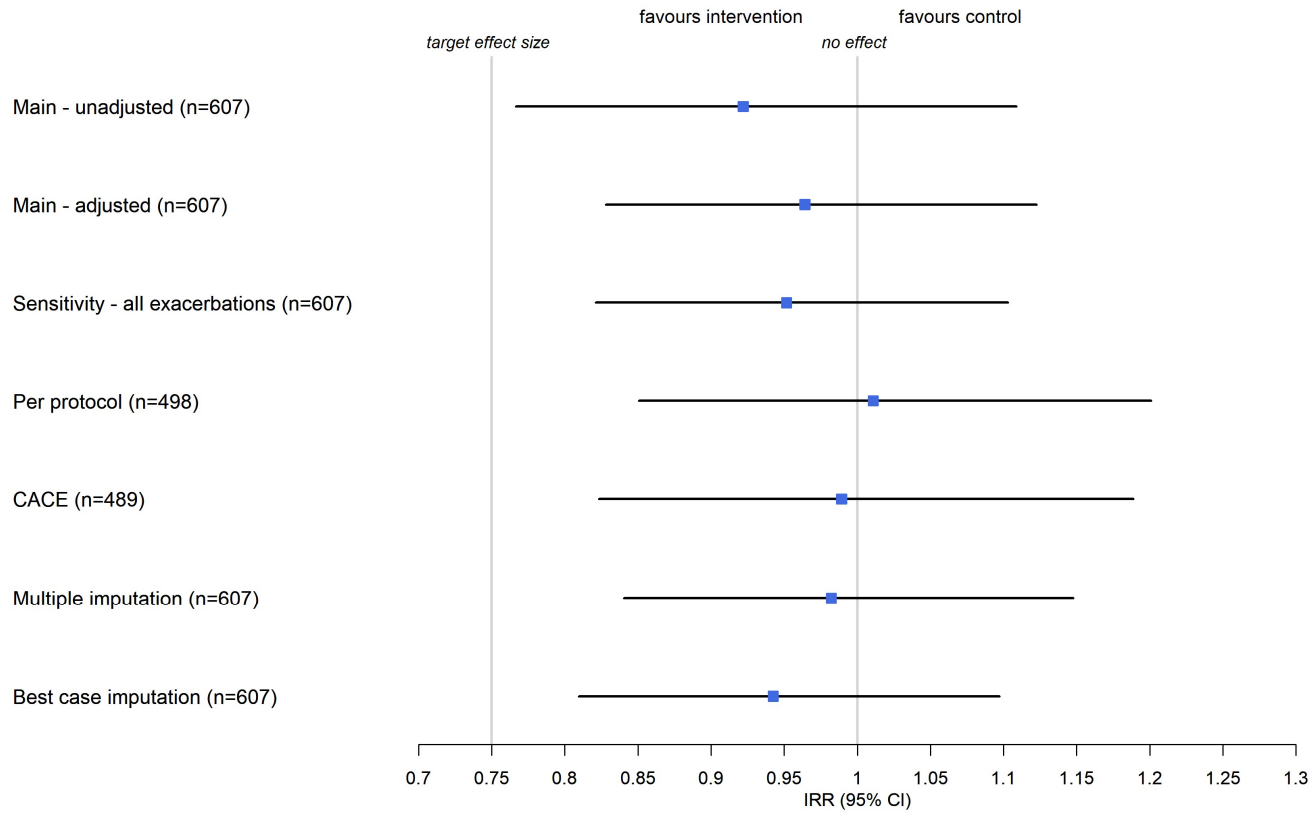

Figure 8 Incidence rate ratios (95% CIs) for primary and sensitivity analyses

The sample size estimation was based on the detection of a 0.5-point difference in the mean number of exacerbations in the year post-consent, assuming an exacerbation rate of 2.0 per year in the usual care arm and 1.5 per year in the intervention arm. This is equivalent to an IRR of 2.0/1.5 = 0.75. Figure 8 shows that none of the lower limits of the 95% confidence intervals cross this ex-ante potentially clinically important boundary.

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6 Secondary outcomes

6.1 Adherence to CF medication

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 SAP).

Table 17 Adherence summary statistics over baseline, six-month and six-to-twelve-month periods (complete case)

		Baseline (weeks 1 & 2)		**Six months (weeks 3-26)**		**Twelve months (weeks 27-52)**	
		Usual care	**Intervention**	**Usual care**	**Intervention**	**Usual care**	**Intervention**
	N	295	296	301	301	282	288
Weekly doses	Mean (SD)	11.3 (11.4)	12.8 (12.5)	9.7 (10.8)	13.3 (12.1)	9.1 (10.5)	12.6 (10.7)
	Median (IQR)	8 (2.5, 18)	9.1 (3.5, 19.4)	6.2 (1.2, 15.3)	11 (4.1, 18.4)	5.7 (0.7, 13.6)	10.7 (3.7, 18.9)
	Range	(0, 53.5)	(0, 102.5)	(0, 47.5)	(0, 95.5)	(0, 45.8)	(0, 52.8)
Numerator-adjusted adherence	Mean (SD)	48.2 (34.4)	56.4 (32.4)	38 (33)	56.3 (31.6)	35.4 (32.7)	55.2 (32.6)
	Median (IQR)	50 (14.3, 81)	61.3 (28.6, 85.7)	29 (6.5, 68.3)	63.6 (31.4, 84.3)	27.6 (4, 64.6)	64 (23.3, 83)
	Range	(0, 100)	(0, 100)	(0, 99.3)	(0, 100)	(0, 99.9)	(0, 99.6)
Numerator-adjusted normative adherence	Mean (SD)	45.6 (34.2)	54 (32.9)	35.9 (32.2)	53.7 (31.7)	33.2 (31.7)	51.9 (32.6)
	Median (IQR)	42.9 (10.7, 76.4)	57.2 (25, 84.2)	25.9 (6.2, 61.6)	58.7 (26.8, 81.4)	24.4 (3.5, 59.8)	56.2 (22.5, 81.4)
	Range	(0, 100)	(0, 100)	(0, 99.3)	(0, 100)	(0, 99.9)	(0, 98.9)

The average weekly adherence post-consent was modelled using a longitudinal linear mixed-effects model which allowed for baseline stratification factors (previous year's IV days and site) and time (week of post-consent follow-up). The random effects structure consisted of participants nested within site with random intercepts and slopes, which allowed for participants to have individual changes (or trajectories) in adherence over time (weeks post-consent). This model also allowed for the correlation between the repeated participant measures of adherence and assumed an exchangeable or equal correlation between participants for each successive week of adherence.

There were 588 (of 608 randomised) participants with sufficient data to be included in the adherence model. Table 18 shows that for these 588 participants the observed average 'baseline' (weeks 1 and 2) weekly adherence was 45.5% in the usual care group and 54.1% in the intervention group.

Table 18 Numerator-adjusted normative adherence summary statistics baseline, six-month and six-to-twelve-month periods (model subset)

		Baseline (weeks 1 & 2)		Six months (weeks 3-26)		Twelve months (weeks 27-52)	
		Usual care	**Intervention**	**Usual care**	**Intervention**	**Usual care**	**Intervention**
	N	295	293	295	293	275	281
Numerator-adjusted normative adherence	Mean (SD)	45.5 (34.1)	54.1 (33.0)	36.6 (32.6)	54.1 (31.7)	34.1 (32.2)	52.2 (32.6)
	Median (IQR)	42.9 (12.5, 76.1)	58.3 (23.8, 84.5)	27 (6.3, 64.4)	59.6 (28.3, 81.9)	25.3 (6.7, 61.1)	57.6 (22.6, 81.3)
	Range	(0, 100)	(0, 100)	(0, 99.3)	(0, 100)	(0, 99.9)	(0, 98.9)

The observed 50-week post-consent follow-up mean (SD) for participants contributing data to the longitudinal model were 34.9 (31.7) % in the usual care arm and 52.9 (31.4) % in the intervention arm. After adjustment for covariates, the adjusted least squares means (SE) from the model were 39.6 (0.8) % in the usual care arm and 49.1 (0.8) % in the intervention arm.

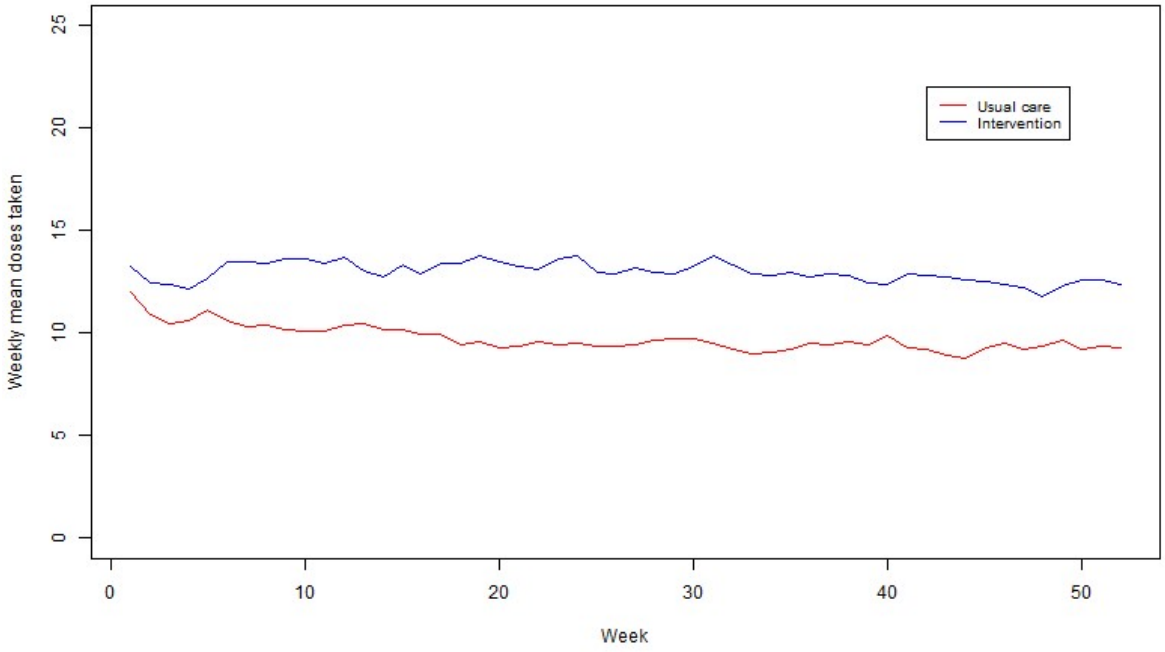

Figure 9 Mean inhaled doses taken per week

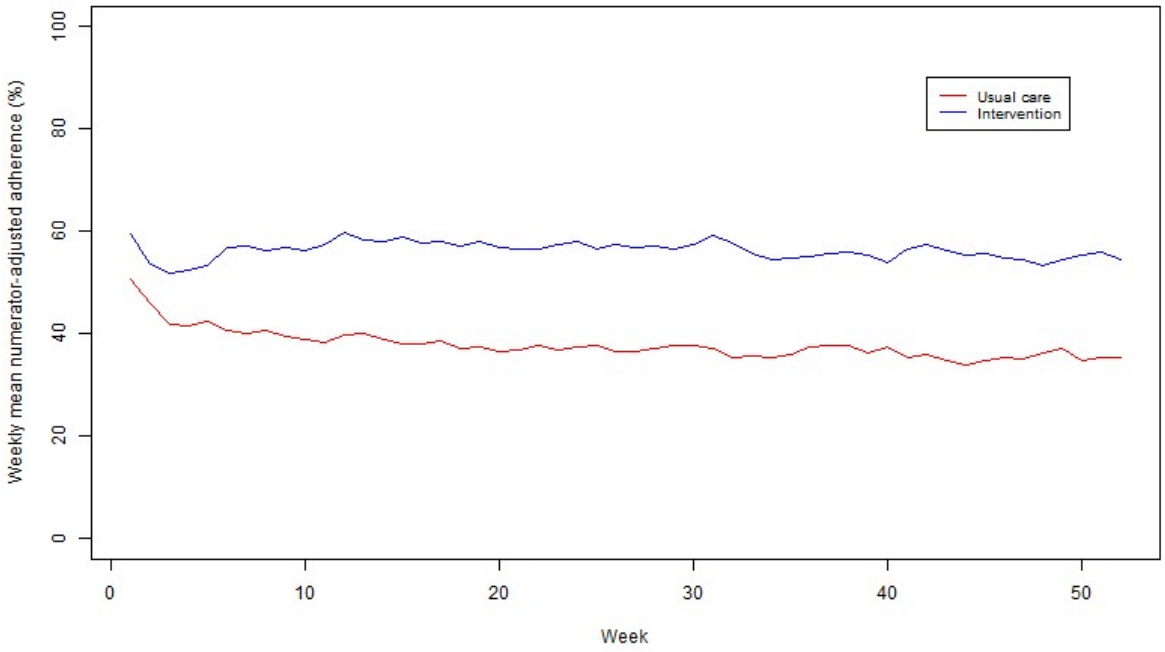

Figure 10 Weekly mean numerator-adjusted adherence

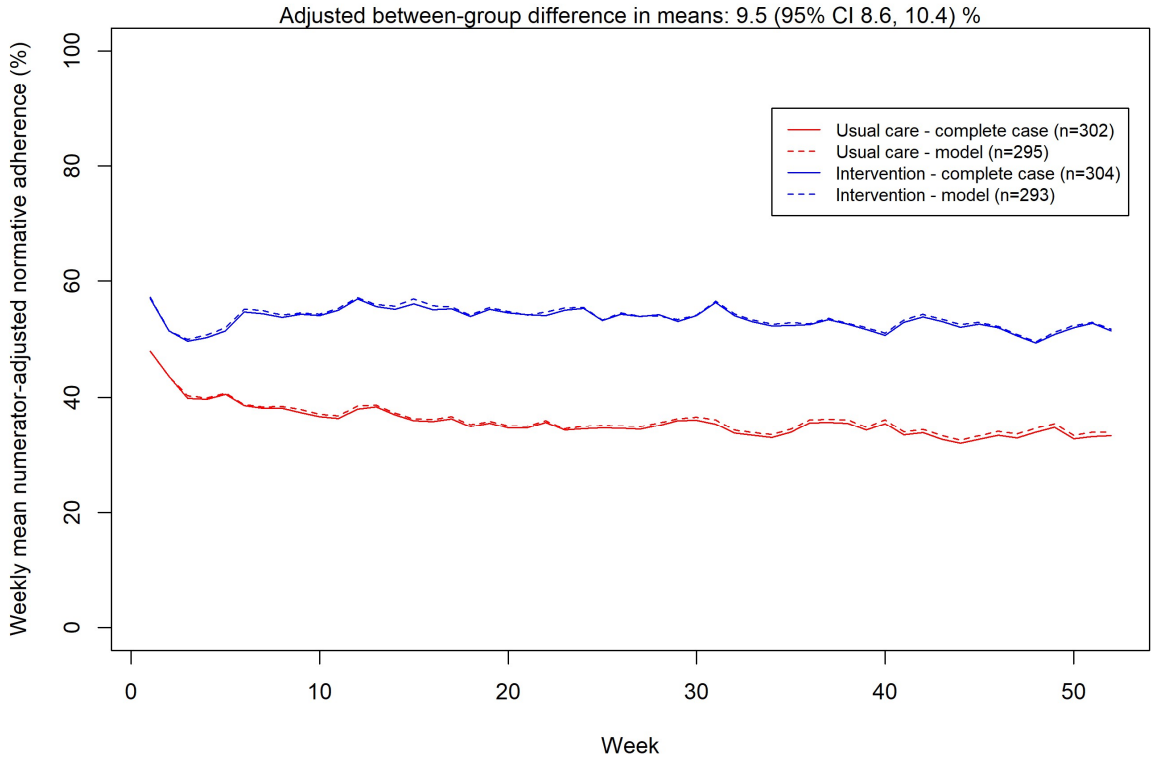

Figure 11 Weekly mean numerator-adjusted normative adherence

Figure 11 shows the mean weekly numerator-adjusted normative adherence for all participants (N=606: usual care 302 and intervention 304) with any (weeks 1 to 52) post-consent adherence data; and the (N=588: usual care 295 and intervention 293) participants with sufficient data to contribute to the inferential statistical model. The figure shows a clear separation between the adherence levels for the usual care and intervention groups. When comparing the usual care complete case group (n=302) and the usual care model group (n=295) the lines coincide, suggesting little or no evidence of a difference in adherence over time. A similar pattern is observed in the intervention complete case vs intervention model subset lines. This implies that any missing participant data is unlikely to be affecting the between-treatment-group estimates of adherence.

The adjusted between-group difference in means from the longitudinal model was 9.5% (95% CI 8.6, 10.4), $p<0.001$ (Table 19) in favour of the intervention group. That is after adjusting for covariates (baseline adherence and previous year's IV days) and week of post-randomisation follow-up, the average difference in weekly adherence was around 10%. Sensitivity analysis with *Pseudomonas* status defined as worst case between Leeds criteria and clinician's judgement gave a between-group difference of 9.9 (95% CI 9.0, 10.8) %, $p<0.001$.

There was no reliable statistical evidence of any time (week of post consent follow-up) by treatment group interaction, so the simpler statistical model without the interaction term was used. Overall, after adjustment for covariates, there was evidence of a small decline over time in adherence of around 0.15% per week.

Table 19 shows similar estimates of the treatment effect and decline over time in a post-hoc analysis using a subset of the data with only weeks 5-52 post-consent follow-up.

Table 19 Numerator-adjusted normative adherence model coefficients

	Parameter estimate (95% CI)	
	Weeks 3-52 follow-up (n=588)	**Weeks 5-52 follow-up* (n=582)**
Fixed effects		
Adherence in weeks 1&2 (baseline)	78.3 (77.0, 79.7)	76.7 (75.2, 78.1)
Previous years' IV days	-0.67 (-1.57, 0.21)	-0.66 (-1.62, 0.31)
Intervention	9.5 (8.6, 10.4)	10.9 (9.9, 11.9)
Week	-0.15 (-0.21, -0.08)	-0.16 (-0.22, -0.09)
Random effects		
Subject within site	0.51 (0.45, 0.57)	0.50 (0.44, 0.56)
Residual	344.8 (339.0, 350.6)	343.1 (337.2, 349.0)

*Post hoc analysis

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6.2 FEV1 percent predicted

The adjusted difference in group means (usual care n=282, intervention n=274) was 1.4 (95% CI -0.2, 3.0), *p*=0.082 (Figure 12).

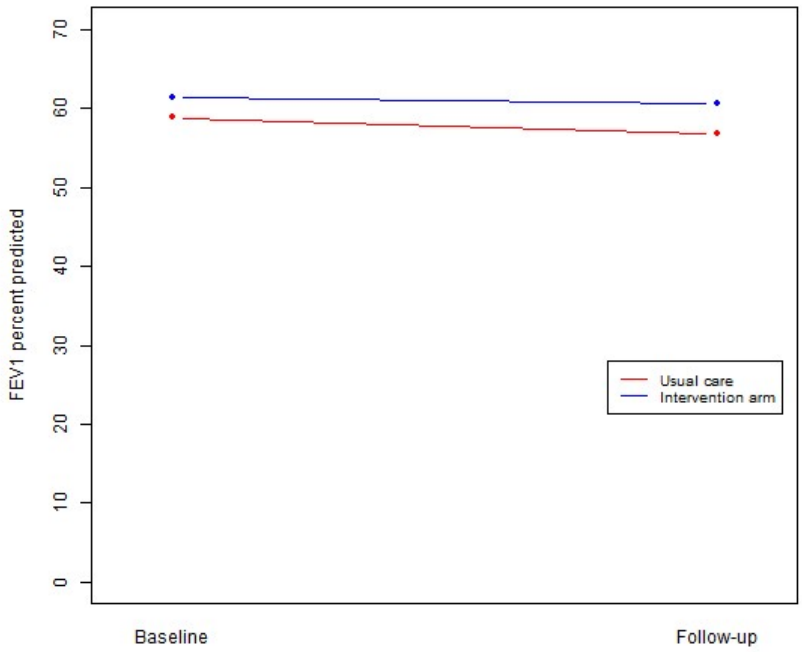

Figure 12 Mean FEV1 percent predicted at baseline and 12-month follow-up

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6.3 Body mass index

The adjusted difference in group means (usual care n=282, intervention n=273) was 0.3 (95% CI 0.1, 0.6), *p*=0.008 (Figure 13).

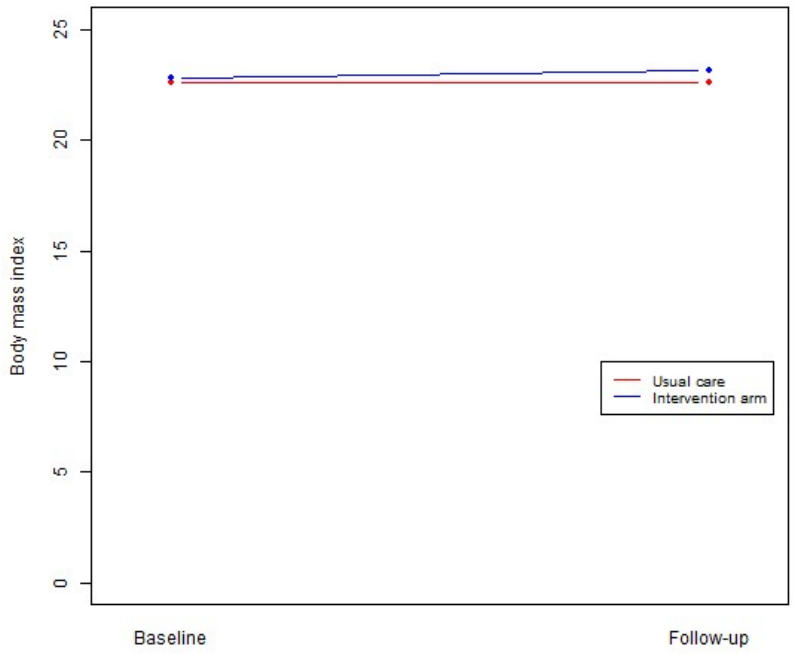

Figure 13 Mean body mass index at baseline and 12-month follow-up

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6.4 Patient-reported outcomes

Table 20 Patient-reported outcomes at 12-month follow-up

	Usual care		Intervention		Adjusted difference in means	Direction of beneficial	Standardised effect
	N	Mean (SD)	N	Mean (SD)	(95% CI)	effect	size
EQ-5D-5L	272	0.81 (0.18)	264	0.84 (0.15)	0.01 (-0.01, 0.04)	Increase	0.09
EQ-5D crosswalk	272	0.74 (0.22)	264	0.77 (0.19)	0.02 (0, 0.05)	Increase	0.11
COM-BMQ concerns	271	2.1 (0.5)	271	2 (0.5)	-0.16 (-0.23, -0.09)	Decrease	0.29
COM-BMQ necessities	271	3.5 (0.7)	271	3.7 (0.8)	0.13 (0.04, 0.23)	Increase	0.18
SRBAI (habit)	271	11.7 (4.9)	261	12.9 (4.9)	1.18 (0.55, 1.81)	Increase	0.24
CFQ-R – physical	274	52.6 (30.6)	264	55.8 (30.2)	2.34 (-0.96, 5.63)	Increase	0.08
CFQ-R – emotion	274	66.5 (24.7)	264	66.6 (22.9)	0.16 (-2.92, 3.23)	Increase	0.01
CFQ-R – social	274	59.6 (20)	264	60.5 (20)	0.28 (-2.15, 2.7)	Increase	0.01
CFQ-R – eating	274	81 (23.2)	264	84 (21.5)	1.93 (-1.32, 5.19)	Increase	0.09
CFQ-R – body	274	65.1 (29.3)	264	67.2 (27.3)	1.7 (-1.39, 4.79)	Increase	0.06
CFQ-R – treatment burden	274	51.5 (19.7)	265	56.6 (19.5)	3.95 (1.19, 6.71)	Increase	0.20
CFQ-R – respiratory	271	56.6 (21.9)	263	58 (22.5)	0.7 (-2.44, 3.83)	Increase	0.03
CFQ-R – digestion	272	80.2 (21.6)	263	80.4 (19.4)	1.09 (-1.67, 3.85)	Increase	0.05
MAD-3 (medication adherence)	245	9.9 (3.6)	237	10.8 (3.3)	0.69 (0.21, 1.17)	Increase	0.20
Behavioural question (effort)	270	3 (1.2)	260	3.3 (1.3)	0.28 (0.08, 0.47)	Increase	0.22
Subjective adherence	267	65.6 (32.8)	258	68.6 (31.3)	1.9 (-2.8, 6.59)	-	0.06
CHAOS-6 (routine)	272	9.6 (3.2)	263	9.4 (3.4)	-0.17 (-0.62, 0.28)	Decrease	0.05
PAM-13 (health-style assessment)	274	64.9 (13)	265	68.1 (15.6)	3.38 (1.33, 5.43)	Increase	0.23
PHQ-8 (depression)	272	6.4 (5)	262	6.3 (5.6)	-0.05 (-0.8, 0.7)	Decrease	0.01
GAD-7 (anxiety)	273	4.5 (4.8)	262	4.9 (5.3)	0.27 (-0.43, 0.96)	Decrease	0.05

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7 Subgroup analyses

Interaction effects between subgroup and treatment arm for the primary exacerbation analysis are presented in Figures 14-19.

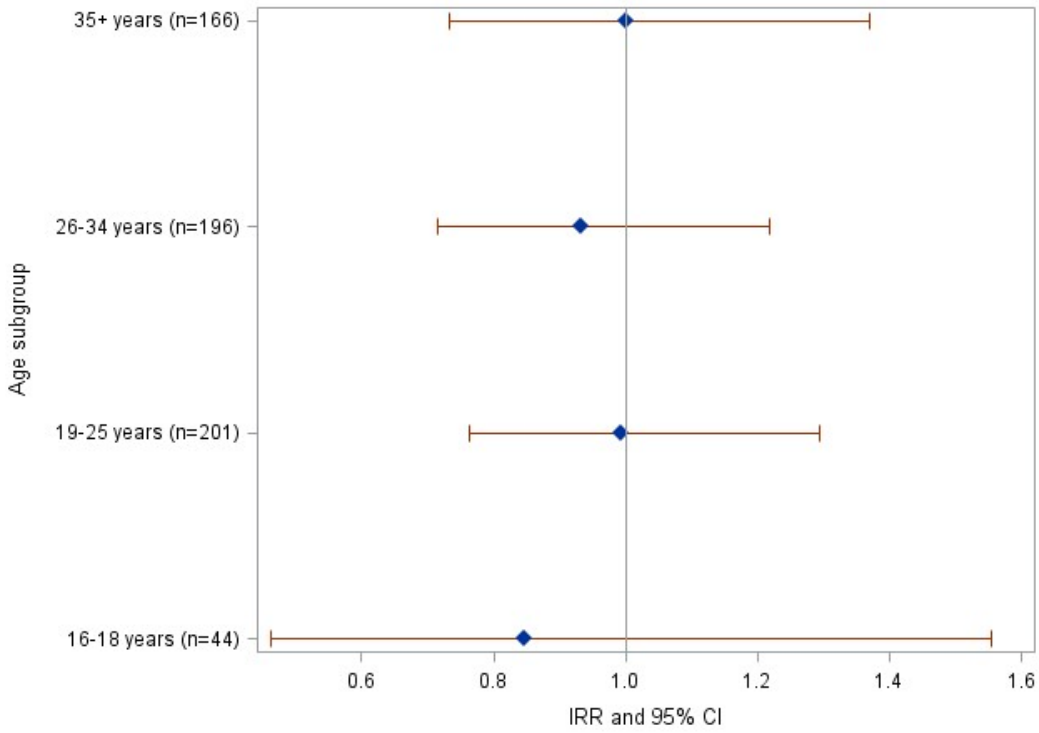

Figure 14 Exacerbation incidence rate ratios by baseline age ($F_{3,580}$=0.11, p=0.953)

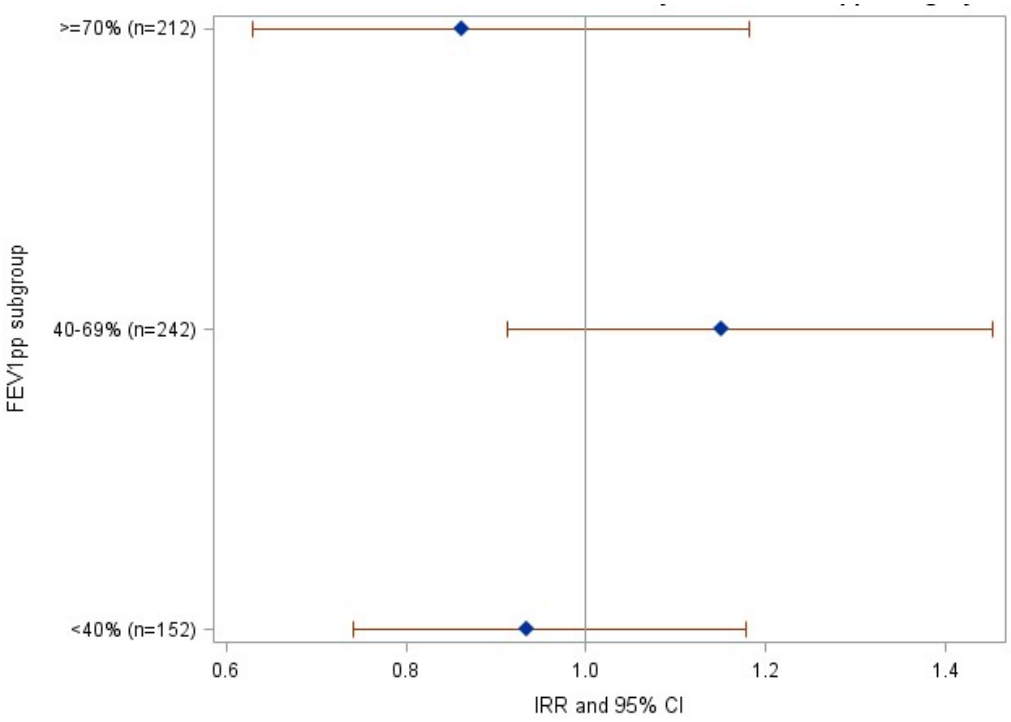

Figure 15 Exacerbation incidence rate ratios by baseline FEV1 percent predicted ($F_{2,581}$=1.30, *p*=0.274)

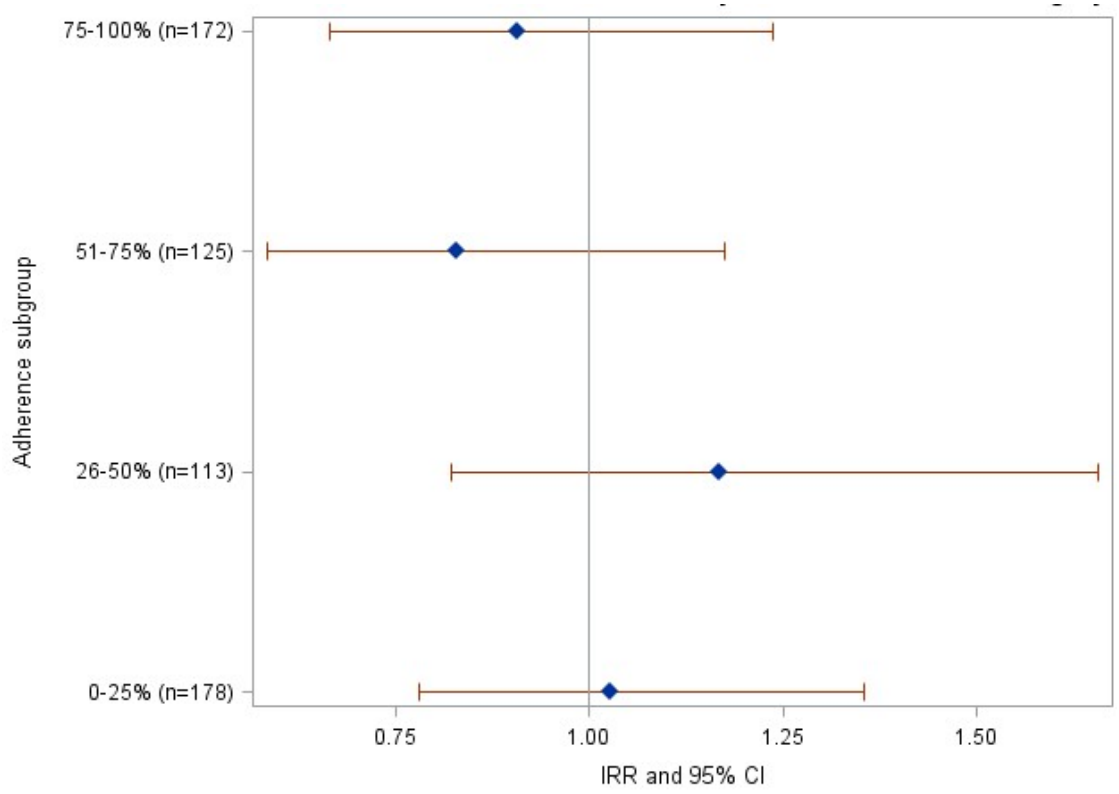

Figure 16 Exacerbation incidence rate ratios by baseline adherence ($F_{3,561}$=0.73, *p*=0.533)

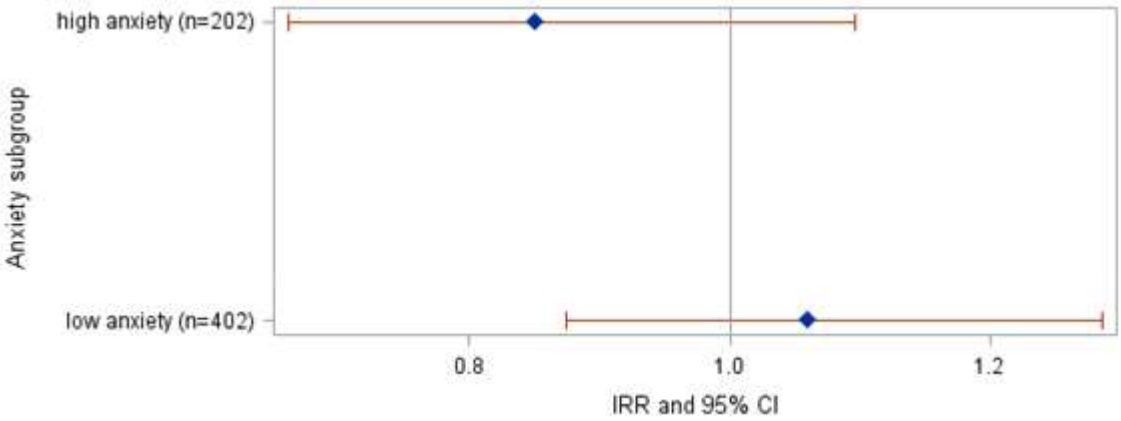

Figure 17 Exacerbation incidence rate ratios by baseline anxiety ($F_{1,581}$=1.82, p=0.178)

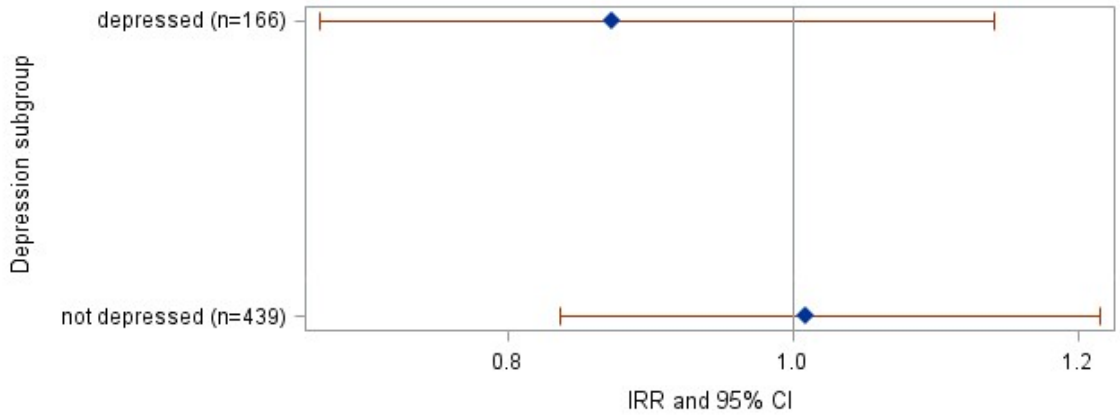

Figure 18 Exacerbation incidence rate ratios by baseline depression ($F_{1,582}$=0.74, p=0.390)

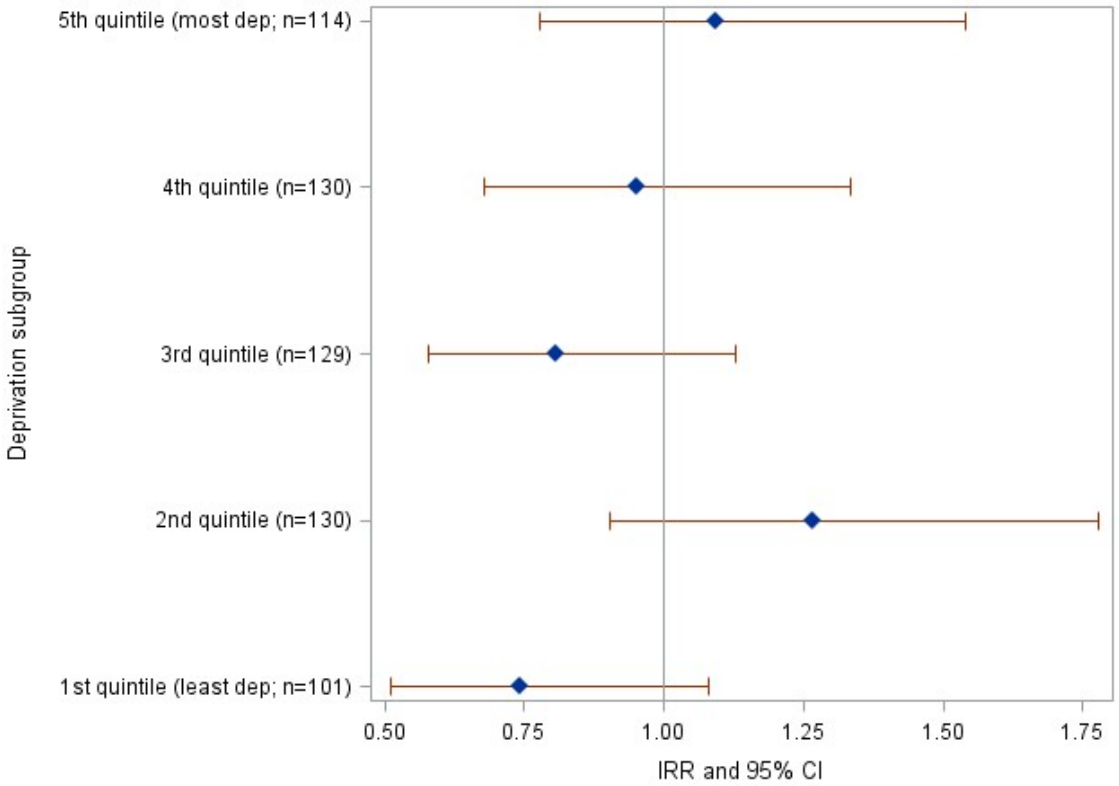

Figure 19 Exacerbation incidence rate ratios by deprivation ($F_{4,575}$=1.49, *p*=0.204)

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8 Safety

8.1 Non-serious adverse events

Table 21 Non-serious adverse events and patients experiencing events

Event	Usual care (n=303)	Intervention (n=305)	Overall (n=608)
All AEs	301 (46.9%)	341 (53.1%)	642 (100.0%)
Participants experiencing at least 1 AE	125 (41.3%)	139 (45.6%)	264 (43.4%)
AEs by category:			
Expected	242 (80.4%)	263 (77.1%)	505 (78.7%)
New depression requiring treatment	1 (0.3%)	5 (1.5%)	6 (0.9%)
Other	58 (19.3%)	73 (21.4%)	131 (20.4%)

8.2 Serious adverse events

Table 22 Serious adverse events and patients experiencing events

Event	Usual care (n=303)	Intervention (n=305)	Overall (n=608)
All SAEs	64 (47.4%)	71 (52.6%)	135 (100.0%)
Participants experiencing at least 1 SAE	43 (14.2%)	56 (18.4%)	99 (16.3%)
SAEs by category:			
Expected	21 (32.8%)	28 (39.4%)	49 (36.3%)
New depression requiring treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	41 (64.1%)	42 (59.2%)	83 (61.5%)
Unknown	2 (3.1%)	1 (1.4%)	3 (2.2%)

There were no SAEs deemed related to the intervention. (Non-serious AEs were not assessed for relatedness.)

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9 Mapping report contents to SAP

SAP v2.0 statistical analysis section	Statistical analysis report section	Table(s)	Figures(s)
7.1 General considerations	-	-	-
7.2 Participant flow	1	Table 1 Reasons for declining trial participation Table 2 Reasons for premature discontinuation of primary outcome data collection Table 3 Reasons for premature discontinuation of adherence data collection Table 4 Reasons for premature discontinuation of trial intervention Appendix 1 Line listings of reasons given for declining trial participation recorded as 'other'	Figure 1 Planned and actual recruitment for the ACtiF trial Figure 2 CONSORT flow diagram
7.3 Baseline characteristics	2	Table 5 Participant characteristics at baseline Table 6 Clinical characteristics at baseline Table 7 Patient-reported outcome measures at baseline	-
7.4 Intervention fidelity	3	Table 8 Interventionists and assessments at each stage Table 9 Fidelity score summaries by session type Table 10 Overall intervention fidelity scores by site	Figure 3 Interventionist fidelity scores over time during which intervention delivered Figure 4 Inter-rater agreement for assessors 1 & 2 Figure 5 Inter-rater agreement for assessors 1 & 3 Figure 6 Inter-rater agreement for assessors 2 & 3

SAP v2.0 statistical analysis section	Statistical analysis report section	Table(s)	Figures(s)
7.5 Compliance with the intervention	4	Table 11 Interventionist session delivery Table 12 Interventionist session delivery time per participant by site Table 13 Interventionist interactions with CFHH with and without participant present Table 14 Participant interactions with CFHH outside intervention sessions Table 15 Participant interactions by CFHH module outside intervention sessions	
7.6 Analysis populations	-	-	-
7.7 Primary outcome	5	Table 16 Primary and sensitivity analysis results	Figure 7 Exacerbation counts by treatment group Figure 8 Incidence rate ratios (95% CIs) for primary and sensitivity analyses
7.8 Secondary outcomes	6	Table 17 Adherence summary statistics over baseline, six-month and six-to-twelve-month periods (complete case) Table 18 Numerator-adjusted normative adherence summary statistics baseline, six-month and six-to-twelve-month periods (model subset) Table 23 Numerator-adjusted normative adherence model coefficients Appendix 2 – Numerator-adjusted normative adherence weekly summaries	Figure 9 Mean inhaled doses taken per week Figure 10 Weekly mean numerator-adjusted adherence Figure 11 Weekly mean numerator-adjusted normative adherence Figure 12 Mean FEV1 percent predicted at baseline and 12-month follow-up Figure 13 Mean body mass index at baseline and 12-month follow-up

SAP v2.0 statistical analysis section	Statistical analysis report section	Table(s)	Figures(s)
		Table 20 Patient-reported outcomes at 12-month follow-up	Appendix 2 – Numerator-adjusted normative adherence weekly summaries
7.9 Safety	8	Table 21 Non-serious adverse events and patients experiencing events Table 22 Serious adverse events and patients experiencing events	-
10.1 Subgroup analysis	7	-	Figure 14 Exacerbation incidence rate ratios by baseline age Figure 15 Exacerbation incidence rate ratios by baseline FEV1 percent predicted Figure 16 Exacerbation incidence rate ratios by baseline adherence Figure 17 Exacerbation incidence rate ratios by baseline anxiety Figure 18 Exacerbation incidence rate ratios by baseline depression Figure 19 Exacerbation incidence rate ratios by deprivation

10 Post hoc analyses

10.1 Additional subgroup analyses

Adherence for each participant was calculated on a daily basis (and capped at 100%) 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 pre-consent and randomisation, so “baseline” adherence was defined and calculated as the average adherence in the first two weeks post-consent.

Baseline adherence was categorised into four subgroups or strata: weekly baseline adherence of 0 to 25%; 26%-50%; 51% to 75%; 76% to 100%. These strata were agreed prior to running the analyses after discussion between the senior co-investigators.

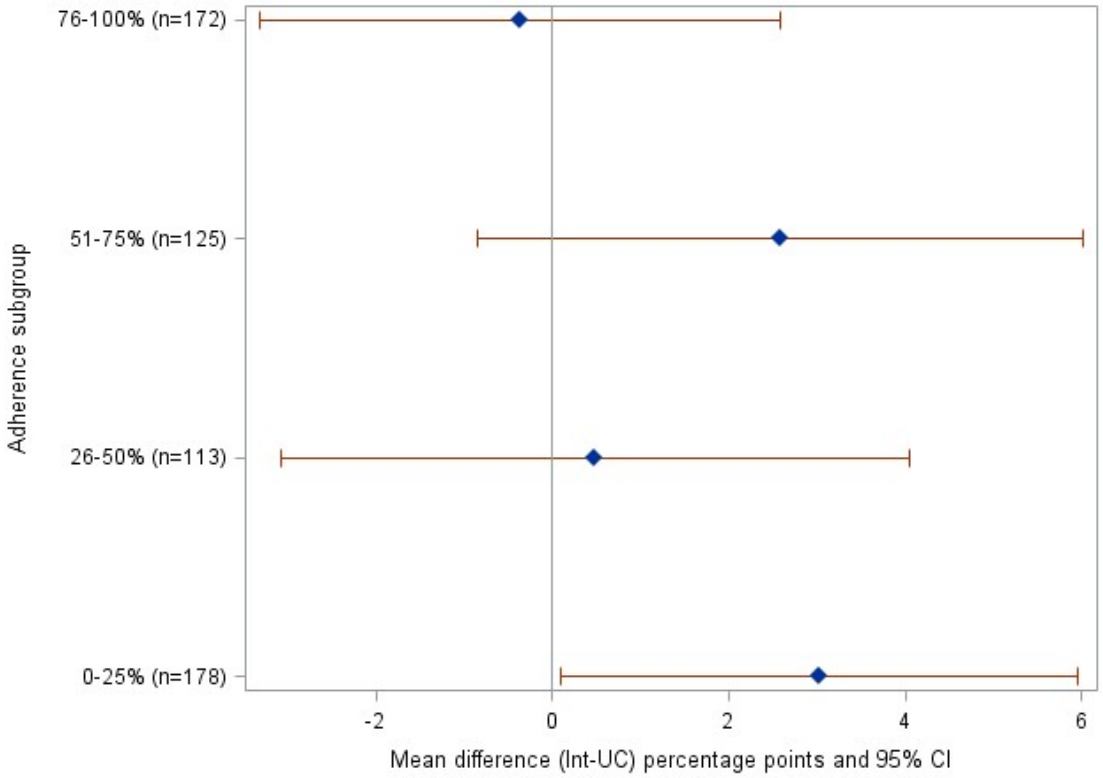

Figure 20 FEV1 percent predicted difference in means by average baseline adherence (weeks 1 & 2) ($F_{3,514}$=1.10, p=0.349)

There was no reliable evidence of an interaction between baseline adherence strata and treatment group in FEV1 percent predicted at the 12-month follow-up.

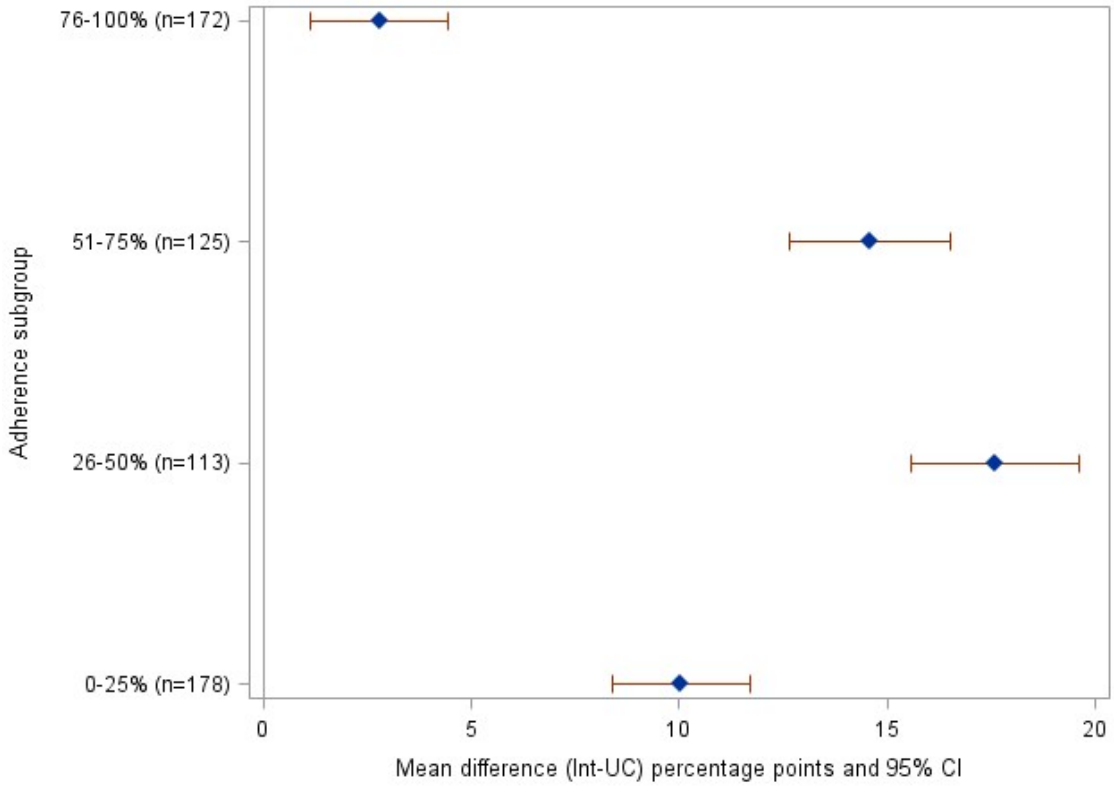

Figure 21 Adherence difference in means by average baseline adherence (weeks 1 & 2) ($F_{3,26000}$=49.31, p<0.001)

There was some evidence of an interaction between baseline adherence strata and treatment group in normative adherence (weeks 3 to 52 post-consent follow-up).

Appendices

Appendix 1 Reasons for declined participation

Line listings of reasons given for declining trial participation recorded as 'other' (n=125)

Not able to contact patient
Not currently taking nebs at present
Compliant with nebs
Wants to do a different study
Going to start Colobreathe
Wants to take part in drug trials
Felt she was very complaint with nebulisers already
Cant take nebulisers at present
Not taking nebuliser treatment at present
Is not taking nebulisers
Travelling for months at a time in Japan.
Uses iNeb aswell as an eFlow - not suitable for study
Feels she is compliant
Unable to use an eFlow due to treatment.
Did not attend clinic
Felt they were a high adherer
Didnt want to take part.
Very compliant and felt would put too much pressure on herself if she misses a dose.
Too busy with new baby
referred for transplant assessment
Lives away at Uni during term times and could not commit to intervention
Not for them
moving to rotterdam
too much on
couldn't see benefit as believed already in good routine and 100% adherent/ didn't like eflow
happy ignoring her CF as much as possible
Social circumstance - childcare. Willing to be reapproached Jan-Feb when circumstances may be different
Lives too far from away from centre when at uni and only returning in long holidays so arranging any face to face appointments if in intervention very difficult
about to have a baby and doesn't feel it is the right time
Doesn't want a further reminder of her CF and feels she is well
Worried he wouldn't be organised to commit to this and geography given he is at university, would love to be in control group
Doesn't want CF to take over her life
Other health problems external to CF taking precedent
Ineligible as prescribed nebulised ceftazidime which can only be taken through a jet compressor
Doesn't like the idea of people seeing her adherence
no intention to take treatment at present and doesn't want to waste anyon'es time therefore doesn't see the benefit despite informing him that this would be okay
Doesn't like the eflow device
Social instability
Doesn't like using the e-flow for all medications

Doesn't want his CF care to extend beyond the hospital and attending frequently as it is without study visits on top

At home his conversations would be overheard and he doesn't want people to know about his treatments, doesn't want to be assigned to intervention arm because of this

Doesn't accept diagnosis of CF and doesn't want to be in a CF study nor be a guinea pig

Only prescribed Dnase and electing to stop so not taking any nebulised medications

Discussed with patient and the team - limited reading of English, to be excluded

Wants to have prescription changed to dry powder

Personal Reasons

Already uses medication tracking apps and completes surveys online for CF

doesn't take nebs regulalry and reports this has been agreed with the clinical team

thinks they're too lazy for it and finds appointments anxiety inducing

Doesn't like to be reminded of CF in daily life so does not want to be part of a CF study.

not interested

Already feels guilty for not doing physio, so knows she will feel even more guilt when not taking treatments. would find these feelings too much.

feels psychological burden would be too much

Has too much going on and feels like she took part in a similar trial called SMART.

couldn't be certain of schedule so couldn't commit to contact.

weren't willing to switch to an etrack to take hypertonic

Patient has not had contact with CF centre since transition. Therefore not appropriate for trial.

Doesn't want to be part of a 'big brother-esque' piece of research. And has also just been started on a manitol trial deeming him ineligible.

wants to get on and live life without being watched or feel like an experiment

Is only on one drug every other day so doesn't see the point of taking part. If nebulised therapies increase then will make contact to take part if still in recruitment period.

Worried about "Big Brother" watching her

Has decided to stop all inhaled medicines

d/w with PI not appropriate for the trial given Asperger syndrome.

already has routine, and doesn't want to change. her adherence is high.

Changed to dry powder on last clinic appointment

no longer taking nebulisers- consultant lead- pt well

1) does not want to change to e.flow 2) feels his compliance is very good 3) work and family life s too busy

Pregnant- 1st child would like to focus on this and potential effects to her health first

Can not switch off I.Neb due to promixcin, can not tolerate colistin via e.flow

Reports would not be good for her mental health and wants to try and lead a normal life- this would be a reminder of her CF

Personal Problems

End of life care for lung cancer- new diagnosis post information given

Not feeling well and too time consuming- could consider re-asking in the new year if needed

CFHH Critera not for filled

New mum in March would like to focus on this

Spends a lot of time at RBH and with ongoing medica care and investgations for his cardiac health does not want to participate in another hospital trial- wants to make the most of retirement and live life.

Lives in Isle of Man would not want to be in intervention group for travel reasons. would only want to be in the control group

very new diagnosis of bowel cancer, difficult time and lots to think about with this new diagnosis- wants to focus on this right now

Has been recruited to another trail now: Vertex

Due to be starting new NTM Rx would like to focus on this first and has a small child to time manage, would find joining a trial at this stage too much

Can not tollerate E.Flow- Haemotysis

Hasnt been well recently all treatments "up in the air" a lot of change, not feeling up to it.

Relocating to Southampton

No the right time for him with other life events

Thinks adherence is good already and no other time with uni work taking priority

Travelling round Asia

T/F'ing care to Sheffield and reports already started on trial.

Work commitments and lives in Birmigham

New Diagnosis of Lung Ca- in contact with pallative care thus would be in exclusion criteria

Travels a lot and not wishing to comitt to study at present

Too intrusive

Not interested in taking nebulisers

Happy with current routine

Happy with curent routine

Reports already 100% compliant

Interested in another clinical trial

States already has routine and not interested

Patient reports already does as many nebs as possible and has good routine

Only does hypertonic saline & ventolin through eflow when required and currently not taking any nebs

Currently not taking any nebulisers

Not returning text messages

No reply from texts

Says only takes nebulisers when unwell

Didn't feel she would benefit as compliance good

Doesn't like eflows - didn't want to consider it and declined follow-up call

not able to contact

not interested

Informed by MDT would not be appropriate to approach as care-giver administers all medication.

RIP

Happy with current routine

Currently other issues in life.

New job & working nights

Going travelling for a year

Hasn't been doing nebulisers for 18 months and does not wish to start them again

Not interested

Living away from home

Awaiting lung transplant

doesn't take nebs and doesn't want to start taking nebs as feels they already have too many meds to deal with

Has young children, wouldn't be able to manage

Unable to get hold of patient to discuss further prior to end of trial recruitment

Currently doing GCSEs didnt want to have to think of something else

Unable to get in contact with patient prior to close of recruitment despite several attempts. Trial not formally discussed with patient

Going travelling for 6 months.

Wishes to focus on A Level studies

Mother unwell at present

Appendix 2 Normative adherence weekly summaries

Tables 23 and Table 24 show the mean observed numerator-adjusted normative adherence weekly summaries by randomised group and baseline adherence strata respectively for weeks 1 to 52 post-consent.

Table 23 Numerator-adjusted normative adherence weekly summaries (complete case)

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)

Week	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
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)
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)

Table 24 Numerator-adjusted normative adherence weekly summaries by baseline (average of weeks 1 and 2) adherence subgroup (model subset)

	0-25%				26-50%				51-75%				76-100%			
	Usual care		Intervention		Usual care		Intervention		Usual care		Intervention		Usual care		Intervention	
Week	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	98	9.6 (12.6)	74	11.8 (14.5)	59	40.4 (17.1)	52	42.1 (15.9)	59	66 (12)	64	70.3 (13.4)	73	91 (12.2)	97	91.3 (9.7)
2	102	6.9 (10.5)	76	7.3 (9.9)	59	33.6 (13.7)	54	37.1 (18.4)	60	58.1 (13.2)	65	57.5 (13.1)	74	90.6 (11.4)	98	89.5 (10.2)
3	102	10.8 (16)	76	12.2 (18.4)	59	28.6 (20.9)	54	36.2 (21.1)	60	48 (22.7)	65	53 (23.1)	74	84 (20.9)	98	84.7 (15.1)
4	101	10.4 (16.1)	75	18.4 (22.9)	59	27 (18.9)	54	30.9 (23)	60	45.5 (25.8)	65	54.2 (26.7)	74	86 (18.6)	98	84.2 (17.9)
5	99	13 (17.2)	75	20.5 (24.4)	59	27.5 (21.2)	54	34.8 (23.7)	59	47.9 (27)	65	53.2 (28.3)	73	83.5 (21.7)	98	84.7 (18.7)
6	98	12.4 (17.2)	75	22.3 (24.6)	58	26.6 (20)	54	42.5 (29.3)	59	43.9 (30.1)	65	55.6 (28.7)	73	79.7 (23.4)	98	86.9 (14.6)
7	98	12.8 (18.8)	74	23.3 (29.1)	58	24.9 (21.8)	54	41.7 (30.2)	59	43.9 (29.3)	65	56.1 (26.2)	73	79 (25.8)	98	85.3 (17.9)
8	98	13.7 (20.5)	74	22.1 (27.8)	58	23.2 (23.8)	54	41.4 (30.7)	59	43.6 (31.3)	65	58.1 (30.6)	73	79.6 (24.7)	98	82.6 (22.1)
9	98	14.5 (21.1)	73	22.7 (27.1)	57	23.7 (23.5)	54	40.9 (29.8)	59	38.8 (30.3)	65	56.9 (29.1)	73	79.6 (23.1)	98	84.1 (16.7)
10	98	13.3 (19.7)	73	21.2 (27.2)	57	23.5 (21.8)	54	43.8 (32.7)	59	38.9 (27.7)	65	57.4 (30.7)	72	78.5 (25.7)	98	82.6 (18.7)
11	97	12.3 (17.7)	73	23.3 (28.3)	57	22.4 (23.3)	54	44.5 (32.3)	59	40.3 (27)	65	57.8 (30.1)	72	78.3 (26.6)	98	83.4 (19.4)
12	97	14.3 (19.6)	73	25.9 (28.2)	57	24.4 (22.5)	54	44.4 (32.3)	59	42.1 (27.6)	65	60.5 (30.4)	72	79.4 (26.2)	98	85.2 (19.8)
13	96	15.9 (23)	72	24.6 (30)	57	26.2 (27)	54	44.9 (35.8)	59	39.7 (29.6)	65	58.6 (29.6)	72	78.3 (24.8)	98	83.1 (20.5)
14	96	15.1 (21)	72	26.4 (32.1)	57	21.8 (22.1)	54	43.4 (34.5)	59	38 (29.7)	65	56.2 (30.6)	72	78.4 (26)	96	84.2 (21)
15	95	14.1 (20.4)	71	26.9 (32.5)	57	21.2 (21.8)	54	45.4 (33.5)	59	38.3 (31.2)	65	58.1 (30.5)	72	75.9 (26.4)	96	84.7 (21.1)
16	93	14.5 (21.3)	71	26.5 (30.1)	57	21.6 (22.7)	54	43.3 (32.7)	58	37.6 (30.3)	65	57.2 (32.3)	72	74.7 (27.7)	96	83.3 (22)
17	93	13.9 (19.7)	71	26.5 (28.5)	57	24.2 (23.9)	54	45.3 (32.6)	58	41.4 (30.3)	65	57.8 (32)	72	72.1 (29.6)	96	81.2 (23.9)
18	92	12.7 (19.4)	71	27 (28.7)	57	21 (20.8)	54	46.9 (34.7)	58	38.1 (29.3)	65	56.6 (31.6)	72	73.2 (29.9)	96	76.7 (27.4)
19	92	12.5 (21.4)	71	24.3 (28.3)	57	21.8 (20.6)	54	48.3 (33.3)	58	38.9 (28)	65	56.2 (29.4)	72	74.2 (28.7)	96	82 (20.6)
20	92	12.7 (21.1)	71	24.3 (30.4)	57	18.5 (17.9)	54	43.8 (34.4)	58	37.9 (30.5)	65	57.2 (29.8)	72	74.3 (29)	96	81.7 (20)
21	91	11.7 (19.7)	71	23.3 (30.6)	56	19.4 (19.8)	54	46.9 (33.5)	58	35.6 (33)	64	54 (34.8)	72	76 (31)	96	81 (22.7)
22	91	11.5 (20.1)	70	24 (31.2)	56	22.9 (22.4)	54	45 (32.6)	58	39 (34)	64	56.8 (32.4)	72	74.7 (31.4)	96	81 (21.3)
23	91	10.7 (20.8)	70	24.5 (32.1)	56	21.2 (20.2)	54	48 (34.3)	58	36 (29.9)	64	60.2 (31.6)	72	73.9 (30.6)	96	78.9 (23.6)
24	91	11.2 (18.5)	70	25.9 (31.2)	56	21.7 (18.2)	53	47.6 (33.7)	58	36.7 (30.3)	64	58.6 (32)	71	74.6 (29.7)	96	79.2 (23.9)
25	91	11.1 (17.3)	70	26.9 (31.7)	56	23.2 (20.3)	53	46.6 (33.2)	58	37 (27.7)	64	52.3 (33.9)	71	73.8 (29.3)	96	76.7 (25.3)
26	91	11.9 (18.8)	70	28.1 (31.5)	55	25.2 (20.6)	53	46.5 (33)	58	34.3 (28.2)	64	54.9 (34.7)	71	72.8 (29.3)	96	78 (25)

	0-25%				26-50%				51-75%				76-100%			
	Usual care		Intervention		Usual care		Intervention		Usual care		Intervention		Usual care		Intervention	
Week	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
27	91	10.6 (16.8)	69	25.5 (31.2)	55	25.2 (21.8)	53	46.3 (33.2)	58	36.2 (29.1)	64	53.2 (35.2)	71	72.4 (31.8)	95	79.4 (24)
28	91	9.6 (16)	69	26 (31.6)	55	25.7 (26.5)	53	45.1 (31.4)	57	36.7 (31.4)	64	55.8 (34.8)	70	76.2 (28.1)	95	77.9 (23.7)
29	91	10.5 (17.7)	68	27.2 (31)	55	28.5 (25.6)	53	44.2 (32.3)	57	35.6 (31.2)	64	54.2 (34.9)	70	76.5 (28.6)	95	76.6 (26.2)
30	90	10.3 (17)	68	25 (30.7)	53	28.4 (25.9)	53	43.7 (32.6)	56	36.9 (33)	64	56.1 (35.8)	70	76.4 (26.9)	95	79.3 (22.2)
31	90	11.2 (18.9)	68	28.8 (31.7)	52	27 (23)	53	44.5 (34.4)	56	36.6 (31.8)	63	57 (35.3)	70	74.8 (29.3)	94	83 (20.6)
32	89	12.2 (20.4)	68	24.6 (29.2)	52	25.7 (22.2)	53	43.7 (34.2)	56	33.6 (29.8)	63	54.7 (35)	70	69.2 (31.1)	94	81.6 (21.4)
33	89	10.4 (17.7)	67	25.2 (30.4)	52	24.3 (23.3)	53	41.6 (33.4)	56	34.7 (29.7)	63	53.4 (36)	70	69.8 (32.2)	94	79.8 (24.4)
34	89	11.7 (19)	67	23.5 (29.1)	52	24.8 (19.9)	52	43.6 (33.3)	56	32.5 (28.7)	63	52.3 (35.9)	70	68.4 (32.5)	94	78.5 (24.5)
35	88	9.2 (16.8)	66	24.6 (29.5)	52	28.6 (23.1)	52	41.8 (33.8)	56	35.9 (29.5)	63	51 (36.1)	70	69.4 (33)	94	79.8 (22.8)
36	88	11.6 (19.8)	66	27 (31)	52	30.8 (28.3)	52	42.2 (34.3)	56	38.3 (30.9)	62	53.6 (37.3)	70	69.2 (32)	94	75.8 (25)
37	88	11 (18.9)	65	25.5 (28.1)	51	33.5 (30)	52	43.6 (34.9)	56	38 (29.3)	61	55.7 (35)	70	68.4 (29.5)	94	77.1 (23)
38	88	11.2 (19)	65	26.1 (29.5)	51	29.4 (26.2)	52	40.2 (34.5)	56	37.5 (31.2)	61	53 (35.5)	70	71.4 (30.5)	94	78 (23.3)
39	88	10.5 (18.7)	65	25.7 (31.1)	51	27.1 (25.6)	52	41.5 (34.7)	56	34.8 (28.2)	61	52.5 (35.1)	70	71 (31.8)	94	75.5 (28.8)
40	88	11.7 (20.1)	65	22.8 (29.4)	51	28.2 (23.4)	51	39.5 (36.1)	56	35.7 (32.2)	61	52.7 (35.6)	70	72.9 (30.4)	92	76.3 (26.5)
41	88	11 (21.2)	64	27.2 (29.9)	51	27.8 (23.6)	51	42.8 (33.5)	56	33.2 (29.2)	61	50.2 (34.6)	70	68 (31.6)	92	79.3 (23.5)
42	88	12.5 (20.4)	64	25.6 (27.9)	51	25 (22.5)	51	45.3 (34.5)	56	35 (30.7)	61	54.8 (36.3)	70	68.1 (30.8)	91	79.1 (22.9)
43	88	8.9 (17.7)	64	25.3 (30.3)	51	26.6 (23.4)	51	44.5 (34.2)	56	32.3 (30.2)	61	53.7 (34.2)	70	69.7 (33.2)	91	78 (25)
44	88	9.2 (17.9)	64	23.9 (30.4)	51	26.1 (24.1)	51	44.8 (35.5)	56	31.2 (29.7)	60	52.4 (35)	70	67.5 (32.9)	90	77.2 (25.7)
45	88	9.4 (18.9)	64	23.1 (29.9)	51	26 (24.3)	51	49.4 (35.4)	56	34.2 (30.3)	60	52.1 (34.7)	70	67.8 (33.1)	90	76.6 (24.7)
46	87	11.5 (19.1)	64	20.6 (27.5)	51	25.2 (21.8)	51	47.4 (32.8)	55	33.3 (32.4)	60	52.4 (35.1)	70	68.9 (32.9)	90	77.2 (24.7)
47	87	9.9 (17)	63	20.2 (27.7)	51	26.7 (22.7)	51	41 (35)	55	31.5 (29.4)	60	52.7 (34.8)	70	69.5 (32.7)	90	76.5 (27.1)
48	87	10.7 (18.7)	63	19.3 (27.7)	51	24.5 (25)	51	39.7 (33.1)	55	34.5 (31.2)	60	51.9 (34.7)	70	71.7 (31.9)	90	74.8 (27.8)
49	87	13 (21.5)	63	20.3 (25.2)	51	23.8 (23.5)	51	45.1 (33.2)	55	36.1 (32.2)	60	51.2 (36.3)	70	71.2 (32)	88	76.9 (25.2)
50	86	9.7 (18.7)	63	22.9 (28.1)	51	20.7 (21.6)	51	44.6 (33.5)	55	36 (33.2)	60	53.4 (34.7)	70	69.5 (33.4)	88	77.2 (23.8)
51	86	10 (19)	63	22.7 (25.4)	50	25.4 (23.8)	51	45.7 (33.2)	55	37.3 (32)	60	52.3 (34)	70	66.5 (34.8)	88	79.2 (24.2)
52	85	12.7 (22.2)	63	23.9 (27.1)	50	25.3 (22.5)	51	42.3 (32.7)	55	34.7 (31.6)	59	51.9 (34.5)	70	65.1 (36.2)	88	77 (27)

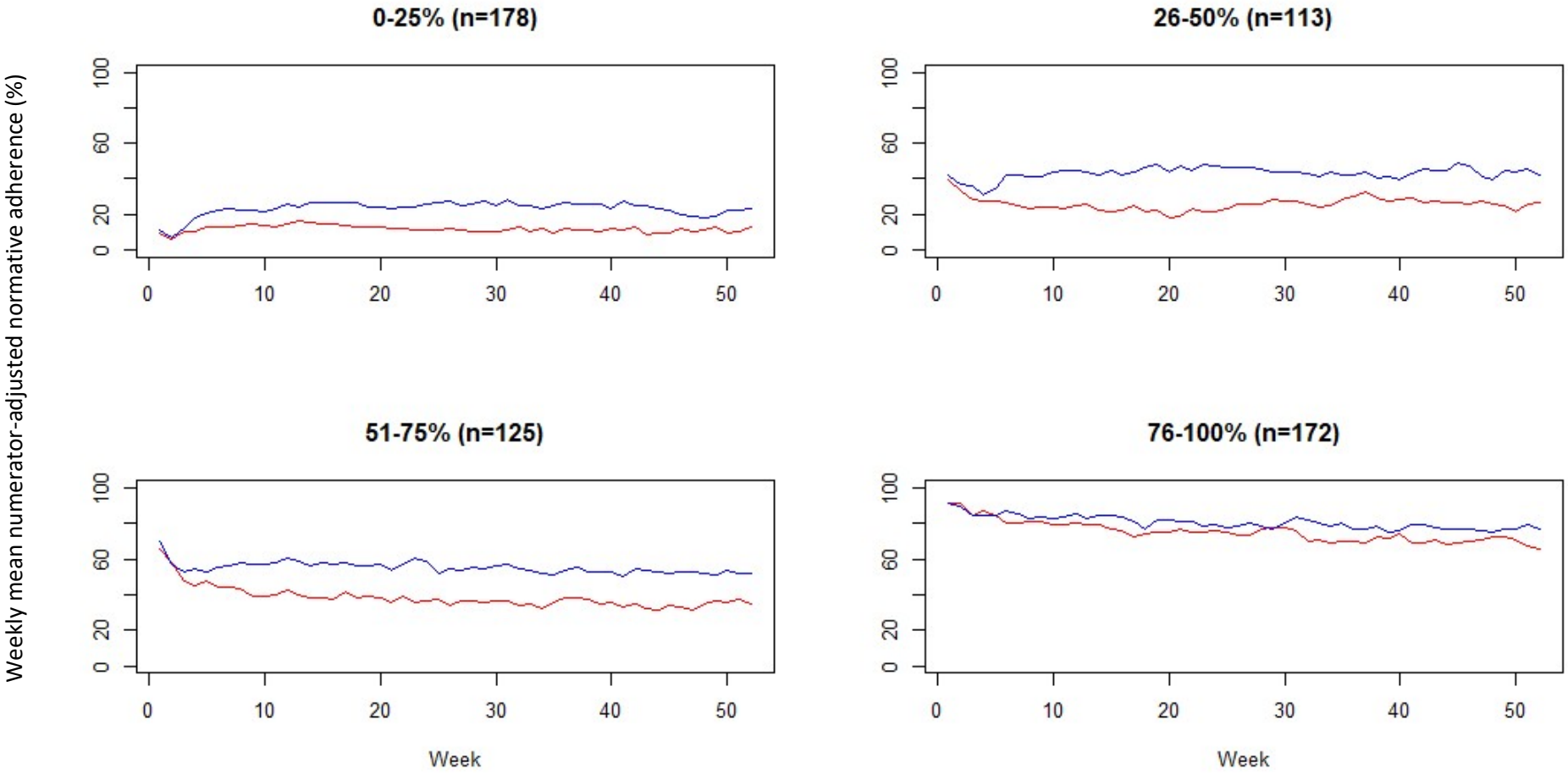

Figure 22 Weekly mean numerator-adjusted normative adherence by average baseline (weeks 1 and 2) adherence subgroup (model subset)