1. Participant Flow

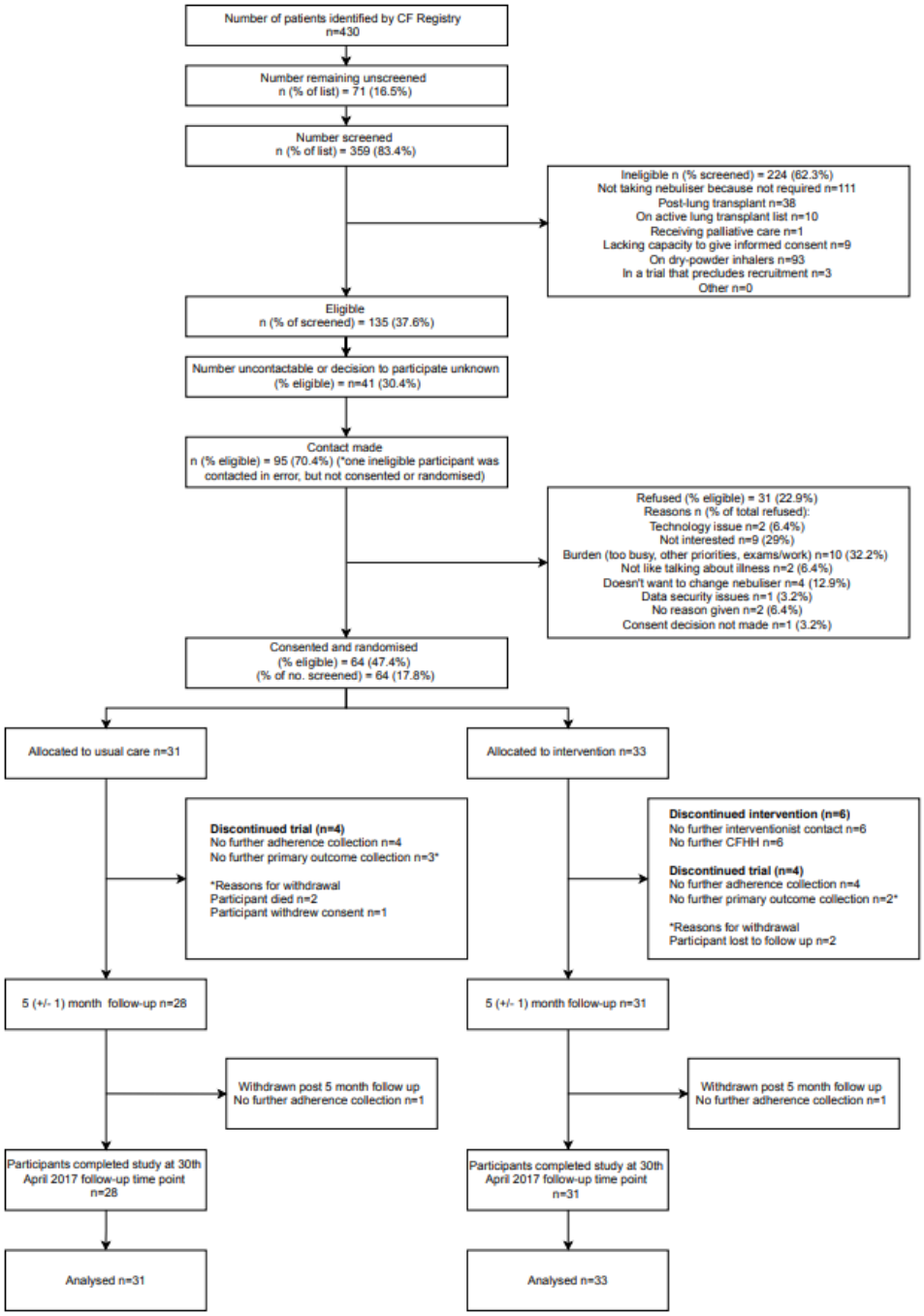

Figure 1. Study CONSORT flow diagram.

2. Baseline characteristics

Table 1. Baseline demographics by treatment arm.

	Intervention	Control	Overall
Age			
n	33	31	64
Mean(SD)	31.6(13.3)	27.8(8.9)	29.7(11.5)
Median(IQR)	28(21,37)	26(20,34)	27(21,36)
Min,Max	(16,69)	(16,50)	(16,69)
Sex			
Male	18(54.5%)	18(58.1%)	36(56.2%)
Female	15(45.5%)	13(41.9%)	28(43.8%)
Socioeconomic Status			
Most deprived	6(18.2%)	1(3.2%)	7(10.9%)
High deprivation	4(12.1%)	7(22.6%)	11(17.2%)
Average	8(24.2%)	8(25.8%)	16(25%)
Low deprivation	6(18.2%)	9(29%)	15(23.4%)
Least deprived	9(27.3%)	6(19.4%)	15(23.4%)
Weight (KG)			
n	33	31	64
Mean(SD)	65.5(18)	63.7(15.6)	64.6(16.8)
Median(IQR)	63(53,76)	62.9(49,74)	63(52.9,74.3)
Min,Max	(35,128)	(35.6,103.7)	(35,128)
Height (cm)			
n	33	31	64
Mean(SD)	168.6(10.5)	167.7(9.6)	168.2(10)
Median(IQR)	170(162,177)	168(159,175)	168.5(160.5,175.5)
Min,Max	(147,193)	(149,186)	(147,193)
BMI			
n	33	31	64
Mean(SD)	22.8(5)	22.4(4.3)	22.6(4.6)
Median(IQR)	22.2(19.7,25.3)	22.1(19.1,25.4)	22.1(19.55,25.35)
Min,Max	(15.8,42.8)	(16,33.9)	(15.8,42.8)

Table 2. Baseline cystic fibrosis (CF) measures by treatment arm.

	Intervention	Control	Overall
No. of IV days in previous 12 months			
n	33	31	64
Mean(SD)	26.3(25.7)	26(22.1)	26.2(23.8)
Median(IQR)	17(7,44)	28(0,44)	17(7,44)
Min,Max	(0,117)	(0,70)	(0,117)
No. of participants requiring IV days in previous 12 months			
At least 1 IV day	26(78.8%)	23(74.2%)	49(76.6%)
Days since last IV start date			
n	31	28	59
Mean(SD)	168.7(245.2)	202.3(325.2)	184.6(283.9)
Median(IQR)	75(45,194)	100(24.5,219.5)	91(39,213)
Min,Max	(6,1085)	(7,1575)	(6,1575)
FEV1			
n	33	31	64
Mean(SD)	2(0.8)	2.3(1)	2.1(0.9)
Median(IQR)	1.9(1.4,2.4)	2.1(1.6,2.8)	1.9(1.5,2.7)
Min,Max	(0.8,4)	(0.6,5)	(0.6,5)
FEV1 % Predicted			
n	33	31	64
Mean(SD)	53.4(19.4)	61.4(22.7)	57.3(21.3)
Median(IQR)	49.2(39.4,61.9)	53.4(43,80)	49.6(41.9,76.7)
Min,Max	(26,103)	(23.2,100.7)	(23.2,103)
Clinician pseudomonas status			
Negative	15(45.5%)	8(26.7%)	23(36.5%)
Intermittent	3(9.1%)	3(10%)	6(9.5%)
Chronic	15(45.5%)	19(63.3%)	34(54%)
Leeds Criteria pseudomonas status			
Negative	15(45.5%)	10(33.3%)	25(39.7%)
Intermittent	4(12.1%)	4(13.3%)	8(12.7%)
Chronic	14(42.4%)	16(53.3%)	30(47.6%)
Subjective adherence			
n	23	20	43
Mean(SD)	65.6(40.1)	67.8(35.4)	66.6(37.6)
Median(IQR)	90(20,99)	80(45,99.5)	90(35,99)
Min,Max	(0,100)	(0,100)	(0,100)
Simple normative adherence (first 2 weeks)			
n	33	31	64
Mean(SD)	0.5(0)	0.5(0)	0.5(0)
Median(IQR)	0.5(0.5,0.5)	0.5(0.5,0.5)	0.5(0.5,0.5)
Min,Max	(0.5,0.5)	(0.5,0.5)	(0.5,0.5)
Treatment Burden			
Low	10(30.3%)	11(35.5%)	21(32.8%)
Medium	16(48.5%)	12(38.7%)	28(43.8%)

High	2(6.1%)	5(16.1%)	7(10.9%)

IV= Intravenous antibiotic, FEV1= Forced expiratory volume in 1 second, FEV1 % predicted = between-group adjusted mean differences for lung function

Table 3. Baseline outcome measures by treatment arm.

	Intervention	Control	Overall
EQ5D-5L			
n	33	31	64
Mean(SD)	0.866(0.121)	0.822(0.151)	0.845(0.137)
Median(IQR)	0.901(0.767,0.951)	0.825(0.737,0.942)	0.872(0.752,0.946)
Min,Max	(0.53,1)	(0.486,1)	(0.486,1)
PAM-13			
n	33	31	64
Mean(SD)	60.4(11.2)	60(13.2)	60.2(12.1)
Median(IQR)	60.6(53.2,67.8)	58.1(48.9,67.8)	60.6(51,67.8)
Min,Max	(36.8,84.8)	(38.1,90.7)	(36.8,90.7)
CHAOS			
n	33	31	64
Mean(SD)	9.8(3.4)	10.1(4)	10(3.7)
Median(IQR)	10(8,11)	10(7,12)	10(8,11)
Min,Max	(4,18)	(4,20)	(4,20)
MAD-3			
n	32	30	62
Mean(SD)	9.8(3.3)	9(3.4)	9.4(3.4)
Median(IQR)	9(8,12.5)	9.5(6,11)	9(8,12)
Min,Max	(3,15)	(3,15)	(3,15)
SRBAI			
n	33	30	63
Mean(SD)	11.5(4.9)	10.2(5.6)	10.9(5.2)
Median(IQR)	12(8,16)	9(4,14)	10(7,15)
Min,Max	(4,20)	(4,20)	(4,20)
GAD-7			
n	33	31	64
Mean(SD)	4.1(4.5)	3.8(3.6)	3.9(4)
Median(IQR)	3(0,5)	3(1,7)	3(0.5,5.5)
Min,Max	(0,15)	(0,11)	(0,15)
PHQ-8			
n	33	31	64
Mean(SD)	7(4.9)	6.5(5.2)	6.8(5)
Median(IQR)	6(3,12)	6(3,8)	6(3,10.5)
Min,Max	(0,16)	(0,18)	(0,18)

EQ5D-5L= EuroQual 5-dimensional measure of health status, PAM-13=13-item Patient Activation Measure, CHAOS= Confusion, Hubbub and Order measure, MAD-3=3-item measure of patient Medication Adherence, SRBAI= Self-Report Behavioural Automaticity Index, GAD-7= 7-item Generalised Anxiety Disorder questionnaire, PHQ-8= 8-item Patient Health Questionnaire.

Table 4. Baseline Cystic Fibrosis Questionnaire-Revised (CFQ-R) domains by treatment arm.

	Intervention	Control	Overall
Physical Functioning			
n	33	31	64
Mean(SD)	48.5(34.8)	49.2(30.8)	48.9(32.7)
Median(IQR)	38(25,88)	42(17,83)	42(21,85.5)
Min,Max	(0,100)	(0,100)	(0,100)
Emotional Functioning			
n	33	31	64
Mean(SD)	70.2(21.1)	62.3(26.1)	66.4(23.8)
Median(IQR)	67(53,93)	67(40,80)	67(53,87)
Min,Max	(27,100)	(7,100)	(7,100)
Eating			
n	33	31	64
Mean(SD)	79.9(24.8)	74.6(27.7)	77.3(26.2)
Median(IQR)	89(67,100)	78(56,100)	89(61.5,100)
Min,Max	(0,100)	(0,100)	(0,100)
Social Functioning			
n	33	31	64
Mean(SD)	65(20.3)	59.6(26.2)	62.4(23.3)
Median(IQR)	67(50,78)	61(44,83)	67(44,83)
Min,Max	(17,100)	(11,100)	(11,100)
Body Image			
n	33	31	64
Mean(SD)	68.5(27.3)	64.9(31.7)	66.7(29.3)
Median(IQR)	78(56,89)	67(44,100)	78(44,89)
Min,Max	(0,100)	(0,100)	(0,100)
Treatment Burden			
n	33	31	64
Mean(SD)	50.5(16.5)	51.6(25.9)	51(21.4)
Median(IQR)	44(44,67)	56(33,67)	50(44,67)
Min,Max	(11,78)	(0,100)	(0,100)
Respiratory			
n	33	31	64
Mean(SD)	53.5(27.5)	54(27.3)	53.7(27.2)
Median(IQR)	50(33,78)	56(33,78)	56(33,78)
Min,Max	(0,100)	(6,100)	(0,100)
Digestion			
n	33	31	64
Mean(SD)	77.9(16.9)	80.4(26.4)	79.1(21.9)
Median(IQR)	78(67,89)	89(78,100)	89(67,100)
Min,Max	(44,100)	(0,100)	(0,100)
Role Functioning			
n	33	31	64
Mean(SD)	65.2(24.3)	64(25.9)	64.6(24.9)

Median(IQR)	67(50,83)	67(42,83)	67(50,83)
Min,Max	(0,100)	(8,100)	(0,100)
Vitality			
n	33	31	64
Mean(SD)	37.8(22.8)	40.6(22)	39.2(22.3)
Median(IQR)	33(17,50)	42(25,58)	42(25,58)
Min,Max	(8,92)	(0,75)	(0,92)
Health Perceptions			
n	33	31	64
Mean(SD)	47.8(27.7)	51.6(24.9)	49.6(26.3)
Median(IQR)	44(22,67)	56(33,67)	44(33,67)
Min,Max	(0,100)	(0,100)	(0,100)
Weight			
n	33	31	64
Mean(SD)	70.7(36.1)	63.4(39.8)	67.2(37.9)
Median(IQR)	100(33,100)	67(33,100)	83.5(33,100)
Min,Max	(0,100)	(0,100)	(0,100)

Table 5. Baseline Capability Opportunity Motivation Behaviour Beliefs Questionnaire (COM-BMQ) domains by treatment arm.

	Intervention	Control	Overall
COM BMQ Necessities			
n	33	31	64
Mean(SD)	3.2(0.7)	3.4(0.8)	3.3(0.8)
Median(IQR)	3.1(2.7,3.7)	3.3(2.9,4.1)	3.1(2.7,4)
Min,Max	(2,4.9)	(2,4.7)	(2,4.9)
COM BMQ Concerns			
n	33	31	64
Mean(SD)	2.1(0.6)	2.2(0.6)	2.1(0.6)
Median(IQR)	2.1(1.5,2.6)	2.1(1.7,2.6)	2.1(1.6,2.6)
Min,Max	(1.2,3.4)	(1.1,3.3)	(1.1,3.4)

3. Outcome measures

At study completion on 30th April 2017: 60 (94%: Intervention=32, Control =28) participants contributed exacerbation data; 57 (89%: Intervention=30, Control=27) contributed FEV1 data; 59 (92%: Intervention=31, Control=28) contributed follow-up questionnaire data and 48 (75%: Intervention=24, Control=24) contributed 5 (±1) months of adherence data.

3.1 Primary outcome measures.

"Number of pulmonary exacerbations of cystic fibrosis is measured using the modified Fuchs Criteria at baseline and 5 (+/-1) months."

Table 6. Summary of exacerbation data by treatment arm.

	Intervention	Control
n	32	28
Exacerbations meeting Fuch's criteria	35	25
Median number of exacerbations per patient	1	0.5
n (%) experiencing at least 1 exacerbation	19 (60%)	14 (50%)
IV days per exacerbation in 6 months		
n	35	25
Mean (SD)	13.6(4.2)	13.7(3.3)
Median (IQR)	14(13,14)	14(13,15)
Min, Max	(2,30)	(7,21)
IV days per participant with exacerbations in 6 months		
n	19	14
Mean (SD)	13.4(2.7)	13.6(3.2)
Median (IQR)	14(11,14)	14(13,15)
Min, Max	(9,21.7)	(8,20)
IV days per exacerbation in whole study		
n	45	36
Mean (SD)	13.7(4.1)	13.9(3.1)
Median (IQR)	14(13,14)	14(13,15)
Min, Max	(2,30)	(7,21)

Table 7. Summary of Fuchs criteria for the exacerbations that were included in the primary outcome (IV days and at least 1 Fuchs criteria in 6 month follow up period).

Description	
Exacerbations included in primary analysis	
n (%) with IV and at least 1 Fuchs	60 (60 %)
Mean (SD) number of Fuchs criteria	4.8 (2.1)
Median (IQR) number of Fuchs criteria	4 (4 , 6)
Min, max number of Fuchs criteria	(1,10)
n (%) of exacerbations with at least 2 Fuchs criteria	58 (96.7 %)
n (%) of exacerbations with at least 3 Fuchs criteria	48 (80 %)
n (%) of exacerbations with at least 4 Fuchs criteria	46 (76.7 %)
n (%) of exacerbations with at least 5 Fuchs criteria	29 (48.3 %)
n (%) of exacerbations with at least 6 Fuchs criteria	20 (33.3 %)
n (%) of exacerbations with at least 7 Fuchs criteria	12 (20 %)
n (%) of exacerbations with at least 8 Fuchs criteria	8 (13.3 %)
n (%) of exacerbations with at least 9 Fuchs criteria	3 (5 %)
n (%) of exacerbations with at least 10 Fuchs criteria	1 (1.7 %)

3.2 Secondary outcome measures.

"1. Generic health status is measured using the EQ5D5L at baseline and 5 (+/- 1) months

2. Assessment of patient knowledge, skill, and confidence for self-management is measured using the Patient Activation Measure -13 at baseline and 5 (+/- 1) months

3. Life chaos is measured using the Confusion, Hubbub And Order Scale -6 at baseline and at 5 +/- 1 months

4. Habit-based behaviour patterns are measured using the Self-Reported Behavioural Automaticity Index at baseline and 5 (+/- 1) months

5. Disease specific health-related quality of life is measured using the Cystic Fibrosis Questionnaire-Revised at baseline and 5 (+/- 1) months

6. Depressive disorder severity is measured using the Patient Health Questionnaire depression scale -8 at baseline and 5 (+/- 1) months

7. Medication adherence is measured using the Medication Adherence Data -3 at baseline and 5 (+/- 1) months

8. Anxiety severity is measured using the General Anxiety Disorder -7 at baseline and 5 (+/- 1) months

9. Perceived necessities and concerns for nebuliser treatment are measured using the Capability Opportunity Motivation–Beliefs about Medicines Questionnaire at baseline and 5 (+/- 1) months

10. Resource use data is collected using the resource use form developed for the study at 5 (+/- 1) months

11. Acceptability of the intervention is determined through qualitative interviews with patients and members of the multidisciplinary CF team at 5 (+/- 1) months

12. Condition severity is measured using FEV1/FVC at routine clinic visits from baseline to study end"

Table 8. Summary of patient-reported outcome measures used in secondary analyses.

	n Intervention	Median (IQR)	Mean (SD)	n Control	Median (IQR)	Mean (SD)	Mean Diff	95% CI
FEV1 Unadjusted	30	1.8(1.17,2.83)	2(0.9)	27	1.9(1.46,2.83)	2.2(1)	-0.21	(-0.73,0.3)
FEV1 Adjusted							0.22	(-0.062,0.51)
FEV1 % Unadjusted	30	51.8(33.46,71.26)	54.2(21.1)	27	50.9(42.49,77.97)	59(23.9)	-4.8	(-17,7.1)
FEV1 % Adjusted							5	(-2,12)
BMI Unadjusted	18	20.5(19.5,26)	22.1(4.2)	15	23.4(20.7, 26.2)	23.8(3.5)	-1.7	(-4.5,1.1)
BMI Adjusted							-0.08	(-1,0.89)
EQ5D-5L Unadjusted	31	0.9(0.76,0.95)	0.9(0.2)	27	0.9(0.77,1)	0.9(0.2)	-0.00062	(-0.084,0.083)
EQ5D-5L Adjusted							-0.016	(-0.087,0.055)
PAM-13 Unadjusted	31	63.1(51,67.8)	58.5(14.3)	28	58.1(51,63.1)	57.9(9.9)	0.56	(-5.9,7)
PAM-13 Adjusted							0.046	(-5.8,5.9)
CHAOS Unadjusted	31	9(7,13)	9.9(3.9)	28	9(7.5,11.5)	9.4(3.3)	0.55	(-1.4,2.4)
CHAOS Adjusted							0.79	(-0.47,2.1)
MAD-3 Unadjusted	31	12(9,13)	10.8(3.9)	26	9.5(7,13)	9.4(3.6)	1.4	(-0.58,3.4)
MAD-3 Adjusted							0.82	(-0.51,2.1)
SRBAI Unadjusted	31	13(8,16)	12.1(5.3)	28	10.5(6,15.5)	10.6(5)	1.4	(-1.3,4.1)
SRBAI Adjusted							0.15	(-1.8,2.1)
GAD-7 Unadjusted	31	3(1,6)	4.1(4.1)	28	2.5(0,7)	4.2(4.4)	-0.05	(-2.3,2.2)
GAD-7 Adjusted							-0.31	(-1.9,1.3)
PHQ-8 Unadjusted	31	7(4,12)	7.3(5.2)	28	4(1.5,7)	5.3(5.1)	2	(-0.68,4.7)
PHQ-8 Adjusted							0.97	(-0.96,2.9)
COM-BMQ Concerns Unadjusted	31	2(1.5,2.3)	1.9(0.5)	27	2.1(1.9,2.4)	2.1(0.5)	-0.22	(-0.48,0.026)
COM-BMQ Concerns Adjusted							-0.21	(-0.38,-0.048)
COM BMQ Necessities Unadjusted	31	3.4(3,4)	3.5(0.6)	27	3.4(2.9,4)	3.5(0.7)	0.011	(-0.35,0.37)
COM BMQ Necessities Adjusted							0.12	(-0.16,0.4)

Table 9. Cystic Fibrosis Questionnaire- Revised (CFQ-R) measure of cystic fibrosis symptoms.

	n Intervention	Median (IQR)	Mean (SD)	n Control	Median (IQR)	Mean (SD)	Mean Diff	95% CI
CFQ-R Physical Unadjusted	31	54(25,88)	54.4(31.6)	28	62.5(33,92)	60.9(31.2)	-6.4	(-23,10)
CFQ-R Physical Adjusted							-2.6	(-13,7.4)
CFQ-R Emotional State Unadjusted	31	67(53,93)	68.3(23.4)	28	73(56.5,90)	72.3(22.7)	-4	(-16,8)
CFQ-R Emotional State Adjusted							-7.7	(-16,0.55)
CFQ-R Eating Unadjusted	31	89(67,100)	80.7(21.6)	28	83.5(67,100)	79.9(20.7)	0.85	(-10,12)
CFQ-R Eating Adjusted							1.1	(-6.5,8.7)
CFQ-R Social Unadjusted	31	67(56,78)	65.4(15.8)	28	64(50,83)	66.4(20.9)	-1	(-11,8.6)
CFQ-R Social Adjusted							-3.7	(-10,2.8)
CFQ-R Body Image Unadjusted	31	78(67,89)	73.3(23.8)	28	78(56,100)	73.1(25.5)	0.19	(-13,13)
CFQ-R Body Image Adjusted							0.62	(-7.2,8.5)
CFQ-R Treatment Burden Unadjusted	31	56(44,67)	56.5(16.6)	28	56(44,67)	57.3(19.9)	-0.83	(-10,8.7)
CFQ-R Treatment Burden Adjusted							1.2	(-6.4,8.8)
CFQ-R Respiratory Unadjusted	31	67(44,78)	59.5(25.2)	27	67(50,83)	65.6(22.7)	-6.1	(-19,6.6)
CFQ-R Respiratory Adjusted							-4.4	(-14,4.8)
CFQ-R Digestion Unadjusted	31	89(67,100)	81.1(18.4)	27	89(78,100)	84.4(23.5)	-3.3	(-14,7.7)
CFQ-R Digestion Adjusted							-2.3	(-11,6.2)
CFQ-R Role Unadjusted	31	75(33,83)	64.8(26.1)	27	75(56,92)	70.3(21.5)	-5.6	(-18,7.1)

CFQ-R Role Adjusted							-8.2	(-17,0.4)
CFQ-R Vital Unadjusted	31	42(25,42)	38.5(19.5)	28	50(33,62.5)	48.7(23)	-10	(-21,0.81)
CFQ-R Vital Adjusted							-7	(-15,0.99)
CFQ-R Health Unadjusted	31	44(22,67)	45.5(25.4)	28	61.5(33,72.5)	56.8(27.6)	-11	(-25,2.6)
CFQ-R Health Adjusted							-6.5	(-16,2.8)
CFQ-R Weight Unadjusted	31	89(67,100)	81.1(18.4)	27	89(78,100)	84.4(23.5)	-3.3	(-14,7.7)
CFQ-R Weight Adjusted							-2.3	(-11,6.2)

3.3 Qualitative interviews.

Interviews were conducted with intervention (n=14) and control (n=5) participants, interventionists (n=3) and CF team members (n=5).

Interviews generated theories explaining low adherence in intervention participants. In particular, interventionists delivered insufficient numbers of review sessions to identify and address low motivation. Concentration on participant recruitment left site staff insufficient time for key intervention procedures. The process evaluation led to 25 key changes to RCT and intervention procedures, including targeting intervention review sessions at participants with lower adherence.

4. Adverse events and Serious Adverse Events

A total of 8 adverse events (AEs) occurred during the trial and 7 participants (10.9%) had a least one AE; 5 of these were deemed to be Serious Adverse Events (SAEs). None of the SAEs were related to the intervention.

Table 10. Summary of adverse events recorded during the study

	Intervention n (%)	Control n (%)	Overall n (%)
All Adverse Events	5	3	8
Participants with at least 1 AE	4(12.1%)	3(9.7%)	7(10.9%)
Type of Adverse Event			
Chest pain or chest discomfort	1(25%)	0(0%)	1(14.3%)
Voice change or Alteration	0(0%)	0(0%)	1(14.3%)
Other	4(100%)	2(66.7%)	6(85.7%)

Table 11.1 Summary of serious adverse events recorded during the study

	Intervention n (%)	Control n (%)	Overall n (%)
All Serious Adverse events	3(9.1%)	2(6.5%)	5(7.8%)
Level of Seriousness			
Death	0(0%)	2(100%)	2(40%)
Hospitalisation	2(66.7%)	0(0%)	2(40%)
Persistent or significant disability/incapacity	1(33.3%)	0(0%)	1(20%)
Frequency			
Isolated	2(66.7%)	2(100%)	4(80%)
Continuous	1(33.3%)	0(0%)	1(20%)
Intensity			
Moderate	3(100%)	0(0%)	3(60%)
Severe	0(0%)	2(100%)	2(40%)
Outcome			
Recovered	1(33.3%)	0(0%)	1(20%)
Improved	2(66.7%)	0(0%)	2(40%)
Death	0(0%)	2(100%)	2(40%)
Expected SAE			
No	3(100%)	2(100%)	5(100%)
Related to Intervention			
No	3(100%)	2(100%)	5(100%)