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Original research

Self-management intervention to reduce pulmonary exacerbations by supporting treatment adherence in adults with cystic fibrosis: a randomised controlled trial

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ABSTRACT

Introduction Recurrent pulmonary exacerbations lead to progressive lung damage in cystic fibrosis (CF). Inhaled medications (mucoactive agents and antibiotics) help prevent exacerbations, but objectively measured adherence is low. We investigated whether a multi-component (complex) self-management intervention to support adherence would reduce exacerbation rates over 12 months.

Methods Between October 2017 and May 2018, adults with CF (aged ≥16 years; 19 UK centres) were randomised to the intervention (data-logging nebulisers, a digital platform and behavioural change sessions with trained clinical interventionists) or usual care (data-logging nebulisers). Outcomes included pulmonary exacerbations (primary outcome), objectively measured adherence, body mass index (BMI), lung function (FEV_1) and Cystic Fibrosis Questionnaire-Revised (CFQ-R). Analyses were by intent to treat over 12 months.

Results Among intervention (n=304) and usual care (n=303) participants (51% female, median age 31 years), 88% completed 12-month follow-up. Mean exacerbation rate was 1.63/year with intervention and 1.77/year with usual care (adjusted ratio 0.96; 95% CI 0.83 to 1.12; p=0.64). Adjusted mean differences (95% CI) were in favour of the intervention versus usual care for objectively measured adherence (9.5% (8.6% to 10.4%)) and BMI (0.3 (0.1 to 0.6) kg/m^2), with no difference for $\%FEV_1$ (1.4 (−0.2 to 3.0)). Seven CFQ-R subscales showed no between-group difference, but treatment burden reduced for the intervention (3.9 (1.2 to 6.7) points). No intervention-related serious adverse events occurred.

Conclusions While pulmonary exacerbations and FEV_1 did not show statistically significant differences, the intervention achieved higher objectively measured adherence versus usual care. The adherence difference might be inadequate to influence exacerbations, though higher BMI and lower perceived CF treatment burden were observed.

Key messages

What is the key question?

► Can a multi-component self-management intervention increase and sustain adherence to inhaled therapies among adults with cystic fibrosis (CF) and does the intervention impact on exacerbation rates?

What is the bottom line?

► The intervention did not show a statistically significant difference in exacerbation rates versus usual care but achieved higher objectively measured adherence to inhaled medications (sustained over 12 months), higher body mass index and lower perceived CF treatment burden.

Why read on?

► This is the largest self-management intervention trial in CF, with 607 participants, and the only trial thus far to demonstrate a sustained difference in adherence versus a control arm, using a theory-based approach including habit formation.

INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic long-term condition (LTC) whereby recurrent pulmonary exacerbations drive progressive lung damage leading to premature death. Inhaled mucoactive agents and antibiotics have proven efficacy in reducing exacerbation frequency.[1 2] CF is therefore an archetypal LTC; a cure is unavailable though efficacious treatments exist to improve health outcomes.

Low medication adherence, described by the WHO as 'a worldwide problem of striking magnitude'[3] is an important cause of treatment failure, poor health outcomes and increased healthcare costs in LTCs. In CF, low adherence to inhaled therapies is associated with more frequent and costly rescue treatments of exacerbations.[4] Real-world

Table 1 Description of the intervention

TIDieR category	Description of the CFHealthHub intervention
	CFHealthHub digital platform (website and smartphone application) that: (1) displays real-time objective adherence data from the nebulisers to the participant and care team, (2) provides behavioural change tools and content (comprises of six modules, see 1)) in a 'My Toolkit' area designed to increase motivation for adherence, to address capability and opportunity barriers and to build habits for taking treatments, and (3) includes an intervention manual, with procedures and worksheets for use by clinical interventionists in their interactions with participants. Behaviour change sessions where the content and behaviour change techniques within each of the six modules were delivered through the participant interactions with site's interventionist.
Why	CFHealthHub aims to support adults with CF to increase adherence to nebuliser treatment using the COM-B framework and to build habits for treatment to enable maintenance.
Who	Interventionists were healthcare professionals employed for the trial (n=32), 18 of whom job shared (with clinical roles in the CF team) and 26 were existing members of the centre's CF multidisciplinary team. There was the WTE of eight physiotherapists, three psychologists, six specialist CF nurses, one pharmacist and one dietitian; that is, one WTE interventionist per centre.
How and where	All intervention sessions were structured by a worksheet to guide delivery and delivered with a person-centred communication style. First intervention sessions were always face to face; review sessions were face to face or by telephone.
When and how much	Intervention participants had access to the digital platform and received tailored flexible support from the interventionist throughout the 12-month trial period. All intervention participants received a first and intermediate review visit, thereafter support was tailored according to response (figure 1; further details in online supplemental 1appendix A). Participants with baseline objectively measured effective adherence ≤80% underwent a normal pathway of six sessions (1× first intervention visit 40–60 min; 2× intermediate reviews 5–15 min; 2× reviews 30–45 min; 1× phase review 20–30 min) over 12 weeks, with phase reviews every 12 weeks thereafter, or every 6 weeks for participants with baseline adherence <25%. Participants with baseline objectively measured effective adherence >80% followed a 'very high adherence' pathway of three sessions (1× first intervention visit; 1× intermediate review; 1× phase review), with phase reviews every 12 weeks thereafter. Following these initial pathways, additional blocks of sessions were offered when: (1) a participant requested further support; (2) a participant's adherence reduced by ≥20% in a 4-week period; or (3) a participant received intravenous antibiotics for an exacerbation.
Tailoring	Each session was tailored to an individual's needs based on: their nebulised medication prescription; their necessity and concern beliefs (BMQ-Specific); and their discussions with interventionists about their motivation and specific capability and opportunity barriers to adherence. For example, the goal setting and review and treatment plan modules are used only for participants who are motivated to increase their treatment adherence and participants with very low motivation spend more time focusing on the my treatment module and on relationship building with the interventionist. While the entire content of the digital platform was available for participants to browse, tailored/personalised aspects were added to the 'My Toolkit' area. For example, content addressing particular participant concerns about treatment, and personal action and coping plans.
Modifications	There were no major changes to the delivery of the intervention through the study.
How well	Fidelity of intervention delivery was assessed throughout the study with two reviewers independently assessing a sample of audio-recording and worksheets from sessions (first intervention session, review, phase review) using a scoring sheet (further details in online supplemental appendix A).

BMQ-Specific, beliefs and medications questionnaire-specific; CF, cystic fibrosis; COM-B, capability opportunity motivation-behaviour; TIDieR, template for intervention description and replication; WTE, whole time equivalent.

objectively measured adherence of 30%–50% is lower than that of 80%–100% usually observed in clinical trials.[5] Therefore, people with CF are unlikely to derive optimal benefit from inhaled therapies.[5–10] At the same time, perceived treatment burden is high among people with CF[11] and the James Lind Alliance Priority Setting Partnership identified 'effective ways of simplifying treatment burden' as the top CF research priority.[12]

Developing strategies to increase adherence is another CF research priority[12] and could improve health outcomes by reducing exacerbation rates.[6] Insufficient evidence exists to promote any particular adherence strategy.[13] Large randomised controlled trials evaluating adherence interventions in CF continue to present negative findings,[14] possibly because interventions are generally under-theorised and insufficiently tailored to individual needs.[15] In addition, objectively measured adherence is largely absent in routine CF care, while self-reported and clinician estimates of adherence are notoriously unreliable,[8] which prevents effective diagnosis, prescribing and provision of person-specific adherence support.

The Capability Opportunity Motivation-Behaviour model, based on a synthesis of frameworks of behavioural change, predicts that treatment taking depends on capability, opportunity and motivation.[16] Reflective motivation is largely dependent on perceived necessity of adherence and treatment concerns[17] and can be increased through education, persuasion and confidence building. For those motivated to adhere, increasing awareness of their objectively measured adherence through self-monitoring increases capability, that is, making visible the gap between objective and subjective adherence.[8] Problem-solving techniques can be used to overcome individual capability and opportunity barriers. Theories of behavioural maintenance[18] predict that supporting people to create habits for treatment, that is, taking treatments in response to specific contextual cues, can help to sustain adherence and to lower perceived treatment burden.[19] We developed a multi-component (complex) self-management intervention to support sustained treatment adherence,[20] incorporating objective adherence measurement, underpinned by behavioural science theory and designed to address gaps in CF care, with extensive input from people with CF. Since exacerbations are disruptive to patient life, they are an important patient-centred outcome and are commonly considered to indicate lung health.[21] Therefore, the objective of this 12-month randomised controlled trial was to investigate the effectiveness of this multi-component self-management intervention compared with usual care in adults with CF using pulmonary exacerbation incidence rate as the primary outcome.

METHODS

Study design, clinical interventionists and participants

We conducted a two-arm, open-label, parallel-group, usual care-controlled randomised clinical trial at 19 UK CF centres (trial registration ISRCTN55504164). The protocol (ethical approval REC: 17/LO/0035, IRAS ID: 218519) and statistical

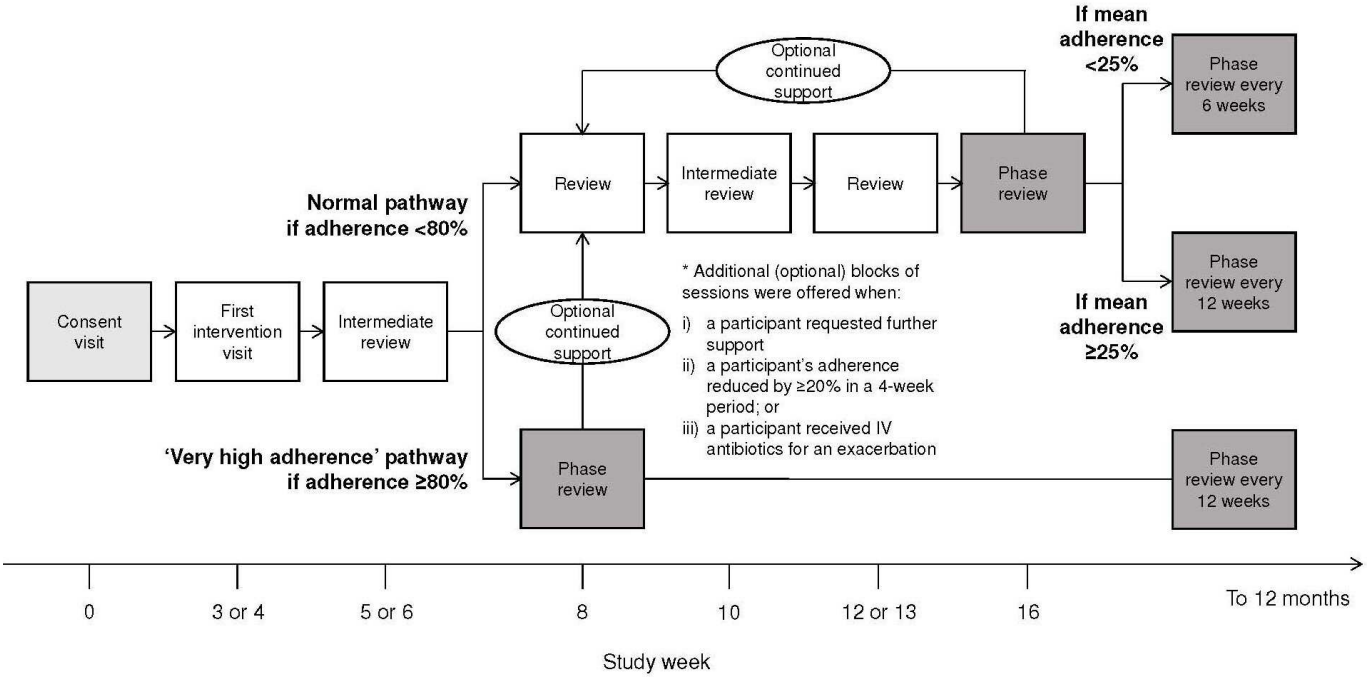

Figure 1 Schedule of intervention delivery: normal and 'very high adherence' pathways. Adherence level to reflect baseline was calculated using objectively measured effective adherence data from weeks 1 and 2, as stated in the 'Methods'.

analysis plan (SAP) are available as supplementary material. The complex behavioural change intervention is designed to increase and sustain adherence to inhaled therapies. The development of the intervention is described elsewhere.[22] Table 1 summarises the intervention, and further descriptions are in online supplemental appendix A. The study was monitored by an independent Trial Steering Committee. Data analysis was performed by the School of Health and Related Research, Sheffield. All authors vouch for fidelity to the protocol.

Full-time interventionists (table 1) were employed and trained to deliver the intervention, underwent competency assessments (a theory test; practical assessments at first intervention visit, review and phase review) and received ongoing support (as detailed in online supplemental appendix A).

Participants were identified from the CF Registry, a UK database of people with CF. Potential participants were contacted by their usual clinical care team to seek permission for interventionists to discuss involvement. Eligible participants were aged ≥16 years and willing to take all inhaled mucoactive agents and antibiotics via eFlow Technology nebulisers with eTrack data-logging Controllers (PARI Pharma GmbH, Starnberg, Germany). Participants were excluded if: on the active lung transplant list; post-lung transplant; receiving care primarily palliative in intent; or using inhaled dry powder devices. All participants provided written, informed consent.

Randomisation and masking

Participants were allocated 1:1 to the intervention or usual care using a computer-generated pseudorandom list with random-permuted blocks of randomly varying sizes, via a central, web-based randomisation system. The allocation sequence was hosted by the Sheffield Clinical Trials Research Unit, with the sequence created by a statistician (not otherwise involved with trial) and held on a secure server. After recruiting each participant, the interventionist logged into the server and entered basic demographic information, then the allocation was revealed to the participants. Stratification was by centre and number of past year intravenous antibiotic days (≤14 and >14) – a predictor of current year intravenous days.[23] The trial statistician remained blind to treatment allocation until database freeze. Participants and health professionals collecting primary outcome data were not blinded.

Treatment arms

All participants were given eTrack data-logging Controllers for their eFlow Technology nebulisers, which sent time-stamped and date-stamped data to a 2net Hub (Capsule Technologies, San Diego, California, USA) for accurate recording of inhalation and adherence calculation.

Intervention participants had access to the CFHealthHub digital platform (website and smartphone application) and received tailored flexible support from the interventionist throughout the 12-month trial period (table 1 and figure 1; further details in online supplemental appendix A).

The usual care arm used eTrack data-logging Controllers for adherence data collection. Contamination was minimised since there was no access to CFHealthHub, behavioural change tools and content. Adherence results were also invisible to participants and care teams.

At the final visit (at 12 months) or when a participant dropped out in either arm, a systems check was performed to ensure that all adherence data had been transferred from the eTrack data-logging Controller, thereby minimising missing data. The eTrack can store 3000 inhalations, which exceed the annual total number of doses even when the maximum prescription of eight daily doses occurred (table 2 gives prescribed doses), ensuring no missing data if eTrack was downloaded at the end of trial.

Outcomes

The primary outcome was the pulmonary exacerbation incidence rate over 12 months. Using modified Fuchs' criteria,[24] an

Table 2 Baseline demographic and clinical characteristics, by randomised treatment group

	Usual care		Intervention	
	N*	Mean±SD†	N*	Mean±SD†
Female, n (%)	303	154 (50.8)	304	156 (51.3)
Age, years	303	30.3±10.8	304	31.1±10.6
Prescribed number of daily nebuliser doses, n (%)				
1	298	60 (20.1)	303	85 (28.1)
2	298	49 (16.4)	303	39 (12.9)
3	298	93 (31.2)	303	91 (30.0)
4	298	38 (12.8)	303	32 (10.6)
5	298	38 (12.8)	303	3 (10.9)
6	298	9 (3.0)	303	10 (3.3)
≥7	298	11 (3.7)	303	13 (4.3)
Socioeconomic deprivation quintiles, n (%)				
1 (least deprived)	302	51 (16.9)	302	50 (16.6)
2	302	71 (23.5)	302	59 (19.5)
3	302	66 (21.9)	302	63 (20.9)
4	302	67 (22.2)	302	63 (20.9)
5 (most deprived)	302	47 (15.6)	302	67 (22.2)
Pseudomonas aeruginosa status, n (%)‡				
Chronic	299	175 (58.5)	304	174 (57.2)
Non-chronic	299	124 (41.5)	304	130 (42.8)
Previous year's intravenous treatment, days	303	27.7±33.0	304	24.2±27.9
Secondary outcomes: baseline values				
Objectively measured effective adherence (weekly), %§	295	45.5±34.1	293	54.1±33.0
FEV_1 % predicted	302	58.3±22.6	304	60.7±23.5
Body mass index, kg/m^2	303	22.5±4.2	304	22.7±4.2
Patient-reported outcomes: baseline values				
CFQ-R (quality of life):				
Physical	302	53.0±30.2	304	54.3±30.6
Emotional	302	66.2±24.1	304	66.5±21.6
Social	302	60.9±20.9	304	61.9±20.0
Eating	302	80.5±24.3	304	82.1±22.5
Body image	302	66.1±29.3	304	65.6±28.0
Treatment burden	302	51.8±20.2	304	54.4±19.8
Respiratory	302	56.6±21.9	304	58.2±22.1
Digestion	302	81.1±19.4	304	79.9±21.5
BMQ-Specific (beliefs about medication):				
Concerns	301	2.1±0.5	304	2.1±0.6
Necessities	301	3.6±0.8	304	3.6±0.7
SRBAI (habit strength for using nebuliser)	300	12.0±4.7	303	12.1±5.0
Perceptions of treatment adherence (three-item scale)	274	9.9±3.4	280	10.2±3.4
Effort of nebuliser treatments (one item)	300	3.1±1.2	302	3.1±1.3
Subjective adherence question – % (self-report estimate of adherence)	298	69.0±30.8	300	69.9±31.0
CHAOS-6 (life chaos or routine)	300	9.5±2.9	303	9.5±2.9
PAM-13 (health style assessment)	302	65.3±13.3	304	65.8±14.5
EQ-5D-5L (generic health status)	300	0.84±0.16	303	0.85±0.15
PHQ-8 (depression)	301	6.4±5.1	304	6.4±5.2
GAD-7 (anxiety)	302	4.7±4.7	302	4.6±4.9

Full details and references for all patient-reported outcomes are available in the SAP (provided in online supplemental material).
*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.
†Unless otherwise stated.
‡Consensus definition.
§Weekly objectively measured effective adherence (sum of doses taken/sum of doses prescribed).
¶All patient-reported outcomes based on points, unless otherwise stated. For direction of positive effect and possible range, see table 3.
BMQ, Beliefs About Medicines Questionnaire; CHAOS-6, Confusion, Hubbub and Order six-item Scale; EQ-5D-5L, EuroQol 5-dimension and 5-level; GAD-7, Generalised Anxiety Disorder seven-item scale; PAM-13, Patient Activation 13-item Measure; PHQ-8, Patient Health Questionnaire eight-item depression scale; SAP, statistical analysis plan; SRBAI, Self-Report Behavioural Automaticity Index.

exacerbation occurred if intravenous antibiotics were administered for any one of 12 prespecified symptoms. Exacerbation forms were completed by a healthcare professional (clinical team or interventionist), and documented assessments were conducted at each clinical encounter (generally every 3 months) determined whether a participant was displaying an exacerbation.

To reflect effective medication use, adherence was calculated as normative (effective) adherence[9 10] using objective data from weeks 3–52 as the outcome and weeks 1 and 2 as the 'baseline'. Objectively measured effective adherence was calculated daily as a composite of all inhaled medications then aggregated weekly for analysis (appendix B), as we have detailed elsewhere.[9 10] Other secondary endpoints were percent predicted FEV_1), measured at each clinical encounter, and body mass index (BMI), calculated at baseline and 12 months. Patient-reported outcomes collected at baseline and 12 months included: CF Questionnaire-Revised (CFQ-R; eight subscales), measuring quality of life and including a perceived CF treatment burden subscale; Beliefs About Medicines Questionnaire (BMQ)-specific concerns and necessities; Self-Report Behavioural Automaticity Index (SRBAI), measuring habit strength; perceptions of treatment adherence (three-item scale); perceived effort of nebuliser treatments (one item); subjective adherence (self-reported % adherence); Confusion, Hubbub and Order 6-item Scale (CHAOS-6); Patient Activation 13-item Measure (PAM-13); and EuroQol 5-dimension and 5-level generic health status. Patient Health Questionnaire eight-item depression scale and Generalised Anxiety Disorder seven-item scale (GAD-7) were safety measures to understand whether the intervention worsens depression or anxiety. Adverse events were recorded using case report forms and were categorised as whether or not expected in relation to medications, or common among people with CF. Full details and references for outcomes are in the protocol and SAP.

Statistical analysis

Power calculations (online supplemental table 1) informed the choice of pulmonary exacerbation as the primary outcome and individual (vs cluster) randomisation. Cluster trials are complicated by recruitment bias. While contamination that reduces effect size may be a risk with individual randomisation, this can usually be overcome by increasing the sample size, which often still requires a smaller sample than cluster randomisation.[25] The sample size was predicted based on reducing two exacerbations per year to 1.5 per year (equivalent to an incidence rate ratio of 2.0/1.5=0.75). Assuming a mean difference of 0.5 pulmonary exacerbations between the intervention and usual care arms over 12 months, an SD of 1.5, a design effect of 1.16 to allow for any clustering of outcomes by centre (intraclass correlation 0.01; cluster size 17) and an attrition rate of 20%, 556 participants were required to provide 90% power at a two-sided 5% level of significance.

Baseline characteristics were reported descriptively using summary statistics. The primary outcome incidence rate ratio, 95% CI and p value were estimated using a negative binomial regression model, with a random effect to adjust for clustering by centre. Log follow-up time was an offset in the model, and past year intravenous days (≤14 and >14 days) and treatment arm were fixed effects. Details of the sensitivity analyses performed on the primary outcome data (including adjustment for missing data) are in the SAP. Objectively measured effective adherence was analysed using a linear mixed-effects model, with random slopes and intercepts; treatment arm, time in weeks, baseline adherence (measured in the first 2 weeks post randomisation) and past year intravenous days were fixed effects. Treatment effects and 95% CI for all other secondary outcomes were produced using a mixed-effects model adjusting for baseline and past year intravenous days and with a random effect to adjust for clustering by centre. To aid interpretation, standardised effect sizes (Cohen's d) were calculated for all secondary outcomes by dividing treatment effect with pooled SD

All analyses were prespecified and performed by intent to treat using R software V.3.6.1 and SAS V.9.4. CI widths were not corrected for multiplicity.

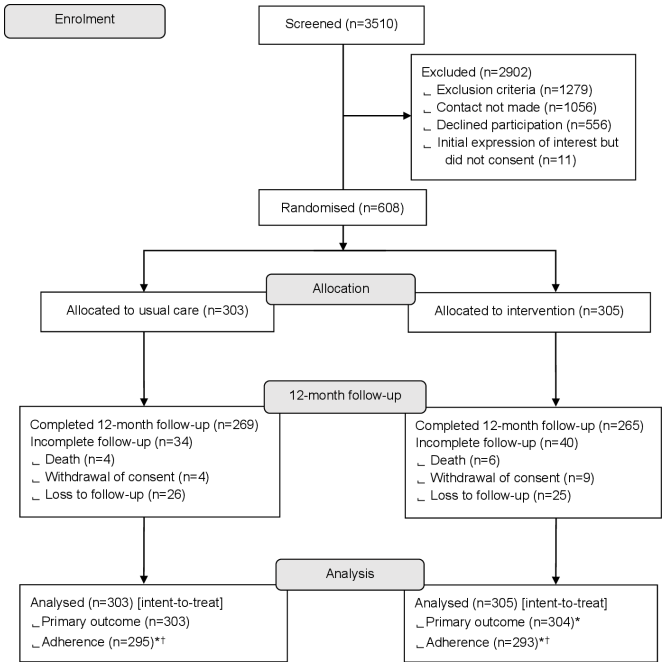

Figure 2 Trial profile. *Exclusions due to missing covariates. †Adherence level to reflect the effect of intervention was calculated using objectively measured effective adherence data from week 3 (ie, from the point of intervention delivery) through to week 52 (ie, the end of the trial), as stated in the 'Methods' and 'Results'. The intervention effect is best reflected by the cumulative adherence level throughout the trial period, similar to the approach of calculating cumulative exacerbation events throughout the trial. Though there were drop-outs during the trial, exacerbation data were available for all participants (expect for a participant who withdrew on the day of randomisation) since exacerbation events prior to drop-out were analysed. In a similar vein, adherence data available prior to the point of drop out were analysed as long as adherence data from week 3 onwards were available. Only 19 participants did not provide any adherence data from week 3 onwards, that is, adherence data were missing for outcome analysis among 19/607 (3%) of participants. Week-by-week breakdown of adherence data completeness is provided in online supplemental table 2.

RESULTS

Between October 2017 and May 2018, 3510 adults with CF were screened, with 608 enrolled and randomised (intervention n=305; usual care n=303) and 556 declined participation (figure 2). Participant recruitment is discussed in appendix C. One participant randomised to intervention withdrew on the day of consent prior to baseline data collection, thus was not included in analyses. The last recruited participant was followed until 30 June 2019, when the trial ended. Baseline demographic and clinical characteristics are in table 2. The intervention group

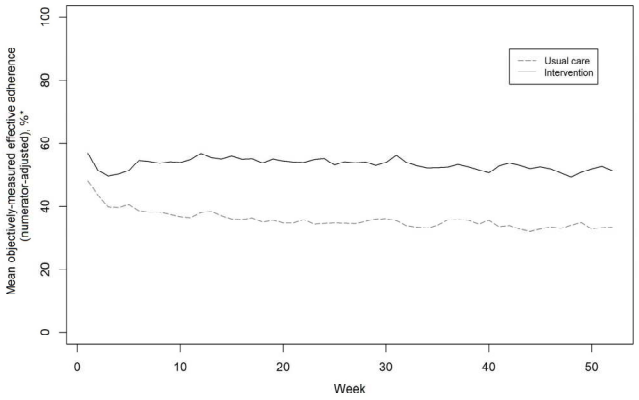

Figure 3 Medication adherence over 12 months, by randomised group (usual care n=295; intervention n=293). *Objectively measured effective adherence (sum of doses taken/sum of doses prescribed) was calculated on a weekly basis, with adjustments made against what may be considered an ideal treatment for effectiveness, as based on the following rules: all participants should receive at least a mucoactive agent; and all participants with chronic *Pseudomonas* should receive at least both a mucoactive agent and an antibiotic. Adherence data were aggregated and plotted weekly for the purpose of detecting whether adherence is actually changing to smooth out daily fluctuations that may just be noise, for example, due to weekday versus weekend differences in adherence.[40]

was slightly older, with slightly higher FEV_1, slightly lower past year intravenous days and slightly higher baseline objectively measured effective adherence (measured 2 weeks post randomisation)—this imbalance is explored in appendix D. Primary outcome data were available for all participants; adherence data were missing for 3.1% (19/607) of participants as explained in figure 2. Week-by-week breakdown of adherence data completeness is in online supplemental table 2.

The median (IQR) number of interventionist sessions per participant was 7.0 (6.0–10.0). The median (IQR) total interventionist delivery time per participant (including contact time and preparation outside of sessions) was 185 (126–263) min. Fidelity of intervention delivery median (IQR) scores were 97.2% (92.3–100.0), 92.6% (87.0–98.1) and 94.4% (91.7–97.2) at the first intervention visits, reviews and phase reviews, respectively (4)).

For the primary outcome, over 12 months, there were 526 pulmonary exacerbations in the usual care arm (adjusted rate 1.77/year, n=303) compared with 482 in the intervention arm (1.63/year, n=304). Incidence rate ratios (95% CI) of the primary analysis (0.96 (0.83 to 1.12); p=0.64), sensitivity analyses (online supplemental table 3) and subgroup analyses (online supplemental figure 1) indicated no significant between-arm difference in exacerbations.

Mean objectively measured effective adherence in weeks 3–52 was 52.9% in the intervention arm versus 34.9% in the usual care arm, with an adjusted mean difference of 9.5 percentage points (95% CI 8.6 to 10.4). Figure 3 shows that adherence declined rapidly at a similar rate in both groups during the first 3 weeks of the trial. The decline among usual care participants continued over the subsequent 12 weeks, then stayed at the level until the end of the trial. In the intervention group, adherence subsequently improved following delivery of the behaviour-change intervention from week 3 onwards (further details in online supplemental appendix D).

Over 12 months, percent predicted FEV_1 declined by 1.4 (from 58.3±22.6 to 56.9±23.0) among usual care and 0.1 (from 60.7±23.5 to 60.6±24.2) among intervention participants. The adjusted mean differences (95% CI) in per cent predicted FEV_1 and BMI at 12 months were 1.4 (−0.2 to 3.0) and 0.3 kg/m^2 (0.1 to 0.6), respectively (table 3).

Of the eight CFQ-R subscales, seven showed no between-group difference, but there was lower perceived CF treatment burden (3.9 (1.2, 6.7) points) in the intervention arm. Of the other 11 patient-reported outcomes at 12 months (including two safety measures; table 3), six showed differences for intervention versus usual care (adjusted difference in means (95% CI)), with increases in beliefs about medication necessities (0.1 (0.0 to 0.2) on BMQ-Specific necessities), habit strength for using nebuliser (1.2 (0.5 to 1.8) on SRBAI), perceptions of treatment adherence (0.7 (0.2 to 1.2) on three-item scale) and patient activation (3.4 (1.3 to 5.4) on PAM-13), and decreases in concerns about treatment (0.2 (0.1, 0.2) on BMQ-Specific concerns) and perceived effort of nebuliser treatments (0.3 (0.1 to 0.5) for one item). Other outcomes, including the safety measures of depression (−0.1 points (−0.8 to 0.7) on PHQ-8) and anxiety (0.3 points (−0.4 to 1.0) on GAD-7), showed no between-group difference.

No intervention-related serious adverse events were reported (online supplemental table 4). Sixty-four serious adverse events (21 in expected categories due to disease or treatment) in 43 usual care participants were recorded and 71 (28 expected) in 56 intervention participants.

DISCUSSION

In this randomised, usual care-controlled trial, we investigated the effectiveness of a self-management intervention designed to reduce pulmonary exacerbation rates among adults with CF, by supporting their adherence to inhaled mucoactive agents and antibiotics. Over 12 months, a significant difference in pulmonary exacerbations or FEV_1 was not detected. However, compared with usual care, the intervention achieved higher objectively measured effective adherence, higher BMI and lower perceived CF treatment burden.

It is possible that the primary outcome was not achieved due to insufficient between-group difference in adherence. It is also possible that using exacerbation as an endpoint was problematic. Exacerbation is a robust, sensitive outcome for blinded efficacy drug trials,[21] but an unblinded, pragmatic evaluation of self-management support presents challenges to its use. There is a discretionary element to the use of intravenous antibiotics as rescue therapy; previous studies suggest only around 50% of events meeting 3/4 Rabin exacerbation criteria or acute 10% decline in FEV_1 receive additional antibiotics.[26] Increasing a person's adherence to treatment may improve their acceptance of intravenous antibiotics,[27] and more intense monitoring can detect more exacerbations.[28] It is possible that increased clinician contact time in the intervention group created differential surveillance that biased the exacerbation rate towards unity (ascertainment bias). In UK practice, intravenous antibiotics will always be started by the CF care team, whereas oral antibiotics can be started in the community and may be much more susceptible to differential surveillance. To avoid this bias, oral courses were not collected. As a consequence, it is possible that improvement in milder exacerbations may have been missed. Adding a standardised criteria, for example, the Fuchs criteria, as part of the definition allowed exacerbation measurement across different centres to be comparable. However, recent work has suggested that this may result in reduced sensitivity.[29]

The graph for objectively measured effective adherence (figure 3) has several features that merit discussion (further

Table 3 Outcomes at 12 months, by randomised treatment group

	Usual care		Intervention		Usual care versus intervention		
	N	Exacerbation rate (no. of exacerbations, person years)	N	Exacerbation rate (no. of exacerbations, person years)	Adjusted difference in means (95% CI)*	Direction of positive effect (possible range)	Standardised effect size
Exacerbations	303	1.77 (526, 297.2)	304	1.63 (482, 294.9)	0.96 (0.83 to 1.12)	Decrease (not applicable)	Not applicable
	Usual care		**Intervention**		**Usual care versus intervention**		
	N	**Mean±SD**	**N**	**Mean±SD**	**Adjusted difference in means (95% CI)†**	**Direction of positive effect (possible range)**	**Standardised effect size**
Objectively measured effective adherence (weekly) – %‡	295	34.9±31.7	293	52.9±31.4	9.5 (8.6 to 10.4)	Increase (0 to 100)	0.29
FEV_1 % predicted	282	56.9±23.0	274	60.6±24.2	1.4 (–0.2 to 3.0)	Increase (0 to 100)	0.06
Body mass index – kg/m^2	282	22.6±4.1	273	23.1±4.4	0.3 (0.1 to 0.6)	Increase (not applicable)	0.07
Patient-reported outcomes§							
CFQ-R (quality of life):						Increase (each 0 to 100)	
Physical	274	52.6±30.6	264	55.8±30.2	2.3 (–1.0 to 5.6)		0.08
Emotional	274	66.5±24.7	264	66.6±22.9	0.2 (–2.9 to 3.2)		0.01
Social	274	59.6±20.0	264	60.5±20.0	0.3 (–2.2 to 2.7)		0.01
Eating	274	81.0±23.2	264	84.0±21.5	1.9 (–1.3 to 5.2)		0.09
Body image	274	65.1±29.3	264	67.2±27.3	1.7 (–1.4 to 4.8)		0.06
Treatment burden	274	51.5±19.7	265	56.6±19.5	3.9 (1.2 to 6.7)		0.20
Respiratory	271	56.6±21.9	263	58.0±22.5	0.7 (–2.4 to 3.8)		0.03
Digestion	272	80.2±21.6	263	80.4±19.4	1.1 (–1.7 to 3.9)		0.05
BMQ-Specific (beliefs about medication):							
Concerns	271	2.1±0.5	271	2.0±0.5	–0.2 (–0.2 to –0.1)	Decrease (1 to 5)	0.29
Necessities	271	3.5±0.7	271	3.7±0.8	0.1 (0.0 to 0.2)	Increase (1 to 5)	0.18
SRBAI (habit strength for using nebuliser)	271	11.7±4.9	261	12.9±4.9	1.2 (0.5 to 1.8)	Increase (4 to 20)	0.24
Perceptions of treatment adherence (three-item scale)	245	9.9±3.6	237	10.8±3.3	0.7 (0.2 to 1.2)	Increase (3 to 15)	0.20
Effort of nebuliser treatments (one item)	270	3.0±1.2	260	3.3±1.3	0.3 (0.1 to 0.5)	Increase (1 to 5)	0.22
Subjective adherence question – % (self-report estimate of adherence)	267	65.6±32.8	258	68.6±31.3	1.9 (–2.8 to 6.6)	Increase (0% to 100%)	0.06
CHAOS-6 (life chaos or routine)	272	9.6±3.2	263	9.4±3.4	–0.2 (–0.6 to 0.3)	Decrease (0 to 24)	0.05
PAM-13 (health style assessment)	274	64.9±13.0	265	68.1±15.6	3.4 (1.3 to 5.4)	Increase (0 to 100)	0.23
EQ-5D-5L (generic health status)	272	0.81±0.18	264	0.84±0.15	0.01 (–0.01 to 0.04)	Increase (–0.224 to 1)	0.09
Patient-reported outcomes – safety measures§							
PHQ-8 (depression)	272	6.4±5.0	262	6.3±5.6	–0.1 (–0.8 to 0.7)	Decrease (0 to 24)	0.01
GAD-7 (anxiety)	273	4.5±4.8	262	4.9±5.3	0.3 (–0.4 to 1.0)	Decrease (0 to 21)	0.05

Full details and references for all patient-reported outcomes are available in the SAP (provided in online supplemental material).
*Exacerbations analysis adjusted for centre and past year intravenous days.
†All other analyses adjusted for past year intravenous days, centre and outcome measure at baseline.
‡Weekly objectively measured effective adherence (sum of doses taken/sum of doses prescribed) averaged over weeks 3–52 postrandomisation.
§All patient-reported outcomes based on points, unless otherwise stated.
BMQ, Beliefs About Medicines Questionnaire; CFQ-R, CF Questionnaire-Revised; CHAOS-6, Confusion, Hubbub and Order 6-item Scale; EQ-5D-5L, EuroQol 5-dimension and 5-level; GAD-7, Generalised Anxiety Disorder seven-item scale; PAM-13, Patient Activation 13-item Measure; PHQ-8, Patient Health Questionnaire eight-item depression scale; SAP, statistical analysis plan; SRBAI, Self-Report Behavioural Automaticity Index.

details in appendix D). The pragmatic trial design of providing data-logging nebulisers and revealing trial allocation to participants on day 1, then measuring baseline adherence in the first 2 weeks of the trial creates complexity. The baseline between-group difference in objectively measured effective adherence was 8.6% in favour of the intervention group (54.1%±33.0% vs 45.5±34.1%), with the intervention group being older yet having higher FEV_1 and lower IV days in the 12 months prior to study entry. Over the 49 weeks of the intervention, there was a between-group difference in objectively measured effective adherence of 18.0% in favour of the intervention group (52.9%±31.4% vs 34.9±31.7%), with an adjusted mean difference of 9.5% (95% CI 8.6% to 10.4%) taking into account the baseline adherence. Analysis comparing the adherence response stratified by baseline adherence (appendix D (figure D2)) shows that a significant between-group difference in adherence emerged at all levels of baseline adherence, emphasising that there was genuine divergence in adherence between the intervention and usual care independent of baseline adherence. It can be seen (figure 3) that in both groups there was an initial rapid decline in adherence. Among usual care participants not receiving any intervention, this decline continued over the next 12 weeks to around 35% and stayed at this level until the end of the trial. Real-world objective inhaled therapy monitoring has demonstrated similar levels of adherence among adults with CF not receiving intervention.[8 9] In the intervention group, the initial rate of decline was similar to usual care until the behavioural change intervention started from week 3 onwards and adherence subsequently improved. Given the rapid initial decline of both groups over the first 3 weeks of the study, it seems possible that the adherence at study entry was a short-term manifestation of device novelty[30] and white coat adherence.[31]

Since people with low adherence may find adherence data threatening,[32] it is important to note that the differential adherence in the intervention arm was achieved without increasing anxiety. The intervention also achieved increase in necessity and reduction in concerns for treatment taking, consistent with literature highlighting that self-management of LTCs may be improved by addressing treatment beliefs.[17] Policy makers who emphasise the importance of patient activation in LTCs[33] can be reassured that the intervention significantly increased knowledge, skills and confidence (patient activation). The intervention achieved clinically important improvements in perceived treatment burden,[34] which was identified as the number one research priority by the CF community.[12] That total nebuliser use should increase while the perceived burden and effort of nebuliser treatment decrease may relate to a moderating role for habit.[18 19] Literature in LTCs emphasises that sustained adherence is generally more strongly associated with habit than reflective motivation, which is more effortful.[35]

In considering the effective components of the intervention, data feedback is an obvious candidate. However, participants consulted data infrequently outside of supervised sessions. A qualitative analysis undertaken as part of the pilot work reported the value of the range of behaviour change techniques used in the intervention as well as the importance of building a relationship with the interventionist.[36] It is unlikely that unsupported feedback alone is sufficient to explain the reduced treatment burden, the improved necessity and concerns for treatment or the increased habit strength.

A strength of the trial is the automatic capture of objective adherence with data-logging nebulisers that record every dose taken. Online supplemental table 2 demonstrates similar levels of week-by-week data completeness for both groups. Robust adherence data allowed us to demonstrate a sustained adherence difference for 12 months, which is the first for inhaled medications in any LTC. Sustained objectively measured adherence benefits for behavioural interventions in other LTCs are limited to two studies, both for oral medications among older adults in the hypertension and post-transplantation settings.[37 38] CFHealthHub as a multi-component self-management intervention has now been established as a digital learning health system (ISRCTN14464661) in >50% of UK adult CF centres. Limitations of the trial include the delivery of both behavioural change and research procedures by interventionists, a period of server downtime that affected intervention delivery, the fact that the trial powered for exacerbation was not designed to detect the observed point estimate in FEV_1 and the recruitment of a convenience sample whereby a third of the participants had objectively measured effective adherence levels >75%. The vulnerability of adherence studies to differential inclusion of more engaged patients is likely to reduce both the impact of the adherence intervention on studied behaviour and reduce the impact on health outcomes.[39] This may mean that the positive behavioural findings observed in this study are particularly noteworthy. The direction of bias and implications of these limitations are further discussed in appendix E.

In this randomised controlled trial, an intervention for adults with CF that combines measurement of objective adherence to prescribed medication using data-logging nebulisers, a digital platform and manualised behavioural-change sessions delivered by trained clinical interventionists did not significantly affect pulmonary exacerbations and FEV_1 but did result in higher objectively measured effective adherence, higher BMI and lower perceived CF treatment burden versus usual care, without increasing anxiety. This is the first iteration of a self-management intervention that may have the potential to be improved by continual iteration in a digital learning health system. Analogous to the overwhelming success in the CF drug pipeline of building on early signals with ongoing developments and trials, we plan to continue iterating and evaluating the CFHealthHub-based intervention by building on signals we have observed to further improve the intervention. Given that adherence is low in LTCs and that prescribed medications only work if taken appropriately, focusing on further evaluation of adherence interventions is important.

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Contributors MJW, AO'C, DH and MAA conceived and designed the study; CFHealthHub study team members collected data; SJW, LM and LS performed data analysis; MJW, AO'C, DH, MA and SJW performed data interpretation, and MJW drafted the manuscript. All authors reviewed and revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MJW and SJW are the guarantors.

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Data availability statement Data are available on reasonable request. Requests for patient level data and statistical code should be made to the corresponding author and will be considered by members of the original trial management group, including the chief investigators and members of clinical trials research unit, who will release data on a case-by-case basis. Data will be shared following the principles for sharing patient level data as described by Tudur Smith C, *et al BMC Medicine* 2015;13:298 (https://doi.org/10.1186/s12916-015-0532-z). The data will not contain any direct identifiers, and we will minimise indirect identifiers and remove free-text data to minimise the risk of identification.

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SUPPLEMENTARY MATERIAL

Self-management intervention to reduce pulmonary exacerbations by supporting treatment adherence in adults with cystic fibrosis: a randomised controlled trial

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CONTENTS

Table S1 Cluster sample size calculations for comparison of continuous data – two independent groups

Mean1, Mean2, SD, IntraCluster Correlation Coefficient
PLEASE ENTER Average Cluster Size

Significance Level	POWER	Mean$_1$	Mean$_2$	SD	Mean Difference	Standardised Effect Size	Intra Cluster Correlation	Mean Cluster Size	iRCT † No. in each group	iRCT † Total Sample Size	iRCT † Total Sample Size Drop out 15%	Design Effect Inflation Factor	cRCT ‡ No. in each group	cRCT ‡ Total Sample Size	cRCT ‡ Total Sample Size Drop out 15%	
Exacerbations Outcome																
5%	90%	3	2	3	1	0.33	0.000	25	191	382	450	1.00	191	382	450	**Original sample calculation with no clustering**
5%	90%	3	2	3	1	0.33	0.010	25	191	382	450	1.24	237	474	558	Original sample calculation with clustering
5%	90%	3	2	3	1	0.33	0.035	70	191	382	450	3.42	653	1306	1538	Cluster RCT calculation
5%	90%	3	2	3	1	0.33	0.010	25	191	382	450	1.24	237	474	558	
5%	90%	3	2.1	3	0.9	0.30	0.010	25	235	470	554	1.24	292	584	688	***Proposed sample size with allowance for contamination and clustering by health team***
FEV$_1$ outcome	**80% power**															
5%	80%	1	0	25	1	0.04	0.010	25	9813	19626	23090	1.24	12169	24338	28634	
5%	80%	2	0	25	2	0.08	0.010	25	2454	4908	5776	1.24	3043	6086	7160	
5%	80%	3	0	25	3	0.12	0.010	25	1092	2184	2570	1.24	1355	2710	3190	
5%	80%	4	0	25	4	0.16	0.010	25	615	1230	1448	1.24	763	1526	1796	
5%	80%	5	0	25	5	0.20	0.010	25	394	788	928	1.24	489	978	1152	
5%	80%	6	0	25	6	0.24	0.010	25	274	548	646	1.24	340	680	800	
5%	80%	7	0	25	7	0.28	0.010	25	202	404	476	1.24	251	502	592	
5%	80%	8	0	25	8	0.32	0.010	25	155	310	366	1.24	193	386	456	
5%	80%	9	0	25	9	0.36	0.010	25	123	246	290	1.24	153	306	360	
5%	80%	10	0	25	10	0.40	0.010	25	100	200	236	1.24	124	248	292	
FEV$_1$ outcome power with N=688 randomised																
5%	7%	1	0	25	1	0.04	0.000	0	292	584	688	1.00	292	584	688	Sample size fixed at N~ 688 randomised
5%	16%	2	0	25	2	0.08	0.000	0	292	584	688	1.00	292	584	688	Size of difference in FEV$_1$ able to detect
5%	30%	3	0	25	3	0.12	0.000	0	292	584	688	1.00	292	584	688	
5%	49%	4	0	25	4	0.16	0.000	0	292	584	688	1.00	292	584	688	
5%	67%	5	0	25	5	0.20	0.000	0	292	584	688	1.00	292	584	688	
5%	76%	5.5	0	25	5.5	0.22	0.000	0	292	584	688	1.00	292	584	688	
5%	83%	6	0	25	6	0.24	0.000	0	292	584	688	1.00	292	584	688	
5%	88%	6.5	0	25	6.5	0.26	0.000	0	292	584	688	1.00	292	584	688	
5%	92%	7	0	25	7	0.28	0.000	0	292	584	688	1.00	292	584	688	
5%	97%	8	0	25	8	0.32	0.000	0	292	584	688	1.00	292	584	688	

*Power calculations demonstrated greater efficiency of pulmonary exacerbations versus FEV$_1$, thereby influencing the choice of pulmonary exacerbations as the primary outcome.

†Randomisation in the trial was on an individual rather than cluster basis because our power calculation indicated a requirement for 1,400 adults across 20 centres for cluster randomisation, which would not be feasible. Although contamination is a risk with individual randomisation, this can often be overcome by increasing the sample size. In most cases, individual randomisation accounting for contamination requires a smaller sample size than cluster randomisation.[1]

FEV_1, forced expiratory volume in one second; RCT, randomised controlled trial (c, cluster; i, individual); SD, standard deviation.

Reference

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Table S2 Objectively-measured effective adherence weekly summaries (complete case), by randomised treatment group

Week	Usual care		Intervention	
	N	Mean (SD)	N	Mean (SD)
1	289	48.0 (35.0)	290	57.0 (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 (35.0)
10	291	36.6 (34.7)	297	54.0 (35.9)
11	290	36.4 (34.8)	297	54.9 (35.6)
12	290	38.0 (34.9)	297	56.9 (35.7)
13	290	38.4 (35.6)	296	55.6 (36.4)
14	290	37.0 (35.2)	294	55.1 (36.9)
15	289	36.0 (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 (36.0)
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	55.0 (36.4)
24	282	34.5 (34.8)	290	55.3 (35.8)
25	282	34.7 (34.0)	290	53.2 (35.9)
26	281	34.6 (33.8)	290	54.3 (36.0)
27	281	34.4 (34.5)	288	53.9 (36.6)
28	279	35.2 (35.9)	288	54.2 (35.7)
29	280	36.0 (35.8)	287	53.1 (36.0)
30	276	36.0 (35.9)	287	54.1 (36.4)
31	275	35.4 (35.5)	285	56.3 (36.5)
32	274	33.7 (34.0)	285	54.1 (36.7)
33	274	33.3 (34.5)	284	53.0 (37.2)
34	274	33.0 (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	32.0 (34.4)	272	52.0 (37.3)
45	271	32.7 (34.9)	272	52.6 (36.6)
46	269	33.3 (34.8)	272	52.0 (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	52.0 (36.0)
51	267	33.1 (35.3)	269	52.7 (35.9)
52	266	33.2 (35.0)	268	51.4 (36.1)

SD, standard deviation.

Table S3. Primary outcome sensitivity analyses over 12 months, by randomised treatment group

Sensitivity analysis*	Usual care				Intervention				Incidence rate ratio (95% CI)	P value
	N	Exacerbations	Person-years	Exacerbation rate	N	Exacerbations	Person-years	Exacerbation rate		
Main – adjusted	303	526	297.2	1.77	304	482	294.9	1.63	0.96 (0.83, 1.12)	0.638
Main – unadjusted	303	526	297.2	1.77	304	482	294.9	1.63	0.92 (0.77, 1.11)	0.387
All exacerbations†	303	558	297.2	1.88	304	504	294.9	1.71	0.95 (0.82, 1.10)	0.511
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, 1.10)	0.444

Model definitions:

Main – adjusted for stratification factors (centre and past-year IV days)

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

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

MICE – missing count data imputed (where missingness not due to death) using randomization group, site, previous year's IV days, age, gender, FEV_1 % predicted, *Pseudomonas* status, and 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

*Recurrent event survival was also calculated: hazard ratio 0.95 (95% CI 0.80, 1.13; p=0.567).

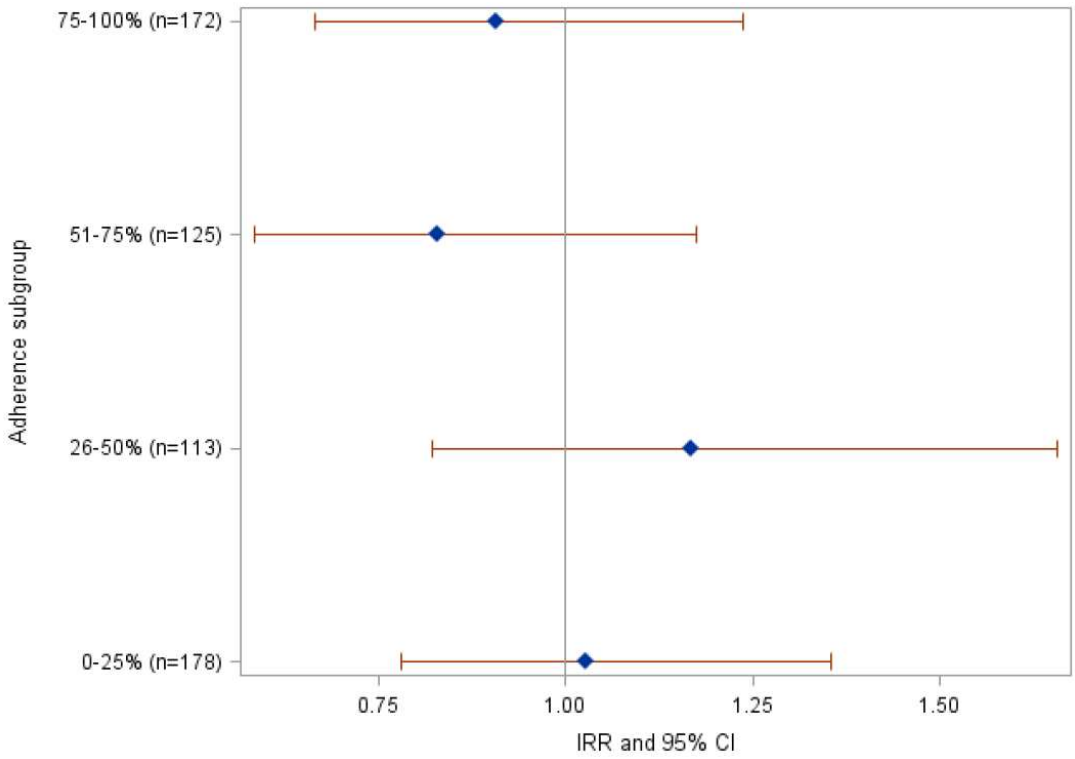
†The difference between 'all exacerbations' and 'main – unadjusted' is the number of IV antibiotic courses that were offered by clinicians but declined by participants. The IV-declined rate was 32/558 (5.7%) for the usual care arm and 22/504 (4.4%) for the intervention arm. These values are far lower than the IV-declined rate observed in the general CF population of around 20%,[1] which provides evidence that the recruited participants may not be representative of the general CF population.

BMI, body mass index; CF, cystic fibrosis; CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension and 5-level; FEV_1, forced expiratory volume in one second; IV, intravenous; MICE, multiple imputation using chained equations.

Reference

1. Hoo ZH, Bramley NR, Curley R, *et al.* Intravenous antibiotic use and exacerbation events in an adult cystic fibrosis centre: a prospective observational study. *Respir Med* 2019;154:109–15.

Figure S1 Primary outcome subgroup analysis according to baseline objectively-measured effective adherence level. CI, confidence interval; IRR, incidence rate ratio.



Statistical significance was not observed in any of the subgroups by baseline objectively-measured effective adherence. “Pulmonary exacerbation” was defined as the administration of intravenous (IV) antibiotics for any of the 12 Fuchs’ symptoms/signs. As discussed in the main manuscript, there is a discretionary element to the use of IV antibiotics as rescue therapy to treat exacerbations. Increasing a person’s adherence to inhaled therapies may also improve their engagement with other treatments, including improving their acceptance of IV rescue antibiotics. It is possible that the exacerbation rate appeared to have somewhat increased in those with baseline adherence 26–50% because this is the subgroup with greatest improvement in adherence, potentially leading to the greatest impact from ascertainment bias (see appendix D [figure D2] for the subgroup analysis of adherence). It should be noted that interactions between exacerbations and adherence are complex, including for example the impact of engagement on IV acceptance, such that interpretation should be made with caution.

Table S4 Adverse events and serious adverse events over 12 months, by randomised treatment group

	Usual Care (N=303)	**Intervention (N=305)**
All AE		
Number of AE, overall – n (% of all AE)	301 (46.9)	341 (53.1)
Number of participants experiencing ≥1 AE – n (% of participants in treatment arm)	125 (41.3)	139 (45.6)
Number of AE, by category – n (% of AE in treatment arm)		
Expected*	242 (80.4)	263 (77.1)
Other	58 (19.3)	73 (21.4)
Serious AE*†		
Number of serious AE, overall – n (% of all serious AE)	64 (47.4)	71 (52.6)
Number of participants experiencing ≥1 serious AE – n (% of participants in treatment arm)	43 (14.2)	56 (18.4)
Number of serious AE, by category – n (% of serious AE in treatment arm)		
Expected*	21 (32.8)	28 (39.4)
Other	41 (64.1)	42 (59.2)
Unknown	2 (3.1)	1 (1.4)

*Certain AE common to CF and associated medications were categorised as expected. Examples of expected AE include acute FEV_1 drop >15% after first dose of medication, increased productive cough and nasal congestion. The full list of expected AE is provided in section 12.3.3 of the protocol (available as supplementary material).

†There were no serious AE deemed related to the intervention (non-serious AE were not assessed for relatedness).

AE, adverse event; CF, cystic fibrosis; FEV_1, forced expiratory volume in one second.

APPENDIX A Description of the CFHealthHub intervention

Aim

The CFHealthHub intervention aims to support adults with cystic fibrosis (CF) to increase and maintain their adherence to prescribed nebulised medication in order to reduce exacerbations and improve or prevent decline in lung function.

Rationale

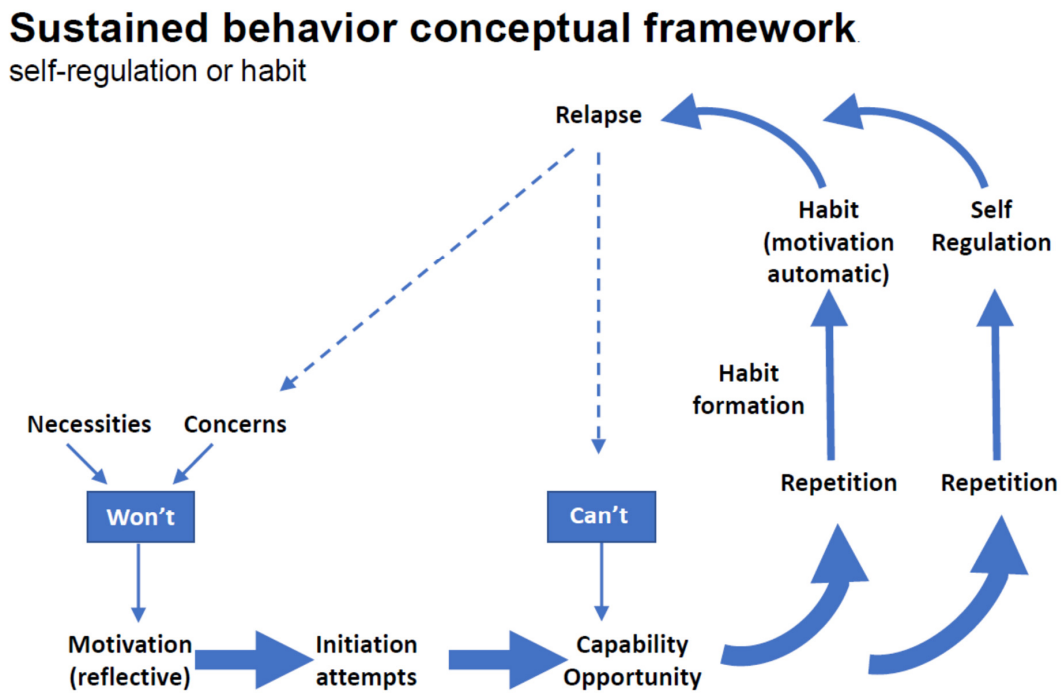
The CFHealthHub intervention is underpinned by the Capability Opportunity Motivation-Behaviour (COM-B) model.[1] It has been developed using the Behaviour Change Wheel approach alongside a person-based approach to intervention development. This process is described in detail elsewhere[2] but broadly consisted of the following stages:

- Identification of barriers and facilitators for nebuliser adherence using the Theoretical Domains Framework
- Identification of appropriate intervention functions and behaviour change techniques to address barriers identified
- Iterative development of the CFHealthHub intervention with patients, using feedback from interviews and 'think aloud' to refine the intervention
- Creation of an intervention manual and training programme for interventionists
- Pilot and feasibility trial including a process evaluation which was used to further refine the intervention, manual and training process

Conceptual framework and theory

The conceptual framework that describes the intervention is provided in figure A1. Consistent with the COM-B model, the framework considers issues of capability, opportunity and motivation, all of which must be present in order for repetition of the behaviour (i.e. medication adherence) to occur. Initially we anticipate that repetition will require effortful self-regulation, but with repetition and strategies to promote habit formation we aim for the behaviour to become more automatic.

Figure A1 Sustained behaviour conceptual framework.



The intervention addresses a range of different barriers and is tailored to meet the specific needs of the person. The intervention draws on key theories in order to address different parts of the proposed process: Social Cognitive Theory,[3] Control Theory,[4] and Habit Theory,[5] as follows:

- Social Cognitive Theory (SCT)[3] proposes that behaviour is influenced by two core constructs: i) perceived self-efficacy, i.e. an individual's beliefs in their capability to adhere to treatment; and ii) outcome expectancies, i.e. an individual's beliefs about the likely consequences of their actions. Self-efficacy can be enhanced through: i) mastery; ii) vicarious experiences, where a role model, similar to the individual successfully achieves behavioural change in a similar situation; or iii) verbal persuasion. Outcome expectancies include beliefs about the positive and negative and short- and long-term consequences of adherence, and in this context include perceived necessities and concerns.[6] According to SCT, outcome expectancies may result in intentions to change one's behaviour. Self-efficacy then influences the translation of that intention into action through the pursuit of goals.

- Control Theory[4] explains the processes of self-regulation. When a behavioural standard or goal has been set, an individual directs their attention through monitoring behaviour to the discrepancy between their current behaviour and their goal. They then use this feedback to regulate their behaviour to meet their goal through action control. This in the context of adherence, once an adherence goal is set, self-monitoring of treatment-taking provides the feedback to prompt action to enable self-regulation of behaviour.
- A habit is where a behaviour is prompted automatically by a situational cue. Habits are created due to the repetition of a behaviour in a specific context[7] which, over time results in a learned cue-behaviour association.[8] In the context of adherence, the repeated taking of treatment in a specific context or in the presence of a specific cue should over time result in the formation of a habit. Habits are particularly advantageous because theory predicts that, once formed, they do not rely on motivational processes and therefore should persist even if motivation wanes.[9] They may therefore play a particularly important role in the promotion of long-term maintenance of behaviour,[10] in this case adherence which is a key aim of the programme.

Materials

The CFHealthHub intervention includes a range of materials as follows:

1. eFlow Technology nebulisers with eTrack data-logging Controllers (PARI Pharma GmbH, Starnberg, Germany)
2. 2net Hub (Capsule Technologies, San Diego, USA)
3. Research procedures manual
4. CFHealthHub web platform
5. CFHealthHub app (available for Apple and Android devices)
6. COM-B Beliefs about Medicines Questionnaire (COM-BMQ) screening tool
7. CFHealthHub Participant manual
8. CFHealthHub Interventionist manual including worksheets for intervention delivery
9. Training slides, and online resources (via Blackboard virtual learning environment [VLE]) for interventionist training
10. Fidelity scoring sheets

Intervention providers

Intervention providers were recruited from each site. The majority of sites recruited individuals who were already members of the multi-disciplinary teams working in CF at that site. Other sites recruited from other parts of the hospital or recruited externally.

Thus, interventionists had a range of backgrounds including:

- Physiotherapists working in CF or other respiratory conditions
- Nurses working in CF
- Psychologists
- Pharmacists
- Dieticians

Procedure

Interventionist training, assessment and support

Interventionists received training in how to deliver the intervention in a variety of ways:

1. Training in use of equipment

Interventionists received training in how to use the eTrack nebuliser and 2net Hub, how to pair the devices, and how to register a new participant onto the CFHealthHub platform and PARI Track system, as part of their research procedures training. This was delivered face-to-face by the study manager and PARI, and supported with a research procedures manual and ad-hoc telephone support throughout the trial.

2. Training in delivery of CFHealthHub intervention

Interventionists received training in how to use the CFHealthHub web platform and how the deliver the CFHealthHub intervention. Training was delivered over a 2-day face-to-face training session, followed by a schedule of online training to be completed over the equivalent of 4 days hosted by the Blackboard VLE. Training consisted of presentations with exercises in small groups or pairs, supported use of CFHealthHub, role play delivery of the intervention and discussion. A training version of the CFHealthHub platform was provided for use during training that included dummy data. Interventionists were paired to form buddies for support and additional role play during the online part of the training.

3. Competency assessment

Interventionists undertook two competency assessments during the training period:

i. Theory test, which assessed understanding of the content of the CFHealthHub web platform content and data. This test was delivered through an online survey on the VLE and consisted of multiple choice and short answer questions. The answers were marked according to a pre-determined marking schedule. Interventionists passed if they received a mark of ≥80%. Individual feedback was provided on the answers given; where the first test was failed, additional tutorial support was provided and the test retaken until passed.
ii. Practical test, which assessed delivery of the first intervention visit of the CFHealthHub intervention. This was assessed through an audio-recorded role play. The part of the participant was played by a member of the study team and the interventionist role-played their part. The intervention delivery was assessed using a competency assessment sheet which consisted of sections on preparation, delivery of intervention components, and the quality of delivery. Two members of the training team looked at the completed worksheet for the session and listened to the accompanying audio-recording. They then discussed the marks and agreed marks where there were any differences. Agreed marks for each section were averaged and the pass mark was 90%. Interventionists received individual feedback on their performance and tutorial support where they had failed. The test was retaken until passed.

Competencies to deliver a review visit and a phase review visit were assessed by listening to the first audio-recorded visit of that kind for each interventionist. Two members of the training team looked at the completed worksheet for the session and listened to the accompanying audio-recording. They then discussed and agreed marks. Agreed marks for each section were averaged and the pass mark was 90%. Interventionists received individual feedback on their performance and tutorial support where they had failed. The next audio-recorded visit of that kind was assessed where the assessment was failed.

4. Ongoing support

Ongoing support for interventionists was delivered via a weekly teleconference, email and telephone support with the training team, technical support via telephone and email. The weekly teleconference provided a space where interventionists could discuss problems, successes and case studies (anonymised), to aid group learning. Individuals could also access members of the team individually and individual interventionists were targeted with support where they had failed their earlier competency assessment or where there were any problems identified.

Intervention schedule of delivery

The intervention schedule of delivery is described in figure A2. The content of each kind of intervention session is described below. Within this schedule there are a number of different paths that were determined during delivery.

Consent visit and set-up

All participants receive their eTrack nebuliser and 2net Hub at the consent visit. They also complete the COM-BMQ screening tool at this visit. An account is created on CFHealthHub into which is added the current prescription data for the participant and the data from the COM-BMQ screening tool. The consent visit takes place ≥4 weeks prior to the first intervention visit. During this time adherence data is transmitted automatically from the eTrack nebuliser via the 2net Hub, which is plugged into their home, to the CFHealthHub platform. Figure A3 shows this process.

Intervention sessions received by all participants

All participants receive their first intervention visit ≥4 weeks following consent (so that the consultation is based on ≥4 weeks' worth of objectively-measured adherence data). This visit is always done face-to-face although can be in a variety of locations, including hospital (in-patient), clinic or home. All participants then receive an intermediate review phone call one week later. Subsequent visits depend on their objectively-measured effective adherence level. Participants with an adherence level of ≥80% follow the 'Very high adherence' pathway while those with adherence level of <80% follow the normal pathway.

Figure A2 Schedule of intervention delivery. IV, intravenous antibiotics.

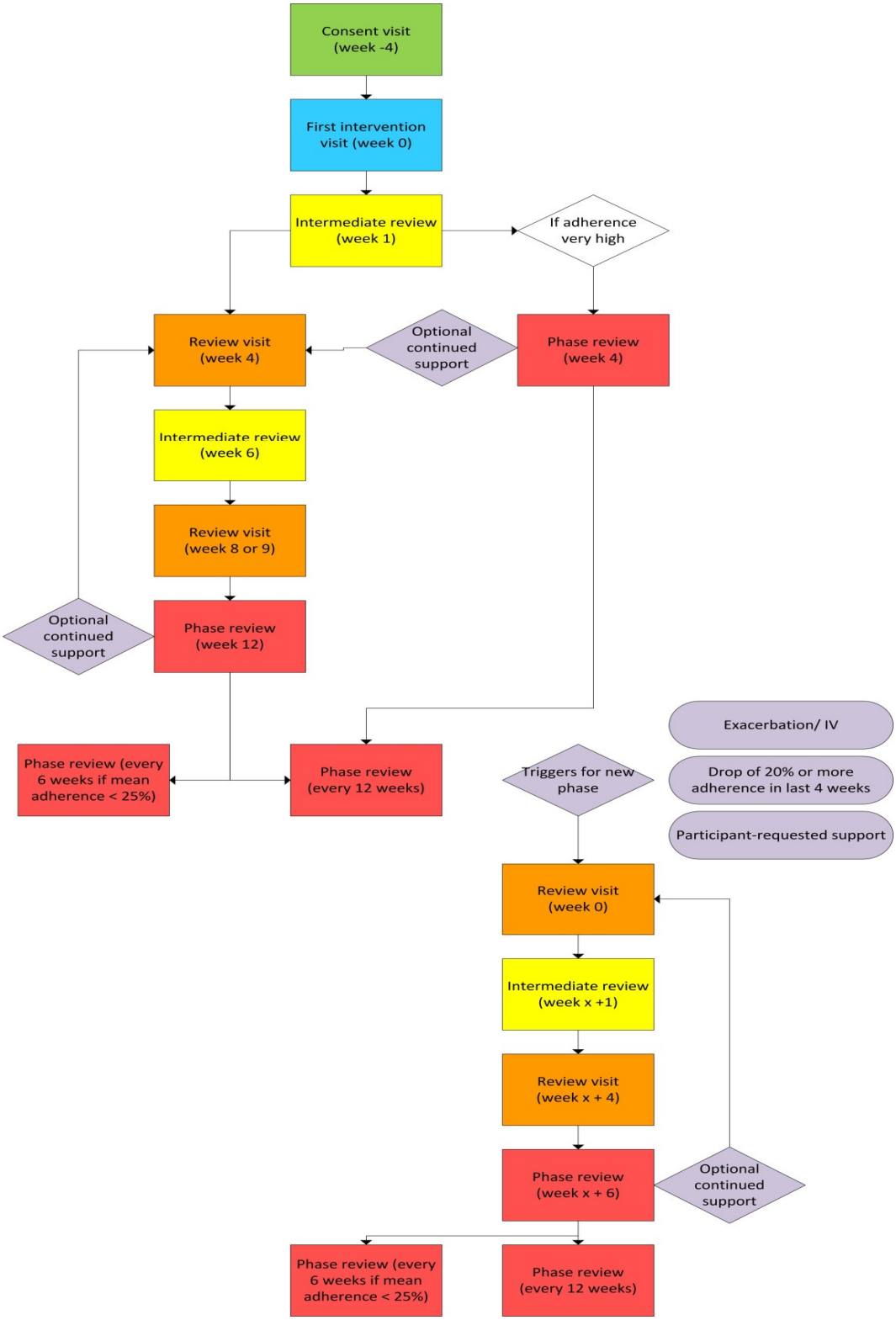
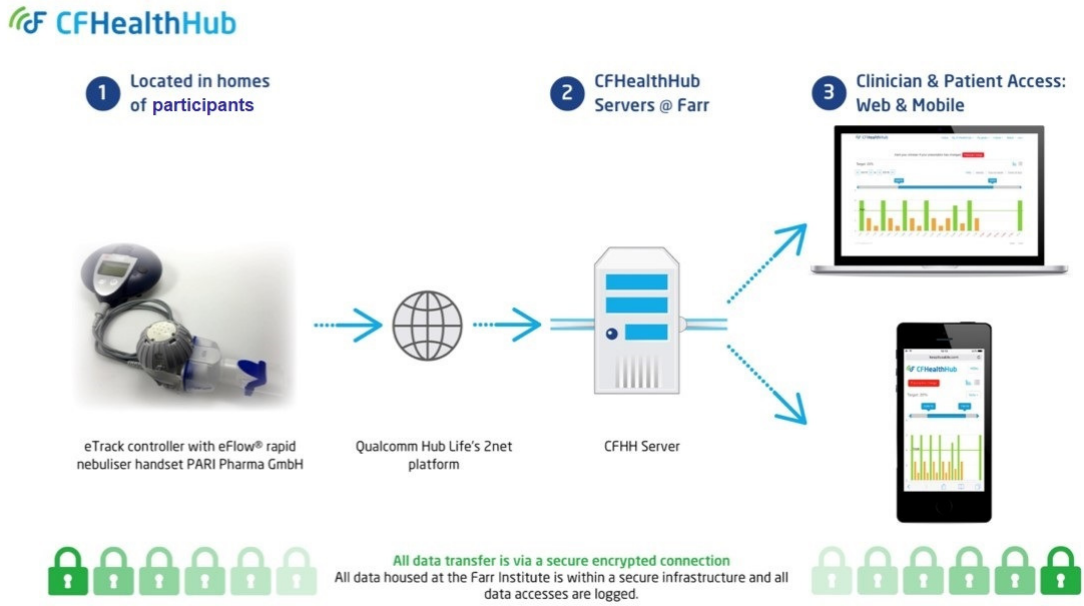


Figure A3 Data transfer process.



Normal pathway (adherence less than 80%)

Participants on this pathway have intervention sessions over a 12-week period. In addition to the first intervention session (at week 0) and an intermediate review (at week 1), they receive a review session at week 4, an intermediate review at week 6, a second review session at weeks 8 or 9, and a phase review at week 12. This pattern of delivery constitutes a phase. They then receive a phase review session every 12 weeks, or every 6 weeks if their objectively-measured effective adherence level is <25%.

Very high adherence pathway (adherence 80% or more)

Participants on this pathway have intervention sessions over a 4-week period. In addition to the first intervention session (at week 0) and an intermediate review (at week 1) they receive a phase review at week 4. They then receive a phase review session every 12 weeks.

Triggers

In addition to the pathways outlined above there are a number of criteria which, if met, trigger a new phase of intervention delivery. These are:

i. Participant requested support. This can be a request for additional support at a phase review in which case an additional intervention delivery period is triggered without a break, or at any other time.

ii. Additional periods of delivery are offered to participants if one or both of the following triggers occurs following the first phase review.

iii. A drop of ≥20% in objectively-measured effective adherence since the phase review.

iv. An exacerbation requiring intravenous treatment.

In any of these situations, participants are contacted, and additional support is offered. If participants agree then the triggered pathway commences with a review session at week 0, an intermediate review 1 week later, a review visit 4 weeks later, and a phase review 6 weeks later. Participants then revert back to phase reviews every 12 weeks intervals (or every 6 weeks for those with an objectively-measured effective adherence level of <25%).

Access to CFHealthHub

Participants have an individual login providing access to the CFHealthHub platform throughout the intervention. It can be accessed on a laptop or via an app available for Apple or Android devices.

Participants are encouraged to access the site regularly and are provided with a participant guide with instructions on how to access and information about what to find where.

Intervention modules

The CFHealthHub contains a number of distinct modules each of which focuses on a different aspect using a range of specific behaviour change techniques (described using the definitions in the behaviour change taxonomy)[11] and modes of delivery. Table A1 describes these techniques, and which aspects of the intervention were delivered using the CFHealthHub platform and which were delivered by the interventionist.

Table A1 Modules, behaviour change techniques and mode of delivery for the CFHealthHub intervention

Module	Behaviour change techniques[11]	Mode of delivery
My treatment	Information about health consequences Credible source Salience of consequences Demonstration of the behaviour Vicarious consequences Self-talk	*CFHealthHub:* • Information about CF, the need for treatment, how each treatment works and the importance of adherence • Information presented in a variety of ways though written text, patient stories, 'talking heads' and animation videos, with links to external content including Cochrane reviews • Range of different credible information sources including people CF, clinicians, links to scientific papers *Interventionist:* • Interventionist introducing and highlighting relevant content on CFHealthHub • Interventionist eliciting self-talk through discussion of motivation
Self-monitoring	Self-monitoring of behaviour Adding objects to the environment (CFHealthHub)	*CFHealthHub* • Charts and tables of objective adherence data presented within CFHealthHub *Interventionist* • Introducing and explaining charts and tables to participants
Confidence building	Demonstration of behaviour Focus on past success	*CFHealthHub* • 'Talking heads' videos of coping stories within CFHealthHub *Interventionist* • Interventionist encouraging focus on periods of higher adherence on charts

Goal setting & review	Goal setting (behaviour) Feedback on behaviour Discrepancy between current behaviour and goal Review behavioural goals Graded tasks Social reward	*CFHealthHub* • Indication of goal line on charts of adherence • Visual indication of goal met on CFHealthHub • (Optional) weekly push notifications indicating whether goal was met • (Optional) reward messages sent when goal met *Interventionist* • Discussion and agreement of goals with interventionist • Review of goals • Suggested steady increase in goal as improvements are made • Feedback and social reward on progress
Treatment Plan	Action planning Habit formation Prompts/cues	*CFHealthHub* • Action planning tool and storage within CFHealthHub *Interventionist* • Help to focus on identifying consistent cues and linking to behaviour (habit formation) • Discussion and identification of appropriate cues - and how to add to the environment (if necessary)
Problem-solving	Problem solving Restructure the physical environment Self-talk Social support (practical) Instruction on how to perform the behaviour Demonstration of the behaviour Behavioural practice/rehearsal	*CFHealthHub* • Solution bank within CFHealthHub (including advice to problem solve, restructure the physical environment, engage social support) • Coping planning, Day planner and Party planner tools and storage within CFHealthHub • Videos demonstrating correct use of nebulisers within CFHealthHub *Interventionist* • Tailored problem solving guided by interventionist • Support to create Day plans/Party plans where appropriate • Support to construct if-then coping plans including identifying self-talk where appropriate

CF, cystic fibrosis

Tailoring and personalisation

The CFHealthHub intervention is not one-size-fits-all and is designed to be tailored and personalised so that it can best meet the needs of a wide range of participants. While the entire content of the CFHealthHub website is available for participants to browse, tailored aspects are emphasised or added into a specific personal 'favourites' area called 'My Toolkit'. Table A2 describes the ways in which the intervention is tailored.

Table A2 Tailoring of the CFHealthHub intervention

Tailored component	**How non-tailored components are accessed**	**How version is determined**
Contents of 'My treatment' and 'Problem-solving' focus on information relevant to current prescription drugs	All generic information is available to all participants to browse Information on treatments not currently prescribed are available but minimised	Prescription is entered into CFHealthHub at consent and altered whenever there is a prescription change CFHealthHub automatically tailors content based on this information
Modules of 'My treatment' are selected and placed into 'My Toolkit' based on the scores on the COM-BMQ questionnaire	Participants can browse all modules of 'My treatment'	Participants responses to the COM-BMQ questionnaire are entered into CFHealthHub at consent. CFHealthHub recommends the most relevant modules based on a scoring algorithm If CFHealthHub recommends >3 modules then interventionists select 3 based on the scores and their judgement based on conversations with the participant Modules can be changed throughout the intervention and these are recorded via CFHealthHub
Modules of 'Problem-solving' are selected and placed into 'My Toolkit' based on the barriers identified in consultations with the interventionist	Participants can browse all modules of 'Problem-solving'	Interventionists can select modules of problem-solving content based on the barriers identified in consultations Modules can be changed throughout the intervention and these are recorded via CFHealthHub

'Talking heads' videos are selected to match key participant characteristics and placed into 'My Toolkit'. This is optional	Participants can browse the entire 'talking heads' video library	Interventionists can select relevant videos that match key characteristics of the participant (e.g. age, gender, occupation, life role, problems experienced) Videos can be changed throughout the intervention and these are recorded via CFHealthHub
Goal-setting and review and Treatment planning are only utilised for participants who are motivated (want to) take more treatment Participants with very low motivation do not receive these parts of the intervention. Instead they spend more time focusing on the content of 'My treatment' and relationship building with the interventionist	Participants can choose to set goals and make plans at any point in a consultation or by contacting the interventionist	Very low motivation is determined by a combination of a low motivation score on the COM-BMQ motivation item and discussion with the participant in a consultation The identification of very low motivation is recorded where this applies

COM-BMQ, COM-B Beliefs about Medicines Questionnaire.

A number of features of CFHealthHub are individually personalised for each participant. These are described in table A3.

Table A3 Personalisation of the CFHealthHub intervention

Personalised component	**How personalisation is achieved**
Graphs and charts show personal data	Participants eTrack nebuliser collects and send adherence data to CFHealthHub via the 2net Hub for display
Target line on graph	Participants determine their adherence goal in consultation with the interventionist. This is displayed on their charts
Plans	Participants make individual plans based on discussions with the interventionist. These are made using the tools within CFHealthHub and recorded in 'My Toolkit'. New plans can be added and CFHealthHub records all plans for each participant

Home page	Participants can select an image to display on their home page from a default selection, or can upload their own image
Notifications	Participants can optionally choose to receive personalised notifications via the CFHealthHub app. These send a message to let the participant if they have met their goal in the previous week or an encouraging messaging to keep going if they did not
Reminders	Participants can optionally choose to receive reminders via the CFHealthHub app. These send a reminder message if the participant has not accessed their CFHealthHub account for a period of 2 weeks
Reward messages	Participants can optionally choose to receive reward messages via the CFHealthHub app. These send a reward message if the participant has met their goal in the last week, 2 weeks or month

Types of intervention visit

Broadly, the intervention visits all have the same aim, which is to enable participants to look at their data, reflect on why adherence is important, set goals to increase their adherence and make plans as to how they will achieve these, and problem-solve any barriers that are likely to get in the way. However, the intervention visit types do differ somewhat in their set-up, focus and how in-depth they are, as follows. Detailed information about the structure of the delivery for each type of session is provided in the intervention manual and the relevant worksheets.

First Intervention visit

This session always happens face-to-face, although this can be in a hospital/clinic setting or at home. It lasts between 40 and 60 minutes. It is the first time that the participant accesses the CFHealthHub platform and sees their data. Interventionists must prepare for this session by entering the data from the COM-BMQ screening tool and checking that data are coming through to CFHealthHub from the nebuliser.

The key things that happen in this session are:

- Participant receives their log-in details and accesses CFHealthHub
- Participant (optionally) downloads the CFHealthHub app onto their smartphone

- Modules covered for all:
    - My treatment
    - Self-monitoring
    - Confidence building
- Modules covered for those who want to increase their treatment adherence (sufficiently motivated)
    - Goal setting
    - Treatment plan
    - Problem-solving

Intermediate review

The intermediate review is a short session that is designed to trouble-shoot 'quick' and easy to solve problems (e.g. an action plan that isn't working). It is normally delivered by telephone and lasts 5 to 15 minutes. The review is less structured than other visits.

Ad-hoc review

This follows the same structure as the intermediate review but is delivered where there is unplanned face-to-face contact with a participant (e.g. in clinic).

Review visit

This session normally last 30 to 45 minutes and can be delivered face-to-face or by telephone. The session focuses on the data and what has happened in terms of adherence since the last visit. The precise focus will vary depending on the individual participant, e.g. a session with a participant who has met their goal would have a different focus to one with a participant who has not met their goal (or did not set one).

Broadly thought, the session covers the following modules:

- My treatment
- Self-monitoring
- Confidence building
- Goal setting and review
- Treatment plan
- Problem-solving

Phase review

The focus of this appointment is to facilitate reflection on progress since the intervention (or the current phase of delivery) began and to consider whether continued support is required or whether the participant wishes to manage their adherence independently. Ideally this should be delivered face-to-face but can be delivered by telephone. It normally lasts 20 to 30 minutes.

It covers the following modules:

- My treatment
- Self-monitoring
- Confidence building
- Problem-solving

Fidelity of intervention delivery

Fidelity of delivery was assessed throughout the delivery of the intervention to ensure that interventionists continued to deliver the intervention as specified in the manual and training (assessment of drift). Two reviewers independently assessed a purposive sample of audio-recordings and worksheets associated with the delivery of intervention sessions with participants (first intervention session, review and phase review) using a scoring sheet that was developed and piloted during the feasibility trial.

Sessions were selected to represent a range of different sites, types of sessions with particular focus on interventionists who:

- Had initially failed any of their certification assessments
- Had high withdrawal rates (more than two participants withdrawn from the interventionist contact)
- Had submitted <80% audio-recorded sessions from those participants who provided consent for them to be recorded
- Had completed a lower than expected number of intervention visits and/or had fewer than average action and coping plans recorded in CFHealthHub

Metrics for fidelity of intervention delivery

There were 32 interventionists and a total of 213 fidelity of delivery assessments conducted during the randomised controlled trial.

110 assessments were assessed to explore drift in fidelity over the duration of the trial and a pass mark threshold of 80% was set was drift assessments. Of all paired assessments during the randomised controlled trial there was 97.2% agreement when comparing pass/fail decisions at the 80% threshold (207 of 213 assessments in agreement).

Intervention fidelity delivery scores are summarised by session type in table A4 and by site in table A5. Delivery of the intervention had very good fidelity (overall fidelity by site range 79–97%) with only one site not achieving over the mean threshold (>80%) on drift assessments.

Table A4 Intervention fidelity delivery score summaries by session type

Session type	Assessment*	N	Median	Interquartile range
First intervention visit	First fidelity	27	97.2	92.3, 100.0
	Fidelity reassessment	1	98.6	98.6, 98.6
	Drift	29	95.8	93.1, 97.2
Review	First fidelity	30	92.6	87.0, 98.1
	Fidelity reassessment	9	96.3	94.4, 96.3
	Drift	47	92.6	90.2, 96.3
Phase review	First fidelity	30	94.4	91.7, 97.2
	Fidelity reassessment	6	97.2	93.1, 99.3
	Drift	34	94.4	91.7, 97.2

*Reasons for assessment, with multiple reasons possible: certification (97), reassessment after failed certification (36), high withdrawal rate (18), insufficient audio-recorded sessions (37), fewer than expected intervention visits or action/coping plans created (82), random to ensure total assessment sample ≥20% of all interventionist visits (9).

Table A5. Overall intervention fidelity scores by site

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

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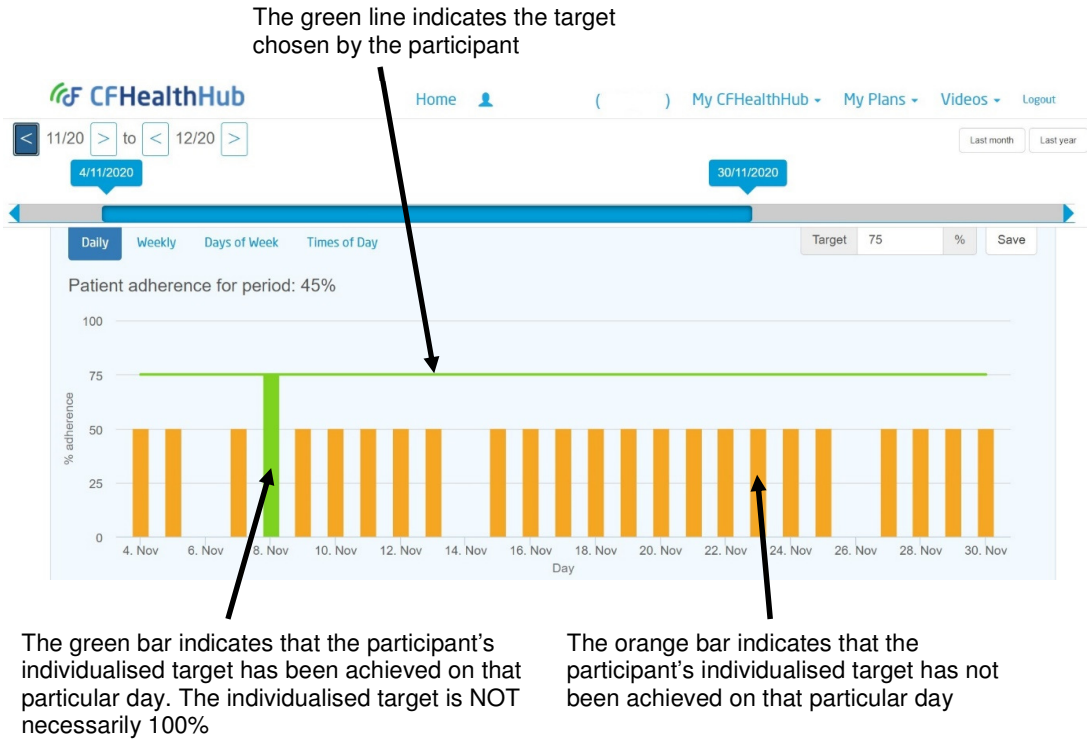
APPENDIX B The choice of adherence measure

In the trial, to reflect effective medication use, adherence was calculated as normative (effective) adherence using objective data from Weeks 3–52 as the outcome and Weeks 1&2 as the "baseline". Objectively-measured effective adherence was adopted as an outcome measure because it better reflects the effectiveness of medication use in comparison to simply calculating percent adherence according to an agreed regimen between adults with cystic fibrosis (CF) and their clinical team, as we have detailed elsewhere.[1-3] The calculation of objectively-measured effective adherence involves numerator adjustment (capping daily maximum nebuliser use at 100%) and denominator adjustment (to define the minimum effective treatment regimen) according to a person's *Pseudomonas aeruginosa* status, as described in section 9.2.1 of the statistical analysis plan (available as supplementary material). For example, a person with chronic *Pseudomonas aeruginosa* infection should be on at least a nebulised muco-active agent and an antibiotic (i.e. three daily doses). If a person with chronic *Pseudomonas aeruginosa* infection only agreed to use nebulised dornase alfa once daily, adherence levels in outcome calculation will use the denominator of three daily doses. If that person was on aztreonam thrice daily and hypertonic saline twice daily, no denominator adjustment will be carried out because denominator adjustment only applies for less than ideal regimen. In particular, the denominator adjustment is important because there is a wide variation in the prescription of inhaled therapies between different centres.[4] By standardising the denominator given the person's clinical characteristics in calculating objectively-measured effective adherence, it is ensured that an increase in percentage adherence is due to an increase in nebuliser use (i.e. increase in the numerator) rather than simply due to a reduction in agreed prescriptions (i.e. decrease in the denominator).

It is important to distinguish the concept of standardisation for effectiveness used as an outcome measure from individualised feedback to participants. Objectively-measured effective adherence allows standardisation based on randomised controlled trial evidence of what treatment is likely to work. Individualised target setting between clinical teams and people with CF continued to be informed by both considerations of effective treatments and considerations of what the person feels they wish to aim for. On occasions within the trial, clinicians and participant may have agreed on regimens that exceed the minimum number of doses that would be considered effective given a participant's characteristics. Since effective adherence denominator adjustments are intended simply to ensure minimum level of effectiveness, no adjustments were necessary in the case of these participants. That is to say the denominator adjustment was a strategic instrument to ensure minimal level of effectiveness is being reflected in the calculation of percent adherence.

Figure B1 Data display of CFHealthHub.



CFHealthHub interventionists were trained to continue to record prescriptions that fulfil the minimum effective dose requirement. In the example of figure B1, the participant is a person with chronic *Pseudomonas aeruginosa* infection who aimed for three daily doses of aztreonam but muco-active agent was not part of their agreed treatment target. Data feedback within CFHealthHub captured individualised targets by displaying a target reflecting the treatment(s) that the participant chose to aim for. If they used all three daily doses of aztreonam, their effective adherence on the day would be 3/(3 + 1) = 75%. This personalised decision would appear as the target set on CFHealthHub in the form of the green line on the graph (at 75% adherence). When fewer than three daily doses were used, the daily adherence bar will be displayed in orange (for example on 23 November). When three daily doses were used, which met their individualised target though it did not achieve an effective adherence of 100%, the daily adherence bar will be displayed in green (for example on 08 November). Therefore, the data display of CFHealthHub feeds back the individualised target. In this example, the agreed prescribed regimen was still recorded as three daily doses of aztreonam and a daily dose of dornase alfa, though the participant was only aiming for three daily doses of aztreonam. By lowering the treatment target rather than reducing prescribed doses, any deviation from effective targets will still be visible on CFHealthHub. It is important to emphasise that this data

display was produced in collaboration with people with CF and reflected their preference for representing individualised targets within the context of the evidence base around optimally effective treatments.

The primary analysis of adherence for randomised clinical trial reporting was standardised using the concept of adherence to a regimen considered to be effective. Any deviation from the guidance to enter effective prescription into CFHealthHub or errors that were made based on a lack of awareness, for example of *Pseudomonas aeruginosa* status, were corrected for in the analysis which ensured that adherence at all sites and for all participants were being compared on an equal basis, i.e. effective adherence. That is to say the analysis of participant data for someone with chronic *Pseudomonas aeruginosa* infection only using inhaled antibiotic recognises it to be a regimen not considered to be maximally effective by international consensus.[5-7] Thus denominator adjustment in this case would ensure that the adherence level analysed against the primary outcome of exacerbation would be not be 100%, but would be capped to a maximum of 75%, as in the example of figure B1. Without such standardisation, a person with more effective nebuliser use would not be identified in the calculation of percent adherence. Rigour around effectiveness is an important element in understanding the relationship between adherence and health outcomes. For example, without denominator adjustment, a person with chronic *Pseudomonas aeruginosa* infection using an average daily dose of one inhaled antibiotic and one dornase alfa but prescribed a total of three daily doses would have adherence of 67% yet a similar person using just a daily dose of dornase alfa but prescribed a total of one daily dose would have adherence of 100%.

By using objectively-measured effective adherence as the method of calculating adherence, we can be confident that an increase in percent adherence reflects more effective medication use. It is important, given the use of effective adherence, to highlight that participants with chronic *Pseudomonas aeruginosa* infection were equally distributed between intervention and usual care. Yet usual care had slightly higher prescribed daily doses (mean 3.1 vs 2.9, see table 2 of main manuscript for breakdown of prescribed doses), meaning that the denominator adjustment would have reduced effective adherence among intervention participants to a greater extent compared to usual care. That is to say the use of objectively-measured effective adherence if anything, would bias against the intervention group.

Figure B2 Mean inhaled doses taken per week.

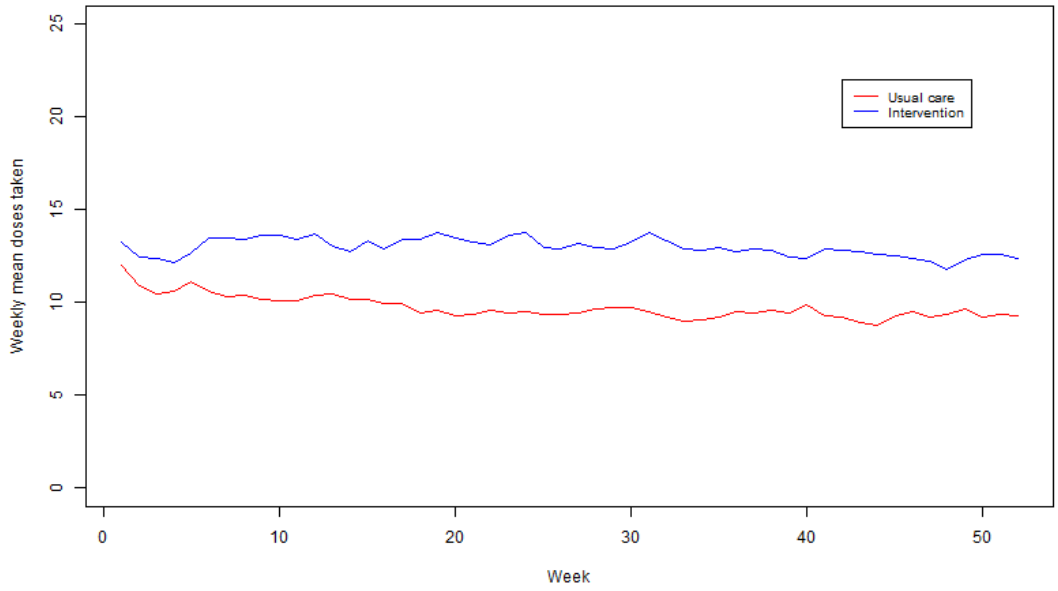
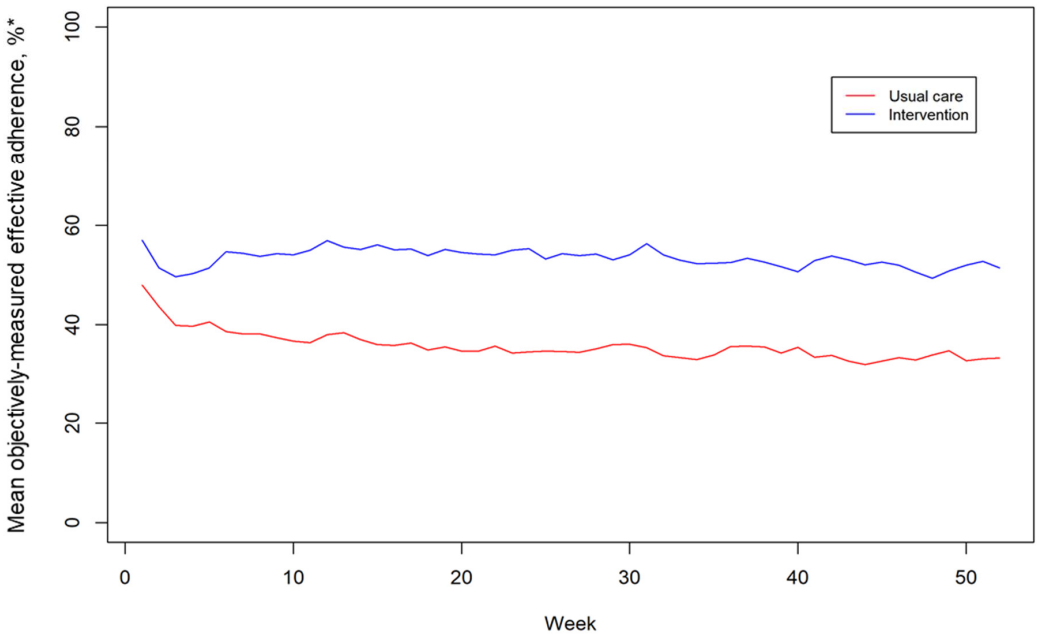


Figure B3 Weekly mean objectively-measured effective adherence.



It is reassuring that as the intervention was delivered, a clear between-group divergence in the mean inhaled doses emerged (figure B2). That is to say the intervention group used more doses of nebulisers, which mirrors the divergence in objectively-measured effective adherence (figure B3). Therefore, the difference in calculated percent effective adherence was driven by the number of doses taken (numerator) among intervention participants rather than prescription (denominator) adjustments. The fact that the absolute number of doses between intervention and control diverges indicates that the use of objectively-measured effective adherence is capturing a difference in absolute treatment use between intervention and control.

The percent objectively-measured adherence without any adjustments also mirrors the difference observed with objectively-measured effective adherence, as shown in table B1.

Table B1 Objectively-measured adherence, by unadjusted and effective calculations

	Usual care	**Intervention**
Baseline (weeks 1 & 2)	N = 295	N = 293
Unadjusted adherence		
Mean (SD)	48.2 (34.4)	56.4 (32.4)
Median (IQR)	50.0 (14.3, 81.0)	61.3 (28.6, 85.7)
Effective adherence		
Mean (SD)	45.5 (34.1)	54.1 (33.0)
Median (IQR)	42.9 (10.7, 76.4)	57.2 (25.0, 84.2)
Weeks 3 to 26	N = 301	N = 301
Unadjusted adherence		
Mean (SD)	38.0 (33.0)	56.3 (31.6)
Median (IQR)	29.0 (6.5, 68.3)	63.6 (31.4, 84.3)
Effective adherence		
Mean (SD)	35.9 (32.2)	53.7 (31.7)
Median (IQR)	25.9 (6.2, 61.6)	58.7 (26.8, 81.4)
Weeks 27 to 52	N = 282	N = 288
Unadjusted adherence		
Mean (SD)	35.4 (32.7)	55.2 (32.6)
Median (IQR)	27.6 (4.0, 64.6)	64.0 (23.3, 83.0)
Effective adherence		
Mean (SD)	33.2 (31.7)	51.9 (32.6)
Median (IQR)	24.4 (3.5, 59.8)	56.2 (22.5, 81.4)

IQR, interquartile range; SD, standard deviation.

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APPENDIX C Participant recruitment

As is discussed in appendix D, "baseline adherence" of the participants may have been exaggerated by novelty effect and white coat adherence. Nonetheless, we also acknowledge that the study may have recruited a convenience sample that was more focused on adherence compared to the general cystic fibrosis (CF) population. The baseline median adherence of the participants was 52% whereas real world median adherence among adults with CF has been reported as closer to 35%.[1,2] Another observation supporting the contention that a more engaged sample was recruited in this trial is the intravenous (IV) antibiotic rejection rate for exacerbations among this sample of around 5% (see table S3 footnote), which is four-fold lower than in real-world dataset where the IV rejection rate is around 20%.[3]

In the CONSORT diagram (figure 2 of main manuscript), we report that 3510 adults with CF were screened and 608 were recruited. The discrepancy between screening and recruitment was driven by a decision to prioritise rapid recruitment because more than two-thirds of large publicly funded trials in the United Kingdom (UK) failed to recruit to time and target.[4] As such, all adults with CF in participating centres were screened using data from the UK CF registry and investigators may have also first approached those they thought would be most amenable to participating. Once a centre reached its recruitment target (around 35 participants per centre), recruitment for the centre would be closed and a large proportion of other screened adults (each centre would have screened on average 150–200 adults) would be unable to participate. This strategy has enabled us to recruit 608 participants in just 8 months (even though not all centres open for recruitment at the same time), which is ahead of the recruitment target.

Although a biased sample that was more focused on adherence may have been recruited as the result of the recruitment strategy, it is important to consider the direction of any resultant bias. As is discussed in appendix D, there is a ceiling effect associated with high baseline adherence.[5,6] It may follow that scope for improvement in adherence in our trial was curtailed in the intervention arm by ceiling effects associated with high baseline adherence and nearly 30% of the participants having baseline adherence >75%. Therefore, any bias associated with the recruitment strategy would be towards null effect and the overall adherence difference of adjusted mean difference of 9.5 percentage points (95% confidence interval 8.6, 10.4) may have been an under-estimate.

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APPENDIX D Between-group imbalance and baseline adherence

Table 2 of the main manuscript suggests there may be some imbalance between usual care and intervention groups at baseline. The intervention group was around 1 year older (mean age 31.1±10.6 years versus 30.3±10.8 years) yet percent predicted forced expiratory volume in one second (FEV_1) was higher by around 2 (60.7±23.5 versus 58.3±22.6) and annual intravenous (IV) antibiotics use was lower by around 3 days (24.2±27.9 days versus 27.7±33.0 days). This may suggest that the intervention participants had slightly better lung health at baseline, which may be due to higher adherence prior to recruitment. Indeed, there is also imbalance of "baseline adherence", that is the objectively-measured effective adherence level measured in the first two weeks post randomisation, which was around 9% in favour of the intervention group (54.1±33.0% versus 45.5±34.1%).

In this section, we deal with the following five issues:

1) Explain how the randomisation process could result in baseline imbalance despite 608 participants being randomised
2) Explore the likely impact of age on the baseline adherence
3) Provide analyses which explore the adherence trajectory for intervention versus usual care after minimising the imbalance of baseline adherence
4) Explore the impact of baseline imbalance in terms of the direction of bias on the observed effect size
5) Explore how these limitations can be minimised to make future trials more efficient

1) The randomisation process

The imbalance in baseline parameters is likely due to a randomisation process which involved two levels of stratification (centre and past-year IV days, as described in Section 9.1 of the protocol [available as supplementary material]) which limits the block size. Each centre recruited around 35 participants and the aim was to achieve approximately similar numbers of usual care and intervention participants in each centre, so that the centre interventionists were not overwhelmed by excess number of intervention participants. Thus the play of chance is not acting on 608 participants but is acting on a maximum block size of 35 with two levels of stratification to randomise participants into usual care and intervention; i.e. the play of chance is constrained by limited block size.

2) Impact of age on the baseline adherence

The intervention group was around 1 year older. The adherence imbalance at the initial part of the trial may in part be influenced by differences in the proportion of participants according to age categories. Multiple studies have demonstrated a strong association between the age categories (16-18 years, 19–25 years, 26–34 years, ≥35 years) and adherence levels.[1,2] The usual care arm has an excess of younger participants with lower adherence and the intervention arm has an excess of older participants with higher adherence (figure D1). There were 27 usual care and 17 intervention participants aged 16–18 years, where the mean baseline adherence for 44 participants was 31%. There were 75 usual care and 91 intervention participants aged ≥35 years, where the mean baseline adherence for 166 participants was 62%. By plotting adherence according to age categories, the effect of age imbalance at the start of the trial is clearer. There is less adherence imbalance at the start of the trial when participants were grouped by age (figure D1) except for the few participants aged 16–18 years (n=44, 7%). Some of the baseline adherence imbalance following age stratification may be due to the transient effect of enhanced white coat adherence in the intervention group who were aware from Day 1 that a planned 3-week meeting with interventionists to review their data would occur. This is consistent with the behaviour change technique of feedback used as part of the intervention and contrasts with the usual care group who were aware that adherence measurement would simply be used for research and neither fed back nor reviewed by interventionists.

Figure D1 Adherence curves according to different age categories.

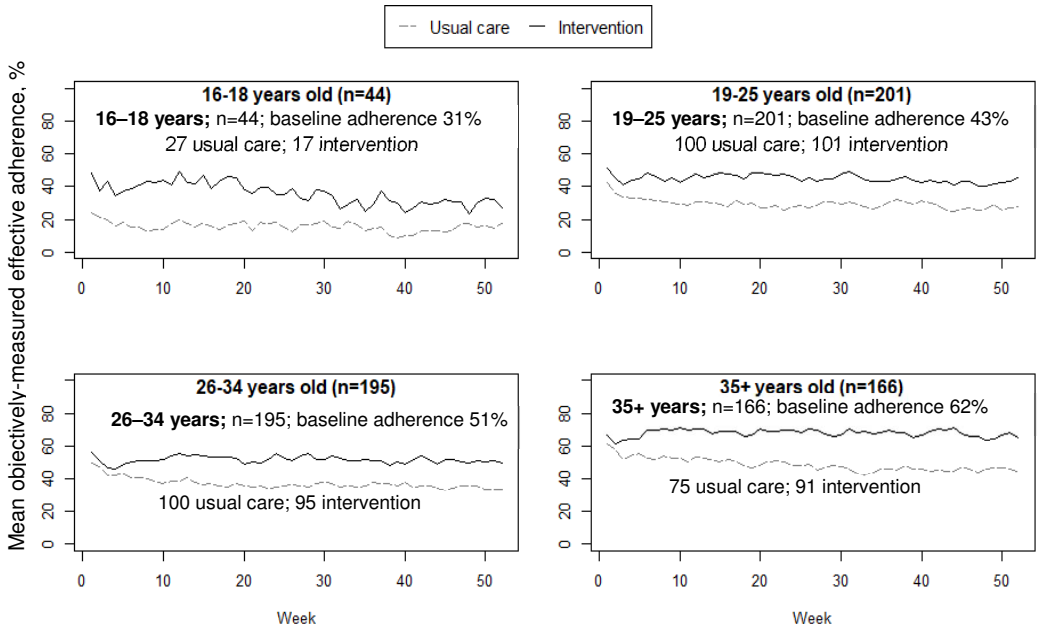
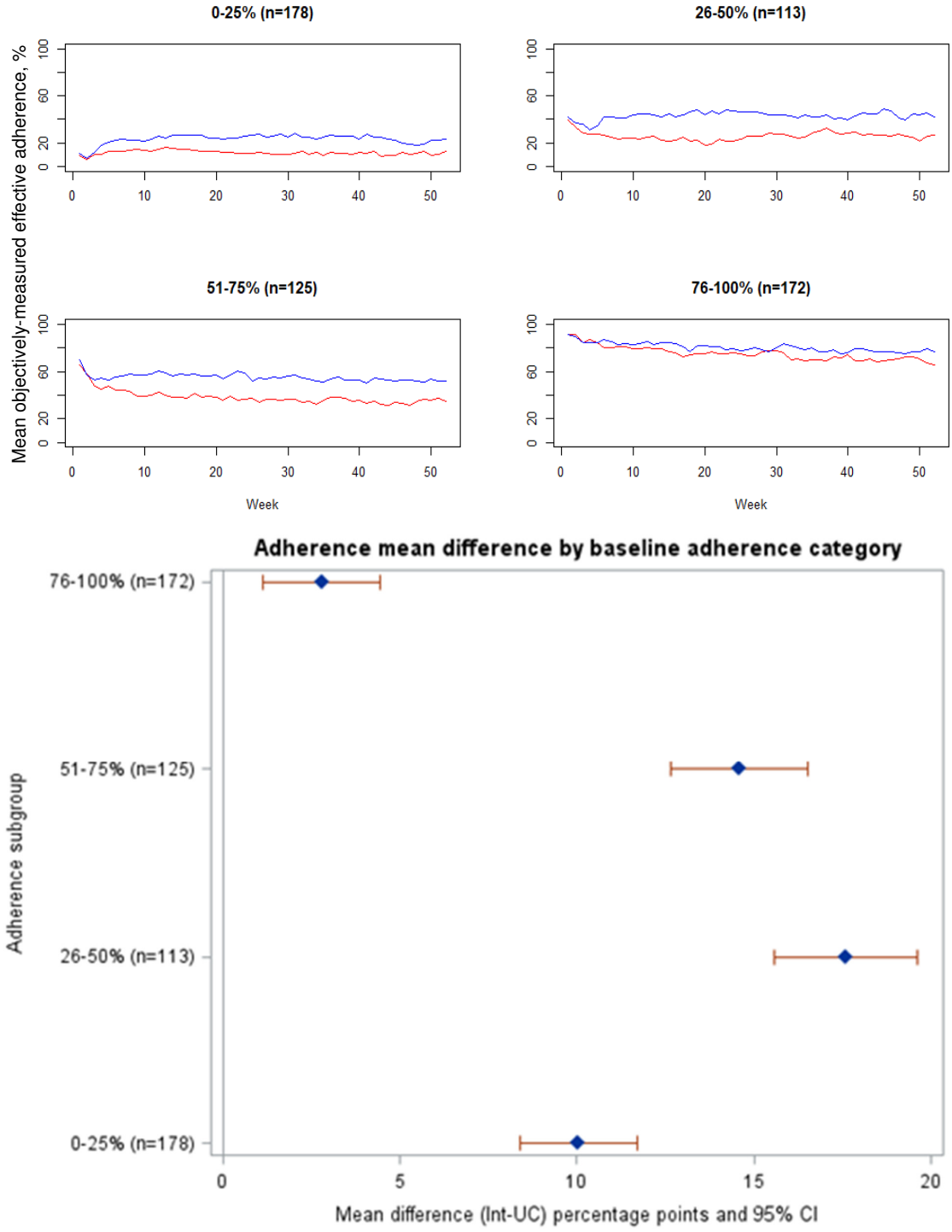


Figure D2 Adherence curves, and mean between-group difference in objectively-measured effective adherence, according to baseline adherence. CI, confidence interval; Int-UC, intervention minus usual care.



3) Explaining the adherence trajectory for intervention versus usual care

Trial participants in both arms had never previously been monitored with data-logging nebulisers and would likely be susceptible to novelty effect and whitecoat adherence at the initial part of the trial,[3-6] with the consequence that adherence in the first two weeks was unrepresentative of their steady-state adherence. Of note, the baseline adherence imbalance was discussed in the previous section and was unrelated to novelty effect or white coat adherence. It is known that novelty effect and whitecoat adherence are relatively short-lived[3-6] and this is reflected in the initial sharp adherence decline for both arms seen in the study (figure 3 of main manuscript; figure D1). Among control participants who did not receive any intervention, this decline continued over the next 12 weeks to around 35%, which is the real-world objective adherence level for inhaled therapies among adults with CF,[7,8] and stayed at this level until the end of the trial. In the intervention group, the initial rate of decline was similar to the controls until the behavioural-change intervention started from Week 3 and adherence subsequently improved. It is also important to note that the separation in adherence curves between intervention and usual care participants occurred regardless of baseline adherence when curves were plotted by adherence categories (figure D2).

4) The impact of baseline imbalance on the direction of bias

There is a ceiling effect associated with high adherence.[9,10] Indeed, subgroup analysis according to baseline adherence (figure D2) indicates minimal end of study between-group difference in objectively-measured effective adherence among those with baseline adherence >75%. It is therefore likely that a preponderance of high adherers among the intervention group would bias the overall adjusted adherence results towards null effect, i.e. the overall adjusted mean difference in objectively-measured effective adherence of 9.5 percentage points (95% confidence interval 8.6, 10.4) may have been larger had those with baseline adherence >75% been excluded.

5) How these limitations can be minimised to make future trials more efficient

As discussed in the main manuscript, the measurement of “baseline adherence” in the first two weeks post randomisation is a limitation of the trial. It would have been ideal to obtain an understanding of the study participants’ actual baseline adherence by measuring adherence over longer periods prior to randomisation, which may allow white coat adherence among adults using data-logging nebulisers for the first time to wear off. The decay of usual care participants’ adherence to baseline took approximately 12 weeks, suggesting the importance

of providing objective adherence monitoring technology to participants for at least 12 weeks before baseline adherence is captured. This would impact time scales for an adherence trial and the funding envelope requested. In our subsequent trials, we plan to nest the evaluation of adherence interventions within a digital learning health system (ISRCTN14464661) so that baseline adherence can be understood prior to randomisation. This has a number of benefits, including recruiting participants in whom adherence can be seen to improve from baseline (effectively removing the impact of whitecoat adherence) and greater efficiency by avoiding the recruitment of potential participants with maximal adherence at baseline.

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Appendix E Other limitations of the trial

In the main manuscript, the limitations of using exacerbation as the primary endpoint which may bias the result towards null effect and the difficulty of discerning the trajectory of intervention effect due to a lack of pre-randomisation steady-state adherence level were discussed. In this appendix, we discuss the other limitations of the trial.

One of the potential limitations is the delivery of both behavioural change and research processes by interventionists. The intervention was delivered via CFHealthHub, which was unavailable to usual care participants. Mixed-methods process evaluation of our two-centre pilot study, which specifically addressed contamination, demonstrated negligible contamination among usual care participants.[1] Outcome data were objective measures unlikely to be biased by interventionists' data collection.[2]

Three other limitations of the trial might bias the observed results towards a null effect. First, a convenience sample was recruited with around 30% of the participants having baseline adherence >75%, a subgroup in whom an impact on outcome measures would be unlikely, rendering the trial less efficient. It is noteworthy that the intravenous (IV) antibiotic rejection rate in this trial was around 5% whereas the real-world IV rejection rate is typically four-fold higher at around 20%,[3] supporting the contention that a more engaged sample was recruited in this trial. The ceiling effect among high adherers means that the effect size would have been larger if high adherers were excluded (see appendices C and D). With this limitation, any observed difference in adherence in the trial could be considered particularly noteworthy. Since trial participants may have better health outcomes than non-participants,[4] there may also be ceiling effect on health outcomes as well as ceiling effect on adherence. If we assume the intervention is able to impact people with lower levels of adherence, the outcomes seen in this opportunistic sample might have a larger effect size in the whole population where median adherence is ~30%. Interestingly, the FEV_1 difference did not include unity in the subset of participants with adherence <25%. This further supports the assertion that focusing an adherence intervention study on participants with lower levels of adherence has the advantage of both trial efficiency and increased probability of impacting health outcomes such as FEV_1.

Second, there was a period of server downtime which affected intervention delivery. Adherence data were not lost but simply inaccessible during the downtime. Interventions were delivered over 80 weeks (9 months for recruitment) and the CFHealthHub server experienced a 43-day outage at one point, which delayed the receipt of data to the server such that the platform was inaccessible to all participants during this period. Intervention sessions would be rescheduled if adherence data were unavailable, meaning that no intervention took place during this period. The server hosting infrastructure was improved following the downtime,

reducing the likelihood of future issues. Fidelity assessments throughout the trial, which required the use of objective adherence data during sessions, showed reassuring scores of 93–97%. Given the importance of the platform for intervention delivery, unavailability would reduce the intervention effectiveness and bias the results towards null effect. However, in the spirit of intent-to-treat analysis, we did not make any adjustments to avoid over-estimating treatment effect. It is important to emphasise that periods where data transfer was delayed did not result in data loss as data were simply backed up and transferred once system transfer was restored.

Third, the trial was underpowered to detect the observed point estimate in forced expiratory volume in one second (FEV_1). Sample size calculation in table S1 showed that the trial has under 80% power to detect a 6 point difference in between-group percent predicted FEV_1. The observed between-group point estimate of 1.4 in percent predicted FEV_1 at 12 months may simply be due to chance but is within the range observed for hypertonic saline at 48 weeks.[5]

Overall, these four limitations (alongside the limitations of exacerbation as the primary outcome) reduced the trial's ability to demonstrate statistically significant improvements in lung health. The significant albeit small difference in body mass index (BMI) with the intervention versus usual care should be noted, and higher BMI has shown an association with higher FEV_1.[6] It is possible that FEV_1 improvement may emerge gradually over time with longer follow-up.

It is also possible that improvement in health outcomes may not be linearly associated with the increase in adherence; for example, there may be both a threshold effect and a ceiling effect. The relationship between improvement in treatment adherence and improvement in health outcomes among people with CF is relatively unexplored, in part because previous adherence trials did not demonstrate improved adherence. Further analyses would be performed using the ACtiF dataset to better understand the relationship between adherence to chronic therapies and health outcomes.

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