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Psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis (Review)

Dawson S, Girling CJ, Cowap L, Clark-Carter D

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[Intervention Review]

Psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis

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ABSTRACT

Background

Adherence to treatment, including inhaled therapies, is low in people with cystic fibrosis (CF). Although psychological interventions for improving adherence to inhaled therapies in people with CF have been developed, no previous published systematic review has evaluated the evidence for efficacy of these interventions.

Objectives

The primary objective of the review was to assess the efficacy of psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis (CF). The secondary objective was to establish the most effective components, or behaviour change techniques (BCTs), used in these interventions.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, which is compiled from electronic database searches and handsearching of journals and conference abstract books.

We also searched databases (PubMed; PsycINFO; EBSCO; Scopus; OpenGrey), trials registries (World Health Organization International Clinical Trials Registry Platform; US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov), and the reference lists of relevant articles and reviews, with no restrictions on language, year or publication status.

Date of search: 7 August 2022.

Selection criteria

We included randomised controlled trials (RCTs) comparing different types of psychological interventions for improving adherence to inhaled therapies in people with CF of any age, or comparing psychological interventions with usual care. We included quasi-RCTs if we could reasonably assume that the baseline characteristics were similar in both groups.

Data collection and analysis

Two review authors independently assessed trial eligibility and completed data extraction, risk of bias assessments, and BCT coding (using the BCT Taxonomy v1) for all included trials. We resolved any discrepancies by discussion, or by consultation with a third review author as necessary. We assessed the certainty of the evidence using GRADE.

Main results

We included 10 trials (1642 participants) in the review (children and adolescents in four trials; adults in five trials; and children and adults in one trial). Nine trials compared a psychological intervention with usual care; we could combine data from some of these in a number of quantitative analyses. One trial compared a psychological intervention with an active comparator (education plus problem-solving (EPS)). We identified five ongoing trials.

Psychological interventions were generally multi-component and complex, containing an average of 9.6 BCTs (range 1 to 28). The two most commonly used BCTs included 'problem-solving' and 'instruction on how to perform the behaviour'. Interventions varied in their type, content and mode of delivery. They included a problem-solving intervention; a paper-based self-management workbook; a telehealth intervention; a group training programme; a digital intervention comprising medication reminders and lung function self-monitoring; a life-coaching intervention; a motivational interviewing (MI) intervention; a brief MI intervention (behaviour change counselling); and a digital intervention combined with behaviour change sessions. Intervention duration ranged from 10 weeks to 12 months. Assessment time points ranged from six to eight weeks up to 23 months.

Psychological interventions compared with usual care

We report data here for the 'over six months and up to 12 months' time point. We found that psychological interventions probably improve adherence to inhaled therapies (primary outcome) in people with CF compared with usual care (mean difference (MD) 9.5, 95% confidence interval (CI) 8.60 to 10.40; 1 study, 588 participants; moderate-certainty evidence). There was no evidence of a difference between groups in our second primary outcome, treatment-related adverse events: anxiety (MD 0.30, 95% CI -0.40 to 1.00; 1 study, 535 participants), or depression (MD -0.10, 95% CI -0.80 to 0.60; 1 study, 534 participants), although this was low-certainty evidence. For our secondary outcomes, there was no evidence of a difference between groups in terms of lung function (forced expiratory volume in one second (FEV_1) % predicted MD 1.40, 95% CI -0.20 to 3.00; 1 study, 556 participants; moderate-certainty evidence); number of pulmonary exacerbations (adjusted rate ratio 0.96, 95% CI 0.83 to 1.11; 1 study, 607 participants; moderate-certainty evidence); or respiratory symptoms (MD 0.70, 95% CI -2.40 to 3.80; 1 study, 534 participants; low-certainty evidence). However, psychological interventions may improve treatment burden (MD 3.90, 95% CI 1.20 to 6.60; 1 study, 539 participants; low-certainty evidence). The overall certainty of the evidence ranged from low to moderate across these outcomes. Reasons for downgrading included indirectness (current evidence included adults only whereas our review question was broader and focused on people of any age) and lack of blinding of outcome assessors.

Psychological interventions compared with an active comparator

For this comparison the overall certainty of evidence was very low, based on one trial (n = 128) comparing an MI intervention to EPS for 12 months. We are uncertain whether an MI intervention, compared with EPS, improves adherence to inhaled therapies, lung function, or quality of life in people with CF, or whether there is an effect on pulmonary exacerbations. The included trial for this comparison did not report on treatment-related adverse events (anxiety and depression). We downgraded all reported outcomes due to small participant numbers, indirectness (trials included only adults), and unclear risk of bias (e.g. selection and attrition bias).

Authors' conclusions

Due to the limited quantity of trials included in this review, as well as the clinical and methodological heterogeneity, it was not possible to identify an overall intervention effect using meta-analysis. Some moderate-certainty evidence suggests that psychological interventions (compared with usual care) probably improve adherence to inhaled therapies in people with CF, without increasing treatment-related adverse events, anxiety and depression (low-certainty evidence). In future review updates (with ongoing trial results included), we hope to be able to establish the most effective BCTs (or 'active ingredients') of interventions for improving adherence to inhaled therapies in people with CF.

Wherever possible, investigators should make use of the most objective measures of adherence available (e.g. data-logging nebulisers) to accurately determine intervention effects. Outcome reporting needs to be improved to enable combining or separation of measures as appropriate. Likewise, trial reporting needs to include details of intervention content (e.g. BCTs used); duration; intensity; and fidelity. Large trials with a longer follow-up period (e.g. 12 months) are needed in children with CF. Additionally, more research is needed to determine how to support adherence in 'under-served' CF populations.

PLAIN LANGUAGE SUMMARY

Psychological interventions to help people with cystic fibrosis take their inhaled treatments

Key messages

Psychological interventions are designed to help people modify their thoughts, feelings and behaviours.

We think that psychological interventions are probably better than usual care at helping people with CF to take their inhaled treatments, and may cause little or no harm (e.g. anxiety or depression) when measured six to 12 months after treatment.

We are uncertain whether motivational interviewing (MI) was better or worse than education plus problem-solving (EPS) at helping people with CF to take their inhaled treatments.

Background

CF is a chronic, genetic condition, usually diagnosed at birth through newborn screening. People with CF experience recurrent chest infections due to the build-up of thick, sticky mucus (or sputum) in their lungs and digestive systems. Inhaled treatments are usually prescribed to either thin sputum (making it easier to clear or cough up), or to treat and control bacteria in the lungs (to reduce infections).

People living with any long-term health condition often struggle to take the number of treatments they are prescribed, and this is no different in CF.

What did we want to find out?

Can psychological interventions help people with CF to take their inhaled treatments, and are there any harmful or unwanted effects of these interventions (e.g. anxiety or depression)?

Which techniques (e.g. goal-setting, problem-solving) work best at helping people with CF to take their inhaled treatments?

What did we do?

We searched for studies comparing different types of psychological interventions, or comparing the interventions with usual care, for helping people with CF of any age to take their inhaled treatments.

We compared and summarised the results of the trials and rated our confidence in the evidence, based on factors such as the trial methods.

What did we find?

We included 10 trials with 1642 people with CF (approximately 54.3% female). Four trials included children and adolescents; five trials included adults; and one trial included both. Nine trials compared a psychological intervention with usual care, and one study compared two psychological interventions (MI versus EPS). People (or in one trial, CF centres) were randomly selected for one group or the other. People were followed up for between six to eight weeks and 23 months.

Psychological interventions were wide-ranging. They included an intervention that combined digital technology (website or app) with support from trained healthcare professionals. Interventions used a range of techniques, with problem-solving and providing instructions on how to take treatments being the most commonly used.

Main results

Psychological interventions are probably better than usual care at helping people with CF to take their inhaled treatments, and may cause little or no harm (e.g. anxiety or depression) when measured six to 12 months after treatment. Psychological interventions may also improve perceived treatment burden (as measured using a quality of life (QoL) questionnaire). There was no evidence of a difference between groups in terms of lung function (a measure of how well someone's lungs are working), the number of chest infections, or perceived chest symptoms (again measured using a QoL questionnaire).

We are uncertain whether MI was better or worse than EPS at helping people with CF to take their inhaled treatments, improving lung function or QoL, or reducing chest infections in people with CF. The included trial did not look at whether MI or EPS caused harm (e.g. anxiety or depression).

What are the limitations of the evidence?

Our confidence in the evidence for psychological interventions being better or worse than usual care ranges from low to moderate. The biggest included trial of psychological interventions (which had results from between six and 12 months after treatment started) focused on adults with CF (aged 16 years and over), whereas the question we wanted to answer was broader (i.e. we cannot be sure if the results would be the same in children). Large trials with a longer follow-up period (e.g. 12 months) are needed in children with CF. It is possible that because people completing the outcome assessments knew which group they were in, this might affect the results for QoL, anxiety and depression.

We are not confident in the evidence comparing MI with EPS. The only trial examining this included a small number of adults, so we cannot be sure if the results would be the same in children or in a larger group of people. We are unsure whether participants were put into the different treatment groups truly at random, so differences between the groups might be due to differences between people rather than the treatments. We are also unsure about people leaving the trial early and how this might affect the results. We also think that because the people completing the outcome assessments knew which group they were in, this might affect the QoL results.

Current evidence on which techniques (e.g. goal-setting, problem-solving) work best at helping people with CF to take their inhaled treatments is limited. Future trials should provide more details on the techniques used in interventions.

How up to date is this evidence?

The evidence is up to date to 7 August 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: psychological interventions compared with usual care

Psychological interventions compared with usual care for improving adherence to inhaled therapies in people with CF

Patient or population: children, adolescents or adults with CF

Settings: single or multicentre; UK-, USA- or Denmark-based; hospital, clinic or community

Intervention: psychological interventions (self-management intervention comprising digital platform and behaviour change sessions; life coaching intervention; problem-solving intervention)

Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Psychological interventions				
Adherence to inhaled therapies: % of prescribed inhaled therapies taken Follow-up: 12 months	The adjusted mean % of prescribed inhaled therapies taken was 9.50% higher in the intervention group compared to usual care.		MD 9.50 (8.60 to 10.40)	588 participants (1 study)	⊕⊕⊕⊖ moderate[a,b]	An objective recorded measure (using data-logging nebulisers) where a higher score indicates higher adherence. We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022).
Treatment-related adverse events **Anxiety:** GAD-7 (Spitzer 2006) Follow-up: 12 months	The adjusted mean anxiety score was 0.3 higher in the intervention group compared to usual care.		MD 0.30 (-0.40 to 1.00)	535 participants (1 study)	⊕⊕⊖⊖ low[b,d]	We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022). Scale from: 0 to 21 (higher score indicates greater anxiety). No evidence of treatment-related adverse events.

Treatment-related adverse events **Depression** PHQ-8 (Kroenke 2009) Follow-up: 12 months	The adjusted mean depression score was 0.10 lower in the intervention group compared to usual care.	MD -0.10 (-0.80 to 0.60)	534 participants (1 study)	⊕⊕⊖⊖ low[b,d]	We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022). Scale from: 0 to 24 (higher score indicates greater depression). No evidence of treatment-related adverse events. One other study assessed depression using 2 measures at this time point (Knudsen 2016). This study also found no difference between groups on any depression measure.
QoL CFQ-R (Quittner 2009) Follow-up: 12 months	**Treatment burden** The adjusted mean treatment burden score was 3.90 higher in the intervention group compared to usual care.	MD 3.90 (1.20 to 6.60)	539 participants (1 study)	⊕⊕⊖⊖ low[b,d]	We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022). Scale from: 0 to 100 (higher score indicates better QoL). 2 other studies assessed treatment burden at this time point (Knudsen 2016; Quittner 2019). These 2 studies found no difference between groups.
	Respiratory symptoms The adjusted mean score for respiratory symptoms was 0.70 higher in the intervention group compared to usual care.	MD 0.70 (-2.40 to 3.80)	534 participants (1 study)	⊕⊕⊖⊖ low[b,d]	We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022). Scale from: 0 to 100 (higher score indicates better QoL). No difference between groups. 2 other studies assessed respiratory symptoms at this time point (Knudsen 2016; Quittner 2019). These 2 studies also found no difference between groups.
Lung function FEV_1 % predicted Follow-up: 12 months	The adjusted mean FEV_1 score was 1.40% predicted higher in the intervention group compared to usual care.	MD 1.40 (-0.20 to 3.00)	556 participants (1 study)	⊕⊕⊕⊖ moderate[a,b]	We report an adjusted MD; adjusted data[c] taken directly from the study (Wildman 2022). A higher score indicates better lung function. No difference between groups. 2 other studies assessed FEV_1% predicted at this time point (Knudsen 2016; Quittner 2019). Post-intervention data were not available in 1 study, so results have been reported narratively (Quittner 2019); no intervention effects were found for any of the secondary outcomes compared to usual care (and FEV_1% predicted was a

					secondary outcome). The other study also found no difference between groups (Knudsen 2016).
Pulmonary exacerbations Follow-up: 12 months	In one trial, there were 526 exacerbations in the control arm (adjusted rate 1.77/year, n = 303) compared with 482 in the intervention arm (1.63/year, n = 304). There was no difference between groups in exacerbation incidence rates (adjusted[e] RR 0.96, 95% CI 0.83 to 1.11; unadjusted RR 0.92, 95% CI 0.77 to 1.10) (Wildman 2022).	Not estimable	607 participants (1 study)	⊕⊕⊕⊖ moderate[a,b]	In this study, pulmonary exacerbations were defined as "Number of exacerbations treated with IV antibiotics with at least 1 modified Fuchs' criteria (e.g. change in sputum, increased cough) (Ratjen 2012)." The authors reported that incidence RRs indicated no between-group difference in exacerbations (MD 0.96 (95% CI 0.83 to 1.12); P = 0.64) (Wildman 2022). One other study assessed pulmonary exacerbations at this time point (Quittner 2019). Post-intervention data were not available in this study and results have been reported narratively. It was also unclear how this study defined exacerbations. The authors did however report that no intervention effect was found for pulmonary exacerbations (Quittner 2019).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised (Quittner 2009); CI: confidence interval; FEV_1: forced expiratory volume at 1 second; GAD-7: Generalized Anxiety Disorder-7 (Spitzer 2006); IV: intravenous; MD: mean difference; PHQ-8: Patient Health Questionnaire-8 (Kroenke 2009); QoL: quality of life; RR: rate ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Non-blinding of outcome assessors would not affect the results as it is an objective measure, so no need to downgrade.
[b]Downgraded once due to indirectness. The evidence includes only adults with CF aged 16 years and older, and was not designed to answer the specific question posed in this review.
[c]The post-intervention MDs are adjusted for past year IV antibiotic days, CF centre, and outcome measure at baseline.
[d]Downgraded once due to unclear risk of detection bias, as outcome assessors were not blinded.
[e]The post-intervention MDs are adjusted for CF centre and past year IV antibiotic days.

Summary of findings 2. Summary of findings: psychological interventions compared with an active comparator

Psychological interventions compared with an active comparator intervention (e.g. education plus problem-solving; EPS) for improving adherence to inhaled therapies in people with cystic fibrosis

Patient or population: adults (aged 16 years and over) with CF

Settings: single CF centre in the USA

Intervention: psychological intervention (MI)

Comparison: active comparator (EPS)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Active comparator (EPS)	Psychological intervention (MI)				
Adherence to inhaled therapies cMPR Follow-up: 12 months	Please see comments.			95 participants (1 study)	⊕⊖⊖⊖ very low[a,b,c]	An objective-count measure (cMPR), which included inhaled therapies (dornase alfa, hypertonic saline, inhaled tobramycin, and aztreonam), as well as one non-inhaled treatment (azithromycin). This study reported only medians and IQRs (Riekert 2013). At 12 months, median (IQR) cMPR was 54 (37 to 73) in the MI group, compared with 51 (17 to 71) in the EPS group. The study authors also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that no intervention effects were found for the cMPR (P = 0.763; no effect size reported or calculable) or any of the individual drugs.
Treatment-related adverse events **Anxiety**	Not reported.					
Treatment-related adverse events **Depression**	Not reported.					
QoL CFQ-R (Quittner 2009)	Please see comments.			95 participants (1 study)	⊕⊖⊖⊖ very low[a,b,d]	Scale from: 0 to 100 (higher score indicates better QoL) This study reported only medians and IQRs for QoL, measured using 3 domains of the CFQ-R (respiratory,

Follow-up: 12 months				physical functioning, and treatment burden) (Riekert 2013). At 12 months, median (IQR) score was 67 (50 to 83) in the MI group and 67 (50 to 72) in the EPS group (respiratory); 79 (60 to 96) in the MI group and 79 (54 to 96) in the EPS group (physical functioning); and 56 (44 to 67) in the MI group and 56 (44 to 78) in the EPS group (treatment burden). The investigators also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that no intervention effects were found for QoL at this time point.
Lung function FEV_1 % predicted Follow-up: 12 months	Please see comments.	125 participants (1 study)	⊕⊖⊖⊖ very low[a,b,c]	A higher score indicates better lung function. This study reported only medians and IQRs (Riekert 2013). At 12 months, median (IQR) FEV_1% predicted was 66% (48 to 85%) in the MI group and 64% (49 to 84%) in the EPS group. The authors also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that the intervention had no effect on lung function (P = 0.773; no effect size reported or calculable).
Pulmonary exacerbations Follow-up: 12 months	Please see comments.	128 participants (1 study)	⊕⊖⊖⊖ very low[a,b,c]	This study reported the percentage of people in each group with at least 1 exacerbation in the past year (Riekert 2013). Method of assessing exacerbations not reported. We calculated the number of participants in each group who had experienced an exacerbation over the 12-month study period. In the MI group, 12 out of 63 participants (19%) experienced an exacerbation compared with 12 out of 65 (18%) in the EPS group. The study authors also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that the intervention had no effect on pulmonary exacerbations (P = 0.929; no effect size reported or calculable).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised (Quittner 2009); cMPR: composite medication possession ratio; EPS: education plus problem-solving; FEV_1: forced expiratory volume at 1 second; IQR: interquartile range; MI: motivational interviewing; QoL: quality of life.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for imprecision; relatively small participant numbers which do not meet the optimal information size.
[b]Downgraded once due to indirectness. The evidence includes only adults with CF aged 16 years and older, and was not designed to answer the specific question posed in this review.
[c]Downgraded once due to unclear risk of selection bias and attrition bias.
[d]Downgraded once due to unclear risk of selection bias (not reported), attrition bias (withdrawals not described), and detection bias (outcome assessors not blinded).

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a chronic, genetic condition affecting over 10,500 people in the UK (UK CF Registry 2019), 30,000 people in the USA (CF Foundation Patient Registry 2019), and around 90,000 people worldwide (Bell 2020). One in 25 people in the UK carries the faulty gene that causes CF, usually without realising it (Cystic Fibrosis Trust 2019). People with CF are prone to recurrent chest infections, or pulmonary exacerbations, due to the build-up of thick, sticky mucus (or sputum) in their lungs and digestive systems.

Although people with CF are living longer, their life expectancy remains well below average, and the median predicted survival age of someone born with CF in 2018 ranges between 47.3 years in the UK (UK CF Registry 2018), 47.4 years in the USA (CF Foundation Patient Registry 2019), and 52.1 years in Canada (Cystic Fibrosis Canada 2019). As lung disease is the primary cause of morbidity and mortality in people with CF, nebulised medications (or inhaled therapies) are usually prescribed (ECFS Patient Registry 2017), with multiple trials demonstrating their efficacy (Smith 2018; Yang 2018). These treatments are delivered directly to the lungs, thereby reducing side effects, and may include antibiotics to treat or control infections (e.g. tobramycin), mucolytics to thin sputum making it easier to clear (e.g. dornase alfa), and osmotics to draw water into the sputum making it easier to cough up (e.g. hypertonic saline).

Whilst advances in medicine mean that many of the symptoms of CF can be managed effectively, 'effective' management itself requires people living with CF to complete a complex daily treatment regimen, comprising daily chest physiotherapy, pancreatic enzymes, nutritional supplements, and inhaled or nebulised therapies. A minimum of one to three nebulised treatments per day are usually prescribed, depending on an individual's characteristics (Hoo 2016), with treatments taking an average of 41 minutes per day (Sawicki 2009).

Treatments are only effective if they are taken, yet evidence suggests that in high-income countries, only 50% of people with a chronic condition adhere to treatment recommendations (WHO 2003). As with other chronic conditions, low adherence to treatments for CF, including inhaled therapies, is a global problem, with widespread implications for the individual and their family, for CF teams supporting the individual, and for society as a whole. Low adherence to all treatments is associated with an increased number of pulmonary exacerbations requiring intravenous (IV) antibiotics (Eakin 2011) and hospitalisations, which incur higher healthcare costs (Quittner 2014). Two trials have demonstrated the importance of adherence to inhaled therapies on health outcomes, with higher adherence to dornase alfa being associated with a shorter length of hospital stay (Nasr 2013); and individuals collecting four or more courses of nebulised tobramycin per year being 60% less likely to be admitted to hospital than those collecting two or fewer courses (Briesacher 2011).

'Adherence' refers to "the extent to which the patient's behaviour matches *agreed recommendations* from the prescriber" (Horne 2005). This term is more patient-centred and is therefore preferable to the outdated term of 'compliance', which is "the extent to which the individual's behaviour matches the prescriber's recommendations" (Haynes 1979). There are different methods of measuring adherence, each of which has varying degrees of objectivity and validity. Self-reported measures (e.g. questionnaires and diaries) are inexpensive and easy to administer, but are subject to a range of biases, including social desirability and recall bias (Osterberg 2005). Objective count measures (e.g. medication possession ratio (MPR)) address these biases, but they too are prone to overestimation as they do not guarantee the treatment has been taken (Osterberg 2005). Objective recorded measures (e.g. electronic monitoring devices) are a more accurate, albeit expensive, method of measuring adherence (Osterberg 2005). With the development of data-logging nebulisers (e.g. I-neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics, Chichester, UK) and eFlow® rapid nebuliser system and eTrack® controller (PARI Pharma GmbH, Starnberg, Germany)) which record time- and date-stamped data, it is possible to measure adherence to inhaled therapies using this method. Trials using objective recorded measures suggest that adherence to inhaled therapies in people with CF is around 31% to 36% in adults (Daniels 2011; Hoo 2019; Hoo 2020; Hoo 2021) and 65% to 67% in children or adolescents (Ball 2013; McNamara 2009). The discrepancy between objective and subjective measurement has also been highlighted (Daniels 2011; Modi 2006b; Thorton 2013; Warnock 2020).

Description of the intervention

Interventions that specifically aim to improve adherence to prescribed medications vary widely (Nieuwlaat 2014). Psychological interventions aimed at improving adherence to inhaled therapies in people with CF can therefore take many forms and may be targeted at: people with CF (e.g. patient education, medication reminders, rewards, psychological therapies); their families (e.g. increasing supervision with medication, family therapy); or the multidisciplinary team (MDT) providing specialist care to the person with CF (e.g. training clinicians to communicate more effectively with people with CF). Interventions may be delivered face-to-face, over the phone, or using digital technology (e.g. smartphone applications or 'apps' that include rewards, reminders, or providing feedback on treatment-taking behaviour).

Given the complexity of many adherence interventions tested to date (Nieuwlaat 2014), and the way in which complex interventions are reported or described in the literature, it is often difficult to determine the content, or the 'active ingredients', of effective interventions that bring about change (Michie 2009). These 'active ingredients', or behaviour change techniques (BCTs), are defined as the "observable, replicable and irreducible components of an intervention designed to alter or redirect causal processes that regulate behaviour" (Michie 2013). Often, few details are provided about the BCTs used in interventions, and the terminology used to describe interventions is inconsistent. This makes it difficult to replicate effective interventions, because the core components, or 'active ingredients', are not known, and time and resources are wasted because ineffective techniques continue to be implemented (Michie 2009). This review therefore aims to identify the content, or the 'active ingredients', of interventions, in terms of the BCTs used, in order to establish the most effective components of interventions for improving adherence to inhaled therapies in people with CF. This will aid understanding of the causal mechanisms underlying adherence behaviour, which will help inform the design of more effective, consistent and cost-effective interventions in the future (Michie 2009). A reliable, consensually-agreed taxonomy (BCT Taxonomy version 1; BCTTv1) contains 93

BCTs and provides a common language to identify and describe intervention content (Michie 2013). At least two other reviews have used the BCTTv1 to code the BCTs present in complex interventions (Black 2020; Lawrenson 2016). Psychological interventions for improving adherence to inhaled therapies in people with CF may incorporate one or more BCTs (e.g. 'problem-solving', defined as "analysing, or prompting the person to analyse, factors influencing the behaviour and generating or selecting strategies that include overcoming barriers and/or increasing facilitators" (Michie 2013)).

In this Cochrane Review, we compare interventions to either an active control group or standard care, which usually consists of an annual review or routine reviews (or combination of both) with a specialist CF MDT.

How the intervention might work

Reasons for non-adherence are wide-ranging and varied, and understanding these reasons is crucial in order to assist with the development of effective, evidence-based interventions. Previous studies have attempted to understand the factors influencing adherence to treatments in people with CF, and commonly reported reasons include being too busy or not having the time to take treatments, forgetting to take a treatment, and the level of treatment burden (Bregnballe 2011; Dziuban 2010; George 2010; Modi 2006a; Sawicki 2015). Treatment beliefs (e.g. lack of perceived benefit, feeling embarrassed about taking treatments in public, believing it is acceptable to miss treatments) have also been reported to influence adherence to treatments in people with CF (Bregnballe 2011; Bucks 2009; Dziuban 2010; George 2010; Sawicki 2015). This is consistent with the Necessity-Concerns Framework (Horne 1999), which posits that beliefs about the necessity of treatments, and concerns about potential adverse consequences, can influence adherence and non-adherence to treatments across a wide range of conditions and medications (Horne 2013).

Whilst treatment beliefs and concerns (i.e. conscious or reflective motivation) may be an important influence on treatment-taking, it is also important to consider the role of automatic motivation influences, with recent trials highlighting the role of habit (i.e. "automatically experiencing an urge to use a nebuliser"; Hoo 2019a) on adherence to inhaled therapies in adults with CF (Arden 2019; Hoo 2017; Hoo 2019a). Objective adherence data, collected using date- and time-logging nebulisers, have demonstrated that, amongst adolescents with CF, adherence to inhaled therapies is greater on school days compared to weekends or holidays (Ball 2013), despite this being a time when adolescents are likely to be busiest and are therefore more susceptible to miss treatments due to burden (Hoo 2017).

Given the complexity and multifactorial nature of adherence, interventions aimed at improving adherence to inhaled therapies are likely to be complex, or contain several interacting components (Craig 2008). A ‘one size fits all’ intervention is therefore unlikely to be effective, as it will need to address issues of capability, opportunity, and motivation (Arden 2019), as highlighted in the Capability, Opportunity, Motivation, and Behaviour (COM-B) model of behaviour (Michie 2011). Interventions may include reminders or alarms to target forgetting, but evidence for the efficacy of reminders on adherence is limited (Choudhry 2017). Although forgetting is often understood to be ‘unintentional’ non-adherence, it may be given as a reason to justify ‘intentional’ non-adherence (Arden 2019; Drabble 2019; George 2010), in a more socially acceptable way (Drabble 2019). Interventions may target the individual's or family members' (e.g. parent/ caregiver) beliefs about the necessity of treatments, and concerns about potential adverse consequences, through psycho-education or problem-solving. They may also focus on supporting people with CF to develop routines and build habits for treatment-taking, e.g. through the use of action planning. Feedback on treatment-taking behaviour may be provided (Demonceau 2013), and interventions may include people with CF self-monitoring their adherence to inhaled therapies, e.g. using chipped nebulisers and digital technology applications. Healthcare professionals also have an important role in supporting adherence to inhaled therapies in adults with CF (Arden 2019). National Institute for Health and Care Excellence guidelines recommend the use of a non-judgemental approach which involves asking open questions and not making assumptions, to promote open and honest conversations in relation to adherence (NICE 2009). Interventions may therefore involve training CF MDT members to communicate more effectively with individuals in relation to adherence, or teaching healthcare professionals how to address necessity beliefs and concerns during consultations (Chapman 2015).

Why it is important to do this review

A previous Cochrane Review concluded that establishing "effective ways to help people follow medical treatments could have far larger effects on health than any treatment itself" (Haynes 2002). Furthermore, “simplifying the treatment burden” and "improving and sustaining adherence to treatment" have been identified as two of the top 10 CF research priorities in the James Lind Alliance Priority Setting Partnership (Davies 2020; Rowbotham 2018). Adherence research has also been identified as a high priority by the World Health Organization (WHO 2008). Despite this, there have been no previously published systematic reviews to assess the efficacy of psychological interventions for improving adherence to inhaled therapies in people with CF. A previous Cochrane Review protocol that focused on adherence to all treatments in CF was withdrawn (Jones 2015). The current Cochrane Review provides a more detailed focus on CF than general adherence reviews (Nieuwlaat 2014), and expands upon other CF reviews focused on self-management interventions (Savage 2014), and psychological interventions for improving a range of outcomes (Goldbeck 2014). We coded interventions in order to establish which BCTs are most effective at improving adherence to inhaled therapies in people with CF. By identifying the 'active ingredients' of interventions, the results of this review will help researchers, intervention designers and clinicians better support people with CF in adhering to their treatments. By focusing on inhaled therapies, this review complements other reviews planned or produced by the group on the theme of adherence (Jones 2020; Smith 2020).

OBJECTIVES

The primary objective of the review was to assess the efficacy of psychological interventions for improving adherence to inhaled therapies in people with cystic fibrosis (CF). The secondary objective was to establish the most effective components, or behaviour change techniques (BCTs), used in these interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and one quasi-RCT (as we could reasonably assume that the baseline characteristics were similar in both groups). We included RCTs of parallel design and one cluster-RCT. If cross-over RCTs had been identified, we planned to include first-period data only from these trials due to the likely carry-over effects of the intervention. We included published and unpublished trials, as well as those published as abstracts only.

Types of participants

We included participants of any age, gender, and ethnicity who had a diagnosis of CF and who were prescribed inhaled therapies (as confirmed in the methodology of each included RCT). We included participants based in either a hospital or community setting. If appropriate, we planned to include trials that enroled participants with CF and participants with other chronic conditions only if there was a distinction made between the different participant groups (so that non-CF participants with other chronic conditions could be excluded from our analyses). We also planned to include MDTs or families of people with CF if they were the target participants of an intervention aimed at improving adherence to inhaled therapies in people with CF.

Given the wide variety of intervention targets included (i.e. children, adolescents and adults with CF, families of people with CF, and specialist CF MDTs), we were aware that it may not be appropriate to combine the results from different populations in statistical analysis.

A previous Cochrane Review highlighted the inclusion bias likely to be present in adherence trials, with many interventions conducted with convenience samples in which participants have higher than average adherence at baseline (Nieuwlaat 2014). This is an important methodological issue to consider as this may reduce the statistical power of an included trial to achieve the primary outcome, as the two groups will be similar (and so more power would be needed to detect a between-group difference, if a difference exists).

Types of interventions

We aimed to assess all potential psychological interventions for improving adherence to inhaled therapies in people with CF as detailed above (Description of the intervention) and which were specifically aimed at people with CF, the families of people with CF, or specialist CF MDTs. We included trials that reported at least one measure of adherence as an outcome.

We used the BCTTv1 to identify the BCTs present in interventions in the included trials (Michie 2013), in order to establish which BCTs were most effective at improving adherence to inhaled therapies in people with CF. We also coded the BCTs present in the active control groups, as the content and effectiveness of these interventions may vary considerably (de Bruin 2016).

Types of outcome measures

We planned to assess the following outcome measures.

Primary outcomes

1. Adherence to inhaled therapies (measured using both objective and subjective measures)
   a. objective recorded measures (e.g. electronic monitoring nebuliser devices such as Philips I-neb AAD system and PARI eFlow® rapid nebuliser system and eTrack® controller which record date- and time-stamped data)
   b. objective count measures (e.g. MPR)
   c. subjective measures (e.g. self-reported adherence; questionnaires; participant diaries)
2. Treatment-related adverse events
   a. anxiety as measured by a validated anxiety scale, e.g. Generalized Anxiety Disorder (GAD-7; Spitzer 2006)
   b. depression as measured by a validated depression scale, e.g. Patient Health Questionnaire (PHQ-8; Kroenke 2009)

We included trials with at least one measure of adherence regardless of whether it was a primary or secondary outcome. If an included trial measured adherence using more than one type of measure, then we reported the most reliable measure (i.e. objective measures preferentially reported over subjective measures, using the hierarchy of validity above). This is consistent with other Cochrane Reviews looking at adherence (Cross 2020; Hollands 2019). We excluded studies that did not measure adherence, even if they measured one or more of the other primary or secondary outcomes.

We expected adherence to be typically defined as a continuous measure (e.g. total number of doses taken as a percentage of the target number of doses prescribed over a given time period). Alternatively, it can be defined as a dichotomous outcome, e.g. reporting whether the treatment is being used to a prespecified degree (e.g. adherent or non-adherent for X number of days; adherence 75% and greater versus less than 75%). However, the often arbitrary cut-off values for distinguishing 'adherence' from 'non-adherence' (Lam 2015) has led to recommendations that research should use measures that are continuous rather than dichotomous (DiMatteo 2002).

Where possible, adherence referred to 'normative adherence', a measure that considers a person's characteristics when defining the minimum required treatment regimen (Hoo 2016). This is in contrast to 'unadjusted adherence', which is where a treatment regimen may be informed by considerations other than treatment effectiveness (e.g. a regimen based on what people with CF feel they can realistically manage rather than a regimen that has been driven by clinical evidence) (Hoo 2016).

Secondary outcomes

1. Quality of life (QoL) as measured by a validated QoL questionnaire, e.g. Cystic Fibrosis Questionnaire-Revised (CFQ-R; Quittner 2009)
2. Lung function (absolute change or percentage change compared to baseline values, or both), measured in forced expiratory volume at one second (FEV_1) L or per cent (%) predicted
3. Pulmonary exacerbations (using the measure specified in the methodology of each trial, e.g. modified Fuchs criteria (Bilton 2011))
   a. number of exacerbations

b. time to next exacerbation
c. duration of exacerbations (as measured by the total number of IV antibiotic days)

If outcomes were reported at multiple time points, we extracted data from all time points. To investigate short- and long-term effects, and to reduce the likelihood of missing an effect in trials that reported outcomes at multiple time points, we grouped outcome data into those measured at: up to three months; over three months and up to six months; over six months and up to 12 months; and over 12 months. If trials recorded outcome data at other time points, then we considered examining these as well.

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: treatment adherence OR mental health in CF OR behaviour.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis. Unpublished work is identified by searching the abstract books of three major CF conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of most recent Register search: 20 September 2022.

In addition, the first review author (SD) searched the following databases:

- PubMed (www.ncbi.nlm.nih.gov/pubmed/; 1946 to 11 August 2022);
- PsycINFO EBSCO (www.search.ebscohost.com; 1887 to 7 August 2022);
- Scopus (www.elsevier.com/en-gb/solutions/scopus; 1823 to 7 August 2022);
- OpenGrey (www.opengrey.eu/; searched 14 November 2020). As of 1 December 2020, the OpenGrey Repository was discontinued and preserved as a closed archive in the DANS EASY data archive, so this search was not updated.

They also searched the following trials registries:

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/; searched 14 August 2022);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 7 August 2022).

See Appendix 1 for details of the search strategies.

Searching other resources

We checked the reference lists of included trials and any relevant systematic reviews identified for further references to relevant trials. We contacted leaders and organisations in the field to obtain additional information on relevant trials.

Data collection and analysis

Selection of studies

One author (SD) imported the search results onto systematic review screening software (Covidence). Three review authors (SD, LC, CG) used Covidence to independently screen all titles and abstracts identified from the search for their relevance for inclusion in the review. This was based on trial design, types of participants and interventions (as detailed above). Two authors independently screened all titles and abstracts (as first author, SD screened all studies; and LC and CG each screened a proportion of all studies). As two of the review authors (SD, CG) had links with two of the included trials (Hind 2017; Wildman 2022), two other review authors (LC, DCC) who had no links with these trials and did not work in CF verified the inclusion of these trials. We tried to obtain full-text publications of those deemed either eligible or potentially eligible, as well as for those where eligibility was unclear. We identified and excluded duplicates and collated multiple reports of the same trial so that each trial, rather than each report, was the unit of interest in the review. After the screening of the titles and abstracts, we independently screened full-text publications and identified trials for inclusion in the review according to the predetermined eligibility criteria. As first author, SD screened all full-text publications, and both LC and CG each screened a proportion of all trials. If we identified non-English trials, we assessed these and, if necessary, planned to translate these with the assistance of a native speaker (e.g. by posting a request on Cochrane TaskExchange). In this review, we obtained one unpublished thesis written in French for full-text screening, which was translated with the assistance of a non-native French speaker. We recorded the reasons for exclusion of trials in the 'Characteristics of excluded studies' table. Two review authors (SD and LC, or SD and CG) resolved any disagreements regarding the inclusion of a trial by discussion. If necessary, we had planned to consult with a third author (LC or CG) who had not been involved with the screening of that trial.

Data extraction and management

SD developed a data extraction form using the Cochrane template, which two review authors (SD, CG) piloted, undertaking any amendments as necessary. We extracted the following main sets of data from each included trial:

1. trial details (lead author; date);
2. methods (trial design and timetable, randomisation, allocation concealment);
3. participants (participant condition(s) and demographics, age, gender, ethnicity, socioeconomic status, numbers of participants in each trial arm, trial participant inclusion and exclusion criteria);
4. interventions (content and format of interventions, including details of information provided, intervention setting and delivery provider);

5. outcomes (outcome measures, assessment time points, analysis, results);
6. additional comments.

Two review authors (SD, CG) independently extracted data and resolved discrepancies through discussion, or through consultation with a third author if necessary (LC). As two of the review authors (SD, CG) had links with two of the included trials (Hind 2017; Wildman 2022), they were not involved in data extraction of those trials. Instead, these trials were extracted by the other two review authors (LC, DCC). The lead review author (SD) entered the data into RevMan, with the second review author (CG) checking the accuracy of the data entry (Review Manager 2020).

We coded the extracted intervention descriptions into component BCTs using the BCTTv1, an established taxonomy of 93 BCTs, as a coding framework (Michie 2013). We coded BCTs for each intended recipient; we also coded each intervention separately, including control arms, and coded BCTs as 'present' or 'absent' for each intervention description. As originally described (Michie 2009), and highlighted in a Cochrane Review (Lawrenson 2016), complex behaviour change interventions are often poorly reported, which makes it challenging to identify the intervention content or BCTs used. As such, SD contacted the authors of included trials about the content of their interventions if there was insufficient information available (Michie 2013). We requested additional materials or information that would provide further detail on the content of the intervention (e.g. trial protocol, letters sent to participants, participant information sheets, intervention manuals (Lorencatto 2013)). We coded received materials using the taxonomy in the same manner as for the corresponding published reports. Two review authors (SD, CG) who had both undertaken BCT coding training (BCT Taxonomy 2021) independently conducted BCT coding, resolving discrepancies by discussion or by consultation with a third author (LC) if necessary. Two trials had already been coded by the study authors in the published reports (Hind 2017; Wildman 2022), and we made no amendments.

We narratively recorded and reported any results that we were not able to formally analyse in RevMan (Review Manager 2020).

Assessment of risk of bias in included studies

Two review authors (SD, CG) independently assessed the risk of bias (or methodological quality) for each included trial, with any disagreements resolved by discussion. SD contacted the trial authors for additional information about the trial methods if necessary. As two of the review authors are or were involved with a wider programme of work linked to two included studies (Hind 2017; Wildman 2022) (though not the trials themselves), they were not involved in the risk of bias or GRADE assessments for these trials. Instead, the other two review authors (LC, DCC) assessed their risk of bias. We used the Cochrane risk of bias (RoB 1) tool to assess the following domains: sequence generation or randomisation; allocation concealment; blinding of participants, personnel and outcomes assessors; incomplete outcome data; and selective outcome reporting (Higgins 2017). However, blinding of participants and personnel is typically not possible in trials of psychological interventions. As such, the assessment of blinding only included the outcome assessors. We categorised the overall risk of bias of included trials as low, high, or unclear, according to the criteria specified by Higgins 2017, and presented this (along with a justification for the judgement) in the 'Characteristics of included studies' table.

Measures of treatment effect

If appropriate (e.g. when interventions, participants and the underlying clinical questions and outcomes were similar enough for pooling to make sense), we had planned to conduct a meta-analysis. When single trials reported multiple trial arms, we had planned to only include the relevant arms. For continuous variables, we calculated mean differences (MDs) with 95% confidence intervals (CIs); or standardised mean differences (SMDs) with 95% CIs when the same outcome was measured on different scales. To interpret SMDs, we used Cohen's effect sizes of 0.2 to represent a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988).

For dichotomous variables, we planned to present risk ratios (RRs) with 95% CIs. For data reported as rates or count data (e.g. number of pulmonary exacerbations), we planned to calculate rate ratios with 95% CIs. As anticipated given the outcome measures listed (e.g. adherence to inhaled therapies; lung function, QoL), most of the data we collected in this review were continuous.

Since most trials reported endpoint data or final scores and only two trials reported the adjusted difference in means between groups (Hind 2017; Wildman 2022), we entered both of these in separate analyses in the analysis section of the review (to avoid selective reporting and ensure the most robust (adjusted) data were presented where available). Change from baseline was presented in one trial (Hind 2017), but since this trial also reported adjusted data which takes baseline into account, we favoured use of the adjusted data.

We narratively described any skewed data reported as medians and ranges.

As detailed in the review protocol (Dawson 2020), if an included trial measured adherence using more than one type of measure, then we reported the most reliable measure (i.e. objective measures preferentially reported over subjective measures, using the hierarchy of validity listed in the 'Types of outcome measures' section).

Unit of analysis issues

For cluster-RCTs, we planned to only include data in the meta-analyses if the available data had been adjusted to account for the clustering (or could be adjusted, based on recommendations (Higgins 2022)). We identified a single cluster-RCT (Quittner 2019), and the authors reported that they used generalised estimating equations to account for clustering within sites. The results of this study were quite difficult to interpret, and we were unable to access additional data despite repeated attempts to contact the trial authors. Two outcomes (exacerbations and lung function) were reported at baseline only; the only results we could interpret were absolute post-treatment mean scores for each QoL domain, which we included in the analyses as if they were from a parallel trial where the unit of analysis is the participant.

If we had identified any cross-over RCTs, we planned to include data from the first period only as we cannot exclude a carry-over effect of the intervention.

If trials reported multiple measurements or observations from each participant for the same outcome (e.g. if data from two measures of depression were reported for each participant), to avoid double-counting of participants or selectively choosing an outcome to report, we presented the data for each measure with no totals or summary statistics for each outcome (added post hoc). In addition, if trials assessed an outcome using a measure that was completed independently by both children/adolescents with CF and parents/caregivers of people with CF (e.g. a child and parent/caregiver score for the same outcome were reported), we included data from the children and adolescents with CF only, to avoid double-counting of participants (added post hoc).

Dealing with missing data

If data (e.g. descriptive statistics) were missing from the included trials, one author (SD) attempted contact with the original trial authors (by email) to obtain these data. In future updates, if data such as standard deviations (SDs) are missing, where appropriate, we will calculate these from standard errors (SEs), CIs, t-values or P values (if reported) (Deeks 2022).

Assessment of heterogeneity

We planned to assess clinical and methodological heterogeneity by considering the variation in the characteristics of the participants, interventions, outcomes and trial designs. We planned to visually inspect forest plots and use the Chi^2 test and the I^2 statistic to measure heterogeneity among the trials included in each analysis (with an I^2 value greater than 50% considered to represent substantial heterogeneity (Higgins 2017)). Due to a lack of data, we were only able to combine limited results from different trials in a small number of analyses; therefore, we have not formally assessed heterogeneity in this version of the review.

Assessment of reporting biases

We used a comprehensive search strategy, which included searching for unpublished trials (grey literature) and searching trials registers (see 'Search methods for identification of studies') to minimise reporting biases. If data were not reported or published in full, the first review author (SD) contacted the trial authors to try to obtain the full data, or the reason for not publishing these data. Although not possible in this review, in future updates, if we are able to pool more than 10 trials in a meta-analysis, we will use funnel plots to assess the possibility of publication bias (Page 2022).

Data synthesis

Although we have entered data into the 'Data and analyses' section of the review, it is not currently possible to identify an overall intervention effect using meta-analysis due to the substantial level of heterogeneity present in the included trials, in terms of participants (age), interventions (content and mode of delivery), and outcomes (measures, number and range of assessment time points). As such, we have presented a narrative synthesis of the 10 included trials and have combined the limited results from nine trials in a small number of quantitative analyses. As specified in the protocol (Dawson 2020), we used a random-effects model as we assumed that there would be variation between studies (e.g. in terms of participants, interventions and outcomes). For future updates, if trials are sufficiently similar in terms of participants, eligibility criteria, interventions (type and intent) and outcomes (including the timeframe of follow-up and type of measure used), we will consider meta-analysis as described above (Assessment of heterogeneity). If appropriate, we will perform a sensitivity analysis using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

For future updates, if sufficient data are available, we will conduct subgroup analyses with respect to:

1. the target intervention participants (e.g. children and adolescents with CF; adults with CF; families of people with CF; or MDTs). In trials that include participants with a range of ages (i.e. children and adolescents or adults or unspecified), we will classify adults with CF as 18 years and over, and children and adolescents with CF as under 18 years of age;
2. studies that focus on adherence to multiple CF treatments (i.e. a combination of inhaled and non-inhaled therapies) compared to those that focus on inhaled therapies only (added post hoc); and
3. the BCTs used.

We planned to investigate the impact of type and number of BCTs on effect size by meta-regression, but this was not possible due to the limited number of included trials in the review.

Sensitivity analysis

We did not undertake any sensitivity analyses in this version of the review. If sufficient data had been available, we would have undertaken sensitivity analyses to assess the robustness of the results by excluding trials with an unclear or high risk of overall bias. This may have involved excluding trials in which adherence was measured using subjective methods (e.g. self-reported adherence; questionnaires; participant diaries). We will consider this in future updates.

Summary of findings and assessment of the certainty of the evidence

We developed a summary of findings table for each comparison presented in the review (psychological interventions versus usual care: Summary of findings 1; and psychological interventions versus active comparator group (e.g. education plus problem-solving; EPS): Summary of findings 2) using the following outcomes at the 'over six months and up to 12 months' time point:

1. adherence to inhaled therapies (% completed treatments) (we planned to report using SMD for all results combined from six to 12 months, but since only one trial was included for this outcome in Summary of findings 1, we instead reported using MD);
2. change from baseline in anxiety (as measured by a validated anxiety scale, e.g. GAD-7 (Spitzer 2006));
3. change from baseline in depression (as measured by a validated depression scale, e.g. PHQ-8 (Kroenke 2009));
4. change from baseline in QoL (as measured by a validated QoL questionnaire, e.g. CFQ-R (Quittner 2009));
5. change from baseline in FEV_1 % predicted;
6. number of pulmonary exacerbations, as measured using the measure specified in the methodology of each trial, e.g. modified Fuchs criteria (Bilton 2011).

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence in the review (Schünemann 2022).

RESULTS

Description of studies

For further details, please see the tables: Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

We identified a total of 5551 trials (5716 references) through our electronic search strategies (Appendix 1). We identified a further five records through other sources (e.g. checking the reference lists of included trials). After removing 2566 duplicate references, we screened the titles and abstracts of the remaining 3155 references. From these, we identified 84 trials (192 references) as potentially eligible for inclusion and obtained the full-texts (including clinical trial register records and conference abstracts). We excluded 69 trials (114 references) which did not meet the inclusion criteria, and have listed five trials (nine references) as ongoing (Jirasek 2022; Phan 2021; O'Hayer 2019; Thee 2021; White 2017). This leaves 10 trials (69 references) for inclusion in this review (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Riekert 2013; Shakkottai 2017; Wildman 2022). Nine of these 10 trials could also be included in limited quantitative syntheses (meta-analyses) (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022). We have shown the details of the selection process in a PRISMA diagram (Figure 1).

Figure 1. Study flow diagram.

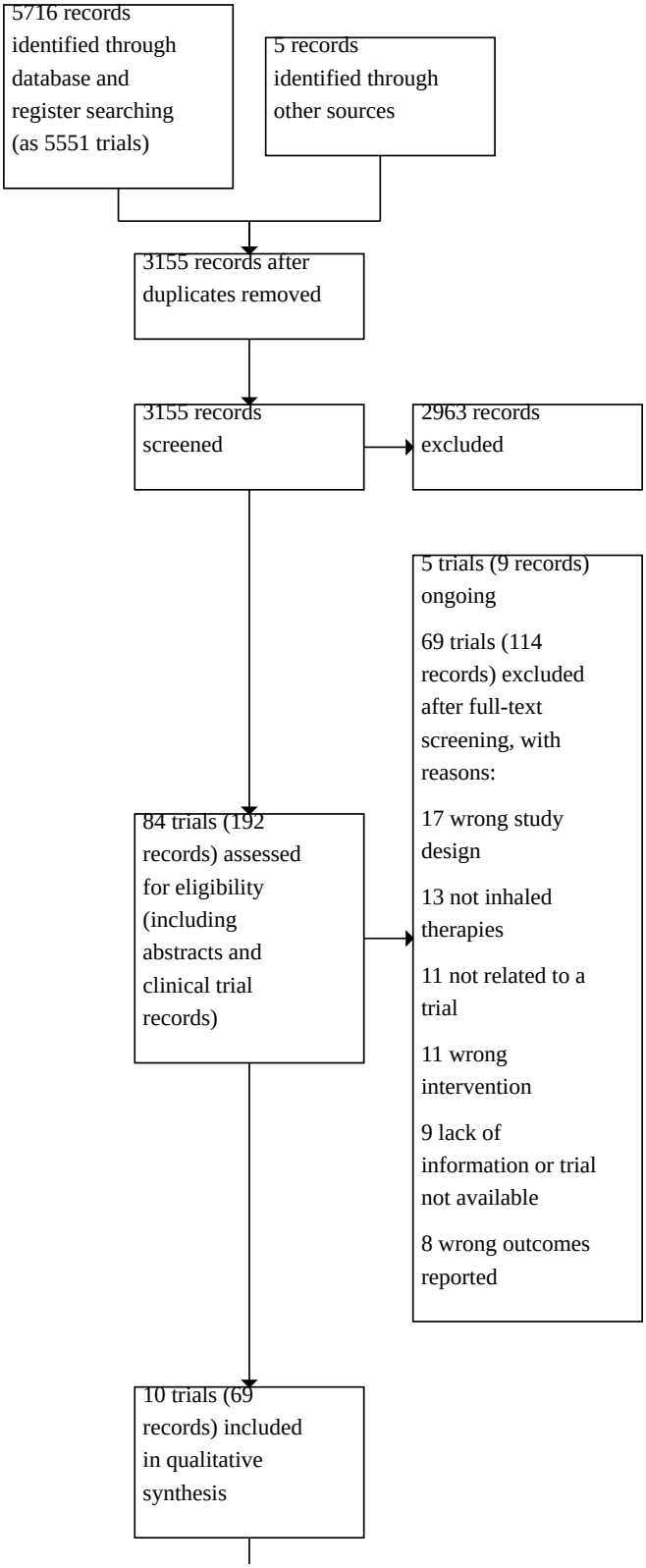
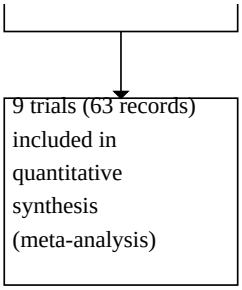


Figure 1. (Continued)



Included studies

Eight of the 10 trials included in this review (published between 1996 and 2021) were available as full-texts published in peer-reviewed journals (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quittner 2019; Shakkottai 2017; Wildman 2022). The results of one trial were reported in a symposium summary only (Riekert 2013), and one trial was reported in a PhD thesis and a conference abstract (Quinn 2004). Further information on the included trials is provided in the table 'Characteristics of included studies'.

Trial design

Nine RCTs used a parallel design (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Riekert 2013; Shakkottai 2017; Wildman 2022) and one was a cluster-RCT (Quittner 2019). The Gur 2016 trial was a quasi-RCT as participants were consecutively assigned to the intervention and control group, but from baseline data provided by the trial authors, we could reasonably assume that the baseline characteristics were similar in both groups.

Six trials were single-centre (Cottrell 1996; Gur 2016; Knudsen 2016; Quinn 2004; Riekert 2013; Shakkottai 2017), and four trials were multicentre (Downs 2006; Hind 2017; Quittner 2019; Wildman 2022). Three trials were conducted in the UK (Hind 2017; Quinn 2004; Wildman 2022), four in the USA (Cottrell 1996; Quittner 2019; Riekert 2013; Shakkottai 2017), one in Denmark (Knudsen 2016), one in Israel (Gur 2016), and one in Australia (Downs 2006).

Participants

A total of 1642 participants (approximately 54.3% female) were recruited and randomised across the 10 trials. The number of participants recruited in each trial ranged from five (Shakkottai 2017) to 641 (Quittner 2019). All interventions targeted people with CF (or caregiver/parent-child dyads). No interventions specifically included MDTs or families of people with CF as the target participants of an intervention aimed at improving adherence to inhaled therapies in people with CF.

One trial included 18 participants aged eight years and over (Gur 2016). Four trials (745 participants) included only children or adolescents: one trial included five participants aged 10 to 14 years (Shakkottai 2017); one trial included 34 participants aged 8 to 18 years (Cottrell 1996); one trial included 641 participants aged 11 to 20 years (Quittner 2019); and one trial included 65 caregiver/parent-child dyads where the children were aged 6 to 11 years (Downs 2006).

Five trials (879 participants) included only adults with CF: three trials included 800 participants aged 16 years and older (Hind 2017; Riekert 2013; Wildman 2022); one trial included 40 adults aged 18 to 30 years (Knudsen 2016); and one trial randomised 39 adults aged 18 years and older (Quinn 2004).

Interventions

All included trials were two-arm RCTs. The types of psychological interventions described were wide-ranging and varied. One trial compared a psychological intervention (motivational interviewing (MI)) to an active comparator or attention control group (education plus problem solving (EPS)) (Riekert 2013). The remaining nine trials compared a psychological intervention (as described below) to a usual care or 'treatment as usual' control group (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022).

Psychological interventions included: a brief MI phone intervention (behaviour change counselling (BCC)) (Quinn 2004); a clinic-based, problem-solving intervention (Quittner 2019); a life-coaching intervention (Knudsen 2016); a telehealth intervention comprising WhatsApp messages and Skype-based video calls (Gur 2016); and a digital intervention involving self-monitoring of lung function and medication reminders delivered by a home spirometer (Shakkottai 2017). Four trials described a 'self-management' intervention (Cottrell 1996; Downs 2006; Hind 2017; Wildman 2022), although the content and mode of delivery of these interventions varied. One of these interventions included training sessions focused on the nature of CF, principles of self-management, types of medications and their appropriate use etc. (Cottrell 1996); another included a paper-based, self-management intervention completed by the parent or caregiver and child at home (Downs 2006); and two trials described a complex intervention comprising a digital platform (CFHealthHub website and smartphone app) and behaviour change sessions with a trained interventionist (Hind 2017; Wildman 2022).

In three trials, interventions focused solely on improving adherence to inhaled therapies (Hind 2017; Quinn 2004; Wildman 2022), whereas in two trials, interventions focused on improving adherence to multiple CF treatments, e.g. aerosol treatments and airway clearance techniques (Downs 2006), or inhaled hypertonic saline, dornase alfa and CF multivitamins (Shakkottai 2017). In five trials, interventions were non-specific and focused on improving

adherence to CF treatments in general (Cottrell 1996; Gur 2016; Knudsen 2016; Quittner 2019; Riekert 2013). In at least three of these trials, participants could choose the focus of the intervention, such as improving adherence to a treatment other than inhaled therapies (Quittner 2019), or on a topic other than adherence (e.g. work-life balance, stress management) (Gur 2016; Knudsen 2016).

A range of healthcare professionals delivered the interventions, including psychologists or registered nurses (Cottrell 1996), or a trainee clinical psychologist (Quinn 2004). One intervention was delivered by a certified life coach (Knudsen 2016). Some of the included trials involved delivery of the intervention by one trained professional (Knudsen 2016; Quinn 2004). Other interventions were delivered by multiple, trained healthcare professionals or researchers (e.g. registered nurses, physiotherapists, social workers, psychologists, research co-ordinators etc.) (Hind 2017; Quittner 2019; Wildman 2022), where there is likely to be more variation in terms of fidelity of the intervention.

The mode of intervention delivery varied across trials. Interventions were delivered face-to-face (Cottrell 1996; Quittner 2019), over the telephone (Quinn 2004), or using a combination of face-to-face and telephone sessions (Knudsen 2016; Riekert 2013). Two interventions involved the use of digital technology: home spirometers that also delivered medication reminders (Shakkottai 2017); and a telehealth intervention comprising WhatsApp messages and Skype video calls with members of the CF team (Gur 2016). One intervention was delivered in the form of a paper workbook (Downs 2006), and two trials combined digital technology with face-to-face sessions (Hind 2017; Wildman 2022). Most interventions were delivered to participants on a 1:1 or individual basis (Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Riekert 2013; Shakkottai 2017; Wildman 2022), with only one delivered in a group setting (Cottrell 1996).

Intervention duration ranged from 10 weeks (Downs 2006) to 12 months (Knudsen 2016; Quittner 2019; Wildman 2022). The 'dose' or intensity of interventions was also wide-ranging and included: six sessions over five months (Hind 2017); six 30-minute Skype video calls and WhatsApp messages sent twice each week over a period of three to six months (Gur 2016); daily medication reminders and weekly home spirometry over a period of three months (Shakkottai 2017); or a workbook chapter per week over a period of 10 weeks (Downs 2006). Two interventions were designed to be brief, comprising four, 10- to 15-minute sessions delivered during clinics over 12 months (Quittner 2019); or up to six fortnightly sessions lasting approximately 15 to 30 minutes each and delivered over three months (Quinn 2004). Two interventions were more intense in the early stages (Knudsen 2016; Wildman 2022). One trial scheduled up to 10 coaching sessions (lasting 60 to 90 minutes) to take place every one to two weeks early in the 12-month programme and every two to four weeks later on (Knudsen 2016). In the second trial, the intensity of the intervention varied depending on participants' adherence at baseline: participants with over 80% adherence were offered three sessions, with phase reviews every 12 weeks thereafter; participants with 80% or lower adherence followed a 'normal' pathway of six sessions over 12 weeks, with phase reviews every 12 weeks thereafter; and those with low adherence of 25% or less were offered more regular sessions (every six weeks) (Wildman 2022). Additional sessions were also offered if participants requested further support; if adherence decreased by 20% or more in a four-week period; or if participants received IV antibiotics for an exacerbation (Wildman 2022). In two trials, the duration and intensity of the intervention was unclear; either because no details were provided on the scheduling of the two six-hour training sessions (Cottrell 1996), or because it was unclear if the information provided (one clinic session and eight phone sessions over six months) was in reference to the intervention or active comparator arm, or both (Riekert 2013).

Five trials stated that they had conducted fidelity assessments, usually using audio-recordings from intervention sessions (Hind 2017; Quinn 2004; Quittner 2019; Riekert 2013; Wildman 2022). Fidelity assessments are important in psychological intervention trials to assess whether an intervention is delivered as conceived and intended (Song 2010). Two trials provided limited details (Quinn 2004; Riekert 2013). There was also variation in the approaches used, ranging from assessing intervention fidelity for the first session only (Quittner 2019), to assessing a sample of sessions throughout the trial, using two independent reviewers (Wildman 2022).

Intervention content in terms of BCTs (coded using the BCT Taxonomy)

Overall, we identified 41 out of the possible 93 BCTs (44.1%) across all trials (drawn from 15 out of the 16 different categories of BCTs within the taxonomy). Interventions were generally multi-component or complex, and contained an average of 9.6 BCTs. The minimum number of BCTs used in an intervention was one (Knudsen 2016) and the maximum number was 28 (Downs 2006). The BCTs used most frequently included '1.2 Problem solving' (coded in seven trials); '4.1 Instruction on how to perform the behaviour' (coded in five trials); and '3.1 Social support (unspecified)', '5.1 Information about health consequences', '7.1 Prompts/cues', '9.1 Credible source', and '12.5 Adding objects to the environment' (each coded in four trials). The remaining BCTs were coded in three trials or fewer.

The nine trials provided no description of the 'usual care' comparator, which precluded BCT coding of the control groups (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022). One trial compared a psychological intervention (MI) with an active comparator intervention (EPS) (Riekert 2013). BCTs were coded in both of these groups, and there was no overlap of the four BCTs used in the intervention group ('2.2 Feedback on behaviour'; 'Feedback on outcome(s) of behaviour'; '3.1 Social support (unspecified)'; and '5.1 Information about health consequences') with the three used in the active comparator arm ('1.2 Problem solving'; '4.1 Instruction on how to perform the behaviour'; and '10.4 Social reward').

Two of the included trials were coded by the trial authors in the published reports, and we made no amendments (Hind 2017; Wildman 2022).

We have presented further information on the BCTs present in the included trials in the additional tables (Table 1). A further table provides definitions and illustrative quotations for each BCT (Table 2).

Outcomes

Adherence

All trials measured adherence to inhaled therapies; this was as a primary outcome in four trials (Quinn 2004; Quittner 2019; Riekert 2013; Shakkottai 2017), a secondary outcome in three trials (Hind 2017; Knudsen 2016; Wildman 2022), and three trials did not specify between primary and secondary outcomes (Cottrell 1996; Downs 2006; Gur 2016). The measures of adherence used varied across trials, as detailed below.

Three trials used objective recorded measures (e.g. dose-counting nebulisers) (Hind 2017; Quinn 2004; Wildman 2022). One trial monitored adherence electronically using an Adaptive Aerosol Delivery device (Prodose) and reported data at two time points (baseline (measured for three months prior to the intervention) and at three months (measured for three months post-intervention) (Quinn 2004). Investigators calculated adherence using four methods; please see 'Characteristics of included studies' for further details.

Two trials assessed adherence to inhaled therapies using the PARI eFlow rapid nebuliser system with an eTrack Controller® at baseline and five months (plus or minus one month) from consent visit (Hind 2017), or at baseline and 12 months (Wildman 2022). These trials calculated and reported adherence in five ways; again, please see 'Characteristics of included studies' for further details.

Three trials measured adherence using objective count measures (e.g. MPR) (Quittner 2019; Riekert 2013; Shakkottai 2017). These trials all reported a composite MPR (cMPR) measure in which the MPRs of each medication were averaged across all included medications (Eakin 2011); but the included medications varied. Two trials reported a cMPR measure of 'chronic pulmonary medications' which included inhaled therapies (e.g. dornase alfa, tobramycin, hypertonic saline, aztreonam lysine), as well as one non-inhaled treatment (e.g. azithromycin), but individual MPRs were not available (Quittner 2019; Riekert 2013). Another trial reported a cMPR of two inhaled therapies (hypertonic saline and dornase alfa) and one non-inhaled therapy (CF multivitamins), but it was possible to estimate MPR for individual treatments from a chart in the paper (Shakkottai 2017). One trial reported results for cMPR at baseline and three months (Shakkottai 2017) and two trials at baseline and 12 months (Quittner 2019; Riekert 2013), although the time frames used to calculate MPR seemed to vary (see 'Characteristics of included studies').

Four trials measured adherence using subjective measures (Cottrell 1996; Downs 2006; Gur 2016; Knudsen 2016). Two of these trials assessed adherence using self-report in participant diaries and converted the information from the diaries into the % of prescribed aerosol treatments taken (Cottrell 1996; Downs 2006). Two trials assessed adherence to dornase alfa and inhaled antibiotics, with Knudsen 2016 assessing participant scores on the Morisky Medication Adherence Scale (MMAS-8) (Morisky 2008), and Gur 2016 using a questionnaire with a five-point Likert scale. In addition to dornase alfa and inhaled antibiotics, Gur 2016 assessed adherence to inhaled steroids, hypertonic saline, and bronchodilators. These trials assessed adherence at different time points: Cottrell 1996 reported at baseline and six to eight weeks post-assessment; Gur 2016 reported at baseline and three to five months post-assessment; Downs 2006 reported at pre-intervention, post-intervention (three to four months after pre-intervention assessment for control group and immediately after completion of 'Airways' for intervention group), six-month follow-up (six months after post-intervention assessment), and 12-month follow-up (six months after six-month follow-up assessment; and Knudsen 2016 reported at baseline, five months (midway), 11 months (post-intervention) and one year post-intervention (follow-up).

Two trials assessed adherence in multiple ways (e.g. using data-logging nebulisers and participant self-report) (Hind 2017; Wildman 2022).

Treatment-related adverse events (depression and anxiety)

Four trials included depression as a secondary outcome (Hind 2017; Knudsen 2016; Quinn 2004, Wildman 2022), and three trials included anxiety (Hind 2017; Quinn 2004; Wildman 2022). Both outcomes were assessed using a variety of measures. Two trials assessed depression using scores on the PHQ-8 (Kroenke 2009); one assessed at baseline and five months (plus or minus one month) from consent visit (Hind 2017), and the second at baseline and 12 months (Wildman 2022). One trial assessed depression using both the Major Depression Inventory (MDI) (Bech 2001) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977) at baseline, five months (midway), 11 months (post-intervention) and one year post-intervention (follow-up) (Knudsen 2016).

Quinn measured depression and anxiety using the hospital anxiety and depression scale (HADS) (Zigmond 1983), and measured anxiety using the State-Trait Anxiety Inventory-short form (STAI-short form) (Marteau 1992); investigators assessed both outcomes at pre-intervention and post-intervention (three months later) (Quinn 2004).

Two further trials measured anxiety as score on the GAD-7 (Spitzer 2006) at baseline and five months (plus or minus one month) from consent visit in one trial (Hind 2017), or at baseline and 12 months in the second trial (Wildman 2022).

All trials expressed depression or anxiety results, or both, as means and SDs (Hind 2017; Knudsen 2016; Quinn 2004; Wildman 2022). One trial also reported unadjusted MDs between groups (Hind 2017), and two trials reported adjusted MDs, adjusting for baseline and CF centre (Hind 2017), or baseline, CF centre and past-year IV days (Wildman 2022).

QoL

Nine trials included QoL as an outcome using a range of measures (Cottrell 1996; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Riekert 2013; Shakkottai 2017; Wildman 2022).

One trial (Cottrell 1996) assessed QoL using the Quality of Wellbeing scale (Kaplan 1989). One trial (Quinn 2004) assessed QoL using scores on the CFQoL (Gee 2000).

Seven trials used scores on the CFQ-R (Quittner 2009) to assess QoL (Gur 2016; Hind 2017; Knudsen 2016; Quittner 2019; Riekert 2013; Shakkottai 2017; Wildman 2022). Three trials assessed QoL across all domains of the CFQ-R (Teen/Adult version) (Hind 2017; Knudsen 2016; Quittner 2019), or both the Teen/Adult and Older Child versions depending on participant ages (Quittner 2019). Three trials assessed QoL using only some domains of the

CFQ-R (Riekert 2013; Shakkottai 2017; Wildman 2022). Wildman 2022 used eight domains of the Teen/Adult version of the questionnaire (physical functioning, emotional functioning, social functioning, eating disturbance, body image, treatment burden, respiratory symptoms, digestive symptoms). Riekert 2013 used three domains (treatment burden, respiratory symptoms, and physical functioning), and Shakkottai 2017 used the treatment burden domain only. Neither Riekert 2013 nor Shakkottai 2017 specified which version they used, but we presumed that Riekert 2013 used the Teen/Adult version (as they included participants aged 16 years and older); and Shakkottai 2017 used the Older Child version (as they included participants aged 10 to 14 years), as well as the Parent/Caregiver version. Investigators of one trial reported using age-appropriate versions of the CFQ-R (Parent/Caregiver and Teen/Adult versions), but they did not specify which domains were used (Gur 2016).

Trials assessed QoL at a range of different time points, including: baseline (pre-intervention) and six to eight weeks post-intervention (Cottrell 1996); baseline (pre-intervention) and three months (Quinn 2004; Shakkottai 2017); baseline and five months (plus or minus one month) from consent visit (Hind 2017); baseline and three to five months post-intervention (Gur 2016); baseline, five months (midway), 11 months (post-intervention), and one year post-intervention (follow-up) (Knudsen 2016); baseline and 12 months (Quittner 2019; Wildman 2022); and baseline, six months and 12 months (Riekert 2013).

Eight trials expressed QoL results as means and SDs (Cottrell 1996; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022). One trial also reported unadjusted MDs between groups (Hind 2017), and two trials reported adjusted MD, adjusting for baseline and CF centre (Hind 2017), or baseline, CF centre and past-year IV days (Wildman 2022). One trial reported only medians and interquartile ranges (IQRs) (Riekert 2013), so we describe results narratively below.

Lung function

Seven trials reported lung function (FEV_1 % predicted) at a range of different time points: baseline and three months (Quinn 2004; Shakkottai 2017); baseline and five months (plus or minus one month) from consent visit (Hind 2017); baseline, five months (midway), 11 months (post-intervention), and one year post-intervention (follow-up) (Knudsen 2016); and baseline and 12 months (Quittner 2019; Riekert 2013; Wildman 2022).

Two trials extracted lung function data from CF registry databases (Quittner 2019; Riekert 2013), one from medical records (Knudsen 2016), and in one trial it was recorded on the home spirometer used as part of the intervention (Shakkottai 2017). In three trials, FEV_1 was taken for the purposes of the trial at each assessment time point (Hind 2017; Quinn 2004; Wildman 2022), in addition to during routine clinic visits in two trials (Hind 2017; Wildman 2022).

Five trials expressed results for FEV_1 % predicted as means and SDs (Hind 2017; Knudsen 2016; Quinn 2004; Shakkottai 2017; Wildman 2022), while one trial reported means and SDs at baseline only (Quittner 2019). One trial also reported unadjusted MDs between groups (Hind 2017), and two trials reported adjusted MDs, adjusting for baseline and CF centre (Hind 2017), or baseline, CF centre and past-year IV days (Wildman 2022). One trial reported only medians and IQRs (Riekert 2013), so we have described results narratively.

None of the included trials reported lung function in litres (i.e. FEV_1 L).

Pulmonary exacerbations

Two trials included pulmonary exacerbations as a primary outcome (Hind 2017; Wildman 2022) and three trials as a secondary outcome (Quittner 2019; Riekert 2013; Shakkottai 2017). Three of these trials assessed the total number of exacerbations during the trial periods of three months (Shakkottai 2017), six months (Hind 2017), or 12 months (Wildman 2022). This was defined as the "number of exacerbations treated with IV antibiotics with at least one modified Fuchs' criteria (e.g. change in sputum, increased cough)" (Ratjen 2012) in two trials (Hind 2017; Wildman 2022). One trial did not provide a definition for an exacerbation (Shakkottai 2017).

One trial reported the total number of exacerbations in each group only (no means, SDs or ratio data) (Shakkottai 2017), while two trials reported the total number of exacerbations in each group along with unadjusted and adjusted exacerbation rates (incidence rate ratios; 95% CI), adjusted for CF centre and past year IV antibiotic days (Hind 2017; Wildman 2022). Hind also reported the mean (SD) and median (IQR) number of exacerbations per group, and the number of participants experiencing one or more exacerbations per group (Hind 2017).

Two further trials measured exacerbations, although the results were more difficult to interpret (Quittner 2019; Riekert 2013). Riekert measured exacerbations as "pulmonary exacerbations (1+ in past year)" with results expressed as percentages. Quittner 2019 measured pulmonary exacerbations as "IV antibiotic treatment (extracted from the CF Registry)" but it was unclear how this was defined (Quittner 2019). The percentage of participants receiving "1+ course of IV antibiotics in the past year" was reported at baseline only.

None of the included trials reported the time to next exacerbation or the duration of exacerbations (total number of IV days).

Excluded studies

We excluded 2963 records by screening titles and abstracts. We excluded a further 69 trials (114 references) following full-text screening, with reasons for each listed in the tables (Characteristics of excluded studies) and summarised as follows. There were 11 references which did not relate to a trial (e.g. they were a commentary or an editorial) (Abbott 2015; Daniels 2013; Dodd 2000; Duff 2014; Geller 2011; Hawkins 2002; Meyers 1975; Ohn 2018; Pendleton 2000; Sadprasid 2021; Strawhacker 2004), and 17 trials were non-randomised or single-arm trials (ACTRN12619001730190; Goldbeck 2013; Grossoehme 2020; Landau 2021; NCT00688051; NCT01025258; NCT02286050; NCT02501369; NCT02906826; NCT03226795; NCT03518697; NCT04017559; NCT04217889; NCT04696484; O'Hayer 2021; Polineni 2017; Schandevyl 2021). A total of 13 trials were not focused on inhaled therapies (ACTRN12607000234415; DRKS00027569; Geirhos 2022; Goodill 2005; Martinez 2017; Modi 2010; NCT03304028; NCT03938324; NCT03992027; NCT04096664; NCT04453358; Parkins 2008; Viviani 2006), and 11 trials did not consider a relevant intervention (i.e. not examining a psychological intervention) (Bingham 2012; Cannon 1999; Elkins 2006; Betz 2019; Hagelberg 2008; Hatziagorou 2017; Montero-Ruiz 2020; Rode 2008; Ruddy 2015; Trapp 1998; Wood 2020). Eight trials did not measure adherence to inhaled therapies (Chan 2013;

Cummings 2011; Davis 2004; Hebestreit 2010; Hebestreit 2022; Hlela 2018; Huang 2014; Petzel 1991). We excluded the remaining nine trials either because there was a lack of information, or the trials were not available after multiple attempts to contact the trial authors (Bryon 2000; Chadelat 2005; Czajkowski 1985; Fischer 2003; Jackson 2017; McDonald 2007; NCT03052231; Quittner 1998; Marciel 2010).

Ongoing studies

To date, we have listed five trials as ongoing (Jirasek 2022; O'Hayer 2019; Phan 2021; Thee 2021; White 2017); we provide further information in the tables (Characteristics of ongoing studies).

Design

Four ongoing trials are parallel in design (O'Hayer 2019; Phan 2021; Thee 2021; White 2017) and one trial is a cross-over trial (Jirasek 2022). One trial is single-centre (White 2017), and four are multicentre (Jirasek 2022; O'Hayer 2019; Phan 2021; Thee 2021). Two trials are being conducted in the USA (O'Hayer 2019; Phan 2021), one in Germany (Thee 2021), one in the Czech Republic (Jirasek 2022), and one in the UK (White 2017).

Participants

Participants include adults with CF, aged 18 years and above in one trial (O'Hayer 2019), and aged between 16 and 60 years in a second trial (White 2017). Two trials include participants with CF aged 12 years and older (Phan 2021; Thee 2021), and one trial includes children and adolescents but does not specify the age of eligible participants (Jirasek 2022).

Interventions

All five ongoing trials are two-arm RCTs, with three trials comparing a psychological intervention to usual care (Phan 2021; Thee 2021; White 2017), and one trial comparing a psychological intervention (Acceptance and Commitment Therapy; ACT) with an active comparator arm (Supportive Psychotherapy) (O'Hayer 2019). In the cross-over trial, participants are randomised to the psychological intervention arm (CF Hero mobile application) for three months and then switch to not using the application for another three months.

The psychological interventions described in the ongoing trials include a coaching and telemonitoring intervention (Thee 2021); an ACT intervention delivered via video calls (O'Hayer 2019); a web-based intervention comprising six interactive online modules (e.g. Respiratory, Antibiotics, Nutrition, etc.) (White 2017); a motivational (reward-based) mobile application (CF Hero) (Jirasek 2022); and a web-based, mobile medication management application designed to reinforce adherence and provide education about treatment regimens (Phan 2021). Intervention duration ranges from six weeks (O'Hayer 2019) through three months (Jirasek 2022) and 24 weeks (Phan 2021) to 12 months (Thee 2021; White 2017).

One intervention is focused on improving adherence to inhaled therapies only (Thee 2021). The other interventions are focused on improving adherence to CF treatments in general (O'Hayer 2019), or multiple CF treatments, including inhaled therapies and oral medications (e.g. azithromycin) (Phan 2021), or inhaled therapies and physiotherapy (Jirasek 2022). One intervention involves participants identifying between one and three treatments from six areas of focus (nutrition, enzymes, liver medications, airways treatments, vitamins and antibiotics), such that participants may choose to focus on improving adherence to a treatment other than inhaled therapies (White 2017).

Outcomes

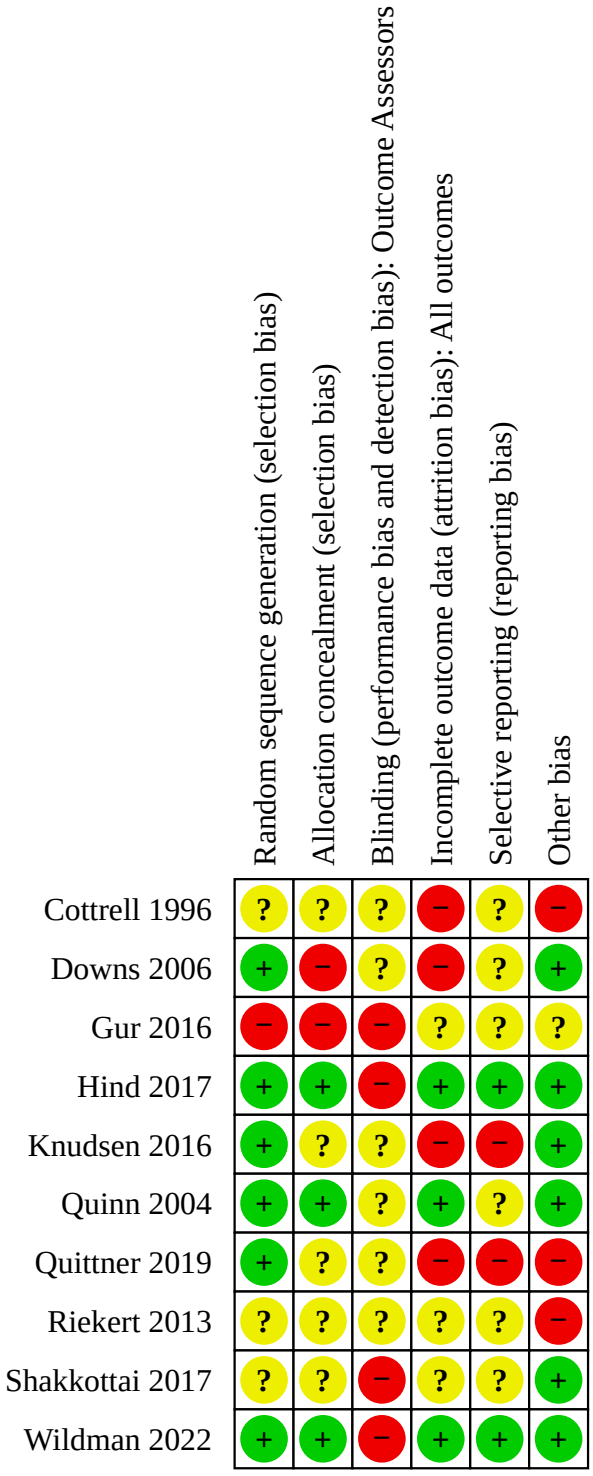
Two trials include adherence as a primary outcome (Jirasek 2022; White 2017), while it is a secondary outcome in the remaining three trials (O'Hayer 2019; Phan 2021; Thee 2021). Two trials are using objective recorded measures (dose-counting nebulisers) to assess adherence (Phan 2021; Thee 2021); one trial is using a subjective measure (self-reported medication adherence questionnaire) (O'Hayer 2019); one trial is using an objective count measure whereby the prescribed amount of medication is compared with the amount consumed after collecting unused or empty medicine containers (Jirasek 2022); and one trial is using an objective count measure (MPR) or self-report questionnaire (White 2017).

Depression is included as a secondary outcome in two trials (O'Hayer 2019; Thee 2021), and anxiety in one trial (O'Hayer 2019). QoL is a secondary outcome in three trials (Jirasek 2022; Thee 2021; White 2017), and four trials include lung function as a secondary outcome (Jirasek 2022; O'Hayer 2019; Thee 2021; White 2017). The number of pulmonary exacerbations is a secondary outcome in two trials (Thee 2021; White 2017), and the time to first exacerbation is the primary outcome in one trial (Thee 2021).

Risk of bias in included studies

A risk of bias summary is shown in Figure 2. Please refer to the risk of bias tables for details for each individual trial (Characteristics of included studies).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

We judged six trials to have a low risk of bias in relation to sequence generation (Downs 2006; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Wildman 2022). One trial used a pseudo-randomisation number-generation technique carried out by a member of staff independent to the trial (Quinn 2004). Four trials used randomised permuted blocks (Downs 2006; Hind 2017; Knudsen 2016; Wildman 2022), with three of these specifying that this was computer-generated (Hind 2017; Knudsen 2016; Wildman 2022). One trial stratified randomisation by age (Downs 2006) and two trials by CF centre and number of IV days in the previous 12 months (Hind 2017; Wildman 2022). One cluster-RCT used the CF centre as the unit of randomisation, to minimise cross-contamination risks from within-site randomisation (Quittner 2019). In this trial, randomisation was completed by the trial statistician, with centres stratified by size (Quittner 2019).

One trial consecutively assigned participants to the intervention or control group (by order of recruitment), therefore, we judged this to have a high risk of bias (Gur 2016). The three remaining trials were described as randomised, but no details of the actual randomisation process were given; therefore, we judged these trials to have an unclear risk of bias (Cottrell 1996; Riekert 2013; Shakkottai 2017).

Allocation concealment

We judged three trials to have a low risk of bias from allocation concealment (Hind 2017; Quinn 2004; Wildman 2022). One of these stated that allocation remained concealed until the participant was ready for Phase 2 of the trial (Quinn 2004); the remaining two trials used a remote, secure internet-based randomisation system which concealed allocation from investigators (Hind 2017; Wildman 2022). We judged five trials to have an unclear risk of bias as they did not report on allocation concealment (Cottrell 1996; Knudsen 2016; Quittner 2019; Riekert 2013; Shakkottai 2017). We judged the remaining two trials to have a high risk of bias (Downs 2006; Gur 2016). One of these trials reported that participants were consecutively assigned to the intervention or control group by one of the physicians during a routine clinic visit (Gur 2016), and the final trial did not provide details of allocation concealment in the published report, but information provided by the lead author on request states that allocation was not concealed (Downs 2006).

Blinding

Blinding of participants and personnel is typically not possible in trials of psychological interventions; as such, the assessment of blinding included only the outcome assessors, as specified in the protocol (Dawson 2020).

We judged the risk of bias from the blinding of outcome assessors to be unclear in six trials (Cottrell 1996; Downs 2006; Knudsen 2016; Quinn 2004; Quittner 2019; Riekert 2013). Three trials failed to provide any details on the blinding of outcome assessors (Cottrell 1996; Knudsen 2016; Riekert 2013). One trial did not provide details of blinding in the published report, but we judged this to have an unclear risk of bias on receipt of information provided by the trial author on request (Downs 2006). One trial attempted to blind outcome assessors (i.e. physiotherapists), but an evaluation as part of the trial revealed that one of the outcome assessors was aware of two allocations into the intervention arm, although both participants had completed the intervention by this time (Quinn 2004). In two trials, outcome assessors were blinded to at least some of the outcomes (Downs 2006; Quittner 2019). In four trials, outcome assessors (i.e. researchers or healthcare professionals involved in conducting the trials and collecting the outcome data) were not blinded, hence we judged there to be a high risk of bias (Gur 2016; Hind 2017; Shakkottai 2017; Wildman 2022).

Incomplete outcome data

Two trials conducted an intention-to-treat analysis with all participants entering the trial; we therefore judged these trials to have a low risk of bias for incomplete outcome data (Hind 2017; Wildman 2022). One trial conducted an intention-to-treat analysis with 35 out of 36 participants (one participant was transferred for heart-lung transplantation), so we also judged this trial to have a low risk of bias (Quinn 2004).

Two trials did not describe withdrawals, and we judged these to have an unclear risk of bias (Riekert 2013; Shakkottai 2017). We also judged a further trial to have an unclear risk of bias after investigators confirmed they did not have any dropouts, yet three participants originally assigned to the intervention group said they would prefer to be in the control group (two were not interested in performing Skype video chats due to busy schedules, and one did not have an Internet connection), so were transferred to the control group (Gur 2016).

We judged four trials to have a high risk of bias for incomplete outcome data (Cottrell 1996; Downs 2006; Knudsen 2016; Quittner 2019). In one trial, 20 out of 34 enrolled participants were analysed, but it is unclear whether the four reported withdrawals occurred pre- or post-randomisation and there was no further information on the 10 additional participants who dropped out (Cottrell 1996). In the Knudsen 2016 trial, only 28 out of 40 participants (nine from the intervention arm and 19 from the control arm) completed the post-intervention follow-up, and 24 out of 40 participants (12 in each arm) completed the one-year post-intervention follow-up. Reasons for withdrawal were only given for the intervention arm and included lack of time, poor health, coaching not helpful, lack of motivation, no need for further coaching, and unknown reasons. Downs 2006 reported significant attrition from the trial and the potential for bias. An intention-to-treat analysis was conducted which included data from participants in the intervention group who commenced the intervention and later withdrew (n = 8). However, 11 participants (seven in the intervention arm and four in the control arm) did not complete pre-test assessments or withdrew from the trial prior to commencing intervention, and so were not included in intention-to-treat analysis (Downs 2006). In the Quittner 2019 trial, there were challenges obtaining pharmacy records, which resulted in a significant amount of missing adherence data. Of the 641 participants who consented, 308 (51%) had analysable pharmacy records at baseline (n = 156 intervention; n = 152 control), and 436 (72%) had analysable pharmacy records at 12 months (n = 205 intervention; n = 231 control). The report states that intervention effects were evaluated based on the intention-to-treat principle, but it is unclear whether this included all participants entering the trial or whether some were excluded.

Selective reporting

We were able to compare two published trials with their protocols and found no evidence of selective reporting, hence we judged these trials to have a low risk of bias (Hind 2017; Wildman 2022). We judged six trials to have an unclear risk of bias for selective reporting (Cottrell 1996; Downs 2006; Gur 2016; Quinn 2004; Riekert 2013; Shakkottai 2017). We were unable to access protocols to assess selective reporting for three trials (Cottrell 1996; Downs 2006; Quinn 2004). One trial reported all outcomes listed on the clinical trial register in the full trial paper, but the listed trial duration changed from 12 to three months, with no further details provided (Shakkottai 2017). We contacted the authors of one trial who provided a copy of the unpublished trial protocol (Gur 2016). Adherence results were not presented in the published report, but results were provided by the trial authors on request. Scores on each CFQ-R domain were not available, however (Gur 2016). Finally, one trial reported additional outcomes not listed on the clinical trial register (e.g. HRQoL, pulmonary exacerbations) (Riekert 2013). We judged two trials to have a high risk of bias as each listed an additional secondary outcome on the clinical trial register that was not reported in the published papers (Knudsen 2016; Quittner 2019).

Other potential sources of bias

We identified no other potential sources of bias in six trials (Downs 2006; Hind 2017; Knudsen 2016; Quinn 2004; Shakkottai 2017; Wildman 2022).

However, we judged one trial to have an unclear risk bias from another source as the unpublished protocol provided by the authors stated they had planned to recruit 66 participants, whereas only 18 were recruited according to the published report (Gur 2016).

We judged three trials to have a high risk of bias from other sources (Cottrell 1996; Quittner 2019; Riekert 2013). In one trial, participants received financial incentives for attending intervention sessions and completing assessments as acknowledgement for participation (Quittner 2019). In addition, this trial was a cluster-RCT in which CF centres interested in adherence-promoting strategies were invited to participate (no other eligibility criteria for CF centres was applied). The first 18 CF centres to sign a contract and obtain relevant approvals were enroled, so it is likely that there could have been differences between those CF centres who volunteered to take part, compared to those who did not (Quittner 2019).

Two trials reported baseline imbalances (which were unadjusted in the results) (Cottrell 1996; Riekert 2013). As highlighted in a previous Cochrane Review (Savage 2014), in one trial, the mean (SD) baseline weight measurement for participants in the intervention group was 89.15 (29.29) lb and for participants in the control group was 101.4 (32.17) lb, which, for CF, indicates a clinically important baseline imbalance (Cottrell 1996). In another trial, the authors reported that the intervention group had higher cMPR scores than the control group ($P = 0.07$) at baseline, and greater perceived treatment burden ($P < 0.01$) (Riekert 2013).

Effects of interventions

See: **Summary of findings 1** Summary of findings: psychological interventions compared with usual care; **Summary of findings 2** Summary of findings: psychological interventions compared with an active comparator

We have graded the certainty of the evidence for those outcomes included in the summary of findings tables (at the 'over six months and up to 12 months' time point). For the definitions of these gradings, please refer to the summary of findings tables (Summary of findings 1; Summary of findings 2).

We only report below those of our predefined outcomes that the included trials reported on. For the first comparison of psychological interventions versus usual care, results were not available for some planned lung function measures (absolute values for FEV_1 L and change from baseline measured either in % predicted or L), or for the time to next exacerbation or duration of exacerbations. For the comparison of active interventions, results were not available for either objective recorded measures of adherence or for subjective measures, for the treatment-related adverse events of anxiety and depression, for some lung function measures (absolute values for FEV_1 L and change from baseline measured either in % predicted or L), or for the time to next exacerbation or duration of exacerbations. For each outcome measure, the number of participants differed due to incomplete data.

Psychological interventions versus usual care

Nine trials (approximately 1514 participants) contributed data to the comparison of psychological interventions versus usual care (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022). We have graded the certainty of the evidence for those outcomes at the 'over six months and up to 12 months' time point (Summary of findings 1).

Primary outcomes

1. Adherence to inhaled therapies

a. Objective recorded measures

Three trials assessed adherence to inhaled therapies using objective recorded measures (e.g. data-logging nebulisers) (Hind 2017; Quinn 2004; Wildman 2022). One trial (35 participants) assessed this outcome at the 'up to three months' time point (Quinn 2004); one trial (55 participants) at over three months and up to six months (Hind 2017); and one trial (588 participants) at over six months and up to 12 months (Wildman 2022). There was insufficient information available to calculate the change from baseline in one trial (Quinn 2004). Therefore, we present results as endpoint (i.e. post-intervention) data for three trials (Hind 2017; Quinn 2004; Wildman 2022).

There was no evidence of a difference in the percentage of prescribed inhaled medications taken between intervention and control arms at up to three months (MD 4.32, 95% CI -26.77 to 35.41) (Quinn 2004) or over three months and up to six months (MD 10.00, 95% CI -6.12 to 26.12) (Hind 2017). Results did, however, show 18% more medication taken in the intervention group than the control group at the 'over six months and up to 12 months' time point (MD 18.00, 95% CI 12.90 to 23.10; Analysis 1.1) (Wildman 2022). The Wildman trial also reported adjusted data, which showed a 9.50% difference in adherence in favour of the intervention at the 'over six months and up to 12 months' time point (95% CI 8.60 to 10.40; moderate-certainty evidence; Analysis 1.2) (Wildman 2022).

b. Objective count measures

One trial (5 participants) assessed this outcome at the 'up to three months' time point (Shakkottai 2017), and a second trial (436 participants) reported at over six months and up to 12 months (Quittner 2019). Both trials reported a cMPR measure which included a combination of inhaled therapies and one non-inhaled therapy (Quittner 2019; Shakkottai 2017). We were not able to combine results in the data analyses since MPR data for individual drugs were not reported or there were missing data. We therefore describe the results narratively below.

Shakkottai 2017 reported mean values (but no SDs) for a cMPR measure comprising two inhaled therapies (hypertonic saline and dornase alfa) and CF multivitamins (not inhaled). After three months, the mean cMPR in the intervention group had increased from baseline by 0.05 and in the control group by 0.04. Mean MPRs for individual drugs in the two groups at baseline and the end of the trial were presented graphically, and we estimated the change in score from baseline. For dornase alfa, we estimated a 0.04 decrease in the intervention group compared to a 0.13 decrease in the control group; for hypertonic saline, we estimated the increase from baseline as 0.09 in the intervention group compared to a 0.13 drop in the control group (Shakkottai 2017).

Quittner 2019 also reported a mean cMPR measure (without SDs) which included inhaled therapies (dornase alfa, hypertonic saline and inhaled antibiotics (tobramycin, colistin and aztreonam)) and oral azithromycin. Due to challenges in obtaining pharmacy records during the trial (procedures were changed halfway through which primarily affected collection of baseline data), cMPR scores were available for 436 participants at 12 months compared with 308 participants at baseline (baseline data were calculated from the baseline date back one year; and the 12-month interval was the baseline date plus one year). After 12 months, the authors reported no intervention effects were found when cMPR fell by 0.181 (18%) in the intervention group compared to 0.170 (17%) in the control group (Quittner 2019).

c. Subjective measures

Four trials measured adherence to inhaled therapies using subjective measures (e.g. questionnaires, participant diaries) (Cottrell 1996; Downs 2006; Gur 2016; Knudsen 2016).

Two trials assessed adherence using self-report in participant diaries, and the authors converted this to a percentage of prescribed aerosol treatments taken for each participant (Cottrell 1996; Downs 2006). One trial (20 participants) assessed this outcome at up to three months (Cottrell 1996), and one trial (intention-to-treat analysis with 51 participants) assessed this outcome at three time points: over three months and up to six months; over six months and up to 12 months; and over 12 months (Downs 2006).

There was insufficient information available to calculate the change from baseline in these trials and results are presented as post-intervention data (Analysis 1.3). There was no evidence of a difference between groups at up to three months (MD 13.00, 95% CI -20.11 to 46.11) (Cottrell 1996). More aerosol treatments were taken by the intervention group at the 'over three months and up to six months' time point (MD 16.60, 95% CI 0.22 to 32.98), but this was not sustained at over six months and up to 12 months (MD 8.60, 95% CI -7.90 to 25.10), or over 12 months (MD 7.10, 95% CI -6.73 to 20.93) (Downs 2006).

Two trials assessed adherence to dornase alfa and to inhaled antibiotics (Gur 2016; Knudsen 2016); Gur 2016 reported the mean score on a self-reported adherence questionnaire and Knudsen 2016 reported participant scores on the MMAS-8 (Morisky 2008). Both trials assessed these outcomes at over three months and up to six months; one trial further reported at over six months and up to 12 months and again at over 12 months (Knudsen 2016). Since these outcomes were measured using different scales across trials (all in the same direction, whereby a higher score indicated higher adherence), we calculated SMDs with 95% CIs. For dornase alfa, there was no evidence of a difference between groups at over three months and up to six months (SMD 0.02, 95% CI -0.62 to 0.67; 2 trials, 46 participants; Analysis 1.4), or at over six months and up to 12 months (SMD 0.43, 95% CI -0.41 to 1.27; 2 trials, 24 participants; Analysis 1.4), but there was higher adherence in the intervention group at over 12 months (SMD 0.91, 95% CI -0.00 to 1.81; 2 trials, 21 participants; Analysis 1.4) (Gur 2016; Knudsen 2016). For inhaled antibiotics, there was no evidence of differences between groups at over three months and up to six months (SMD 0.49, 95% CI -1.01 to 1.98; 2 trials, 43 participants; Analysis 1.5), at over six months and up to 12 months (SMD -0.13, 95% CI -0.99 to 0.72; 2 trials, 23 participants; Analysis 1.5), nor at over 12 months (SMD 0.00, 95% CI -0.91 to 0.91; 2 trials, 19 participants; Analysis 1.5) (Gur 2016; Knudsen 2016).

Gur 2016 also assessed adherence to inhaled steroids, hypertonic saline, and bronchodilators at over three months and up to six months. There was no evidence of a difference between groups for inhaled steroids (MD 1.09, 95% CI -0.66 to 2.84; 1 trial, 17 participants; Analysis 1.6), hypertonic saline (MD -0.12, 95% CI -1.84 to 1.60; 1 trial, 16 participants; Analysis 1.7), or bronchodilators (MD -1.13, 95% CI -3.00 to 0.74; 1 trial, 16 participants; Analysis 1.8).

2. Treatment-related adverse events

a. Anxiety

This result was reported in three trials. One trial (35 participants) assessed anxiety at up to three months (Quinn 2004), one trial (59 participants) at over three months and up to six months (Hind 2017) and one trial (535 participants) at over six months and up to 12 months (Wildman 2022). Two trials explicitly included the outcome of anxiety as a safety measure (Hind 2017; Wildman 2022).

As anxiety was measured using different scales across trials (all in the same direction, whereby a higher score indicated greater anxiety), we calculated SMDs with 95% CIs. There was insufficient information available to calculate the change from baseline in one trial (Quinn 2004). Therefore, results are presented as post-intervention data for the three trials that reported this outcome (Hind 2017; Quinn 2004; Wildman 2022). Since one trial measured anxiety using two outcome measures in the same participants, we have not reported any totals or summary statistics for this outcome (Quinn 2004). Instead, we have presented the data for each measure (Analysis 1.9). There was no evidence of a difference in anxiety between intervention and control groups on any measure at up to three months (Quinn 2004); over three months and up to six months (Hind 2017); or at over six months and up to 12 months (Wildman 2022) (Analysis 1.9).

In addition, two trials reported the adjusted MD for anxiety (Hind 2017; Wildman 2022), measured using the GAD-7 (Spitzer 2006). These results showed that there was no evidence of a difference between groups either at over three months and up to six months (MD -0.31, 95% CI -1.90 to 1.28) (Hind 2017) or at over six months and up to 12 months (MD 0.30, 95% CI -0.40 to 1.00; low-certainty evidence; Analysis 1.10) (Wildman 2022).

b. Depression

This result was reported in four trials. One trial (35 participants) assessed depression at up to three months (Quinn 2004); two trials (88 or 89 participants depending on the measure used) at over three months and up to six months (Hind 2017; Knudsen 2016); two trials (559 or 560 participants depending on the measure used) at over six months and up to 12 months (Knudsen 2016; Wildman 2022); and one trial (24 participants) at over 12 months (Knudsen 2016). Two trials explicitly included the outcome of depression as a safety measure (Hind 2017; Wildman 2022).

Knudsen 2016 firstly assessed depression using the 12-item MDI, where scores range from 0 to 50; with scores of 21 to 25 indicating mild depression, 26 to 30 indicating moderate depression, and 31 to 50 indicating severe depression (Bech 2001); and secondly, using the 20-item CES-D where scores range from 0 to 60, with higher scores indicating greater depressive symptoms, and scores of 16 or more indicating depression (Radloff 1977).

As above, we calculated SMDs with 95% CIs. There was insufficient information available to calculate the change from baseline in two trials (Knudsen 2016; Quinn 2004). Therefore, results are presented as post-intervention data (Hind 2017; Knudsen 2016; Quinn 2004; Wildman 2022). Since one trial used two outcome measures of depression in the same participants at three of the time points, we have not reported any totals or summary statistics (Knudsen 2016). Instead, we have presented the data for each measure (Analysis 1.11). There was no evidence of a difference in depression between intervention and control groups on any measure at any time point (Analysis 1.11).

In addition to the endpoint data, two trials reported the adjusted MD for depression (Hind 2017; Wildman 2022). Using the PHQ-8 (where scores range from 0 to 24, with cut-off scores of 5, 10, 15, and 20 indicating mild, moderate, moderately severe, and severe depression, respectively) (Kroenke 2009), results showed no evidence of a difference between groups at either over three months and up to six months, MD 0.97 (95% CI -0.96 to 2.90; Analysis 1.12) (Hind 2017), or over six months and up to 12 months, MD -0.10 (95% CI -0.80 to 0.60; low-certainty evidence; Analysis 1.12) (Wildman 2022).

Secondary outcomes

1. QoL

Eight trials assessed QoL (Cottrell 1996; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022); the measures used varied across trials and included the Quality of Wellbeing scale (Kaplan 1989), CFQoL (Gee 2000) and CFQ-R (Quittner 2009).

We combined domains from the CFQoL (Gee 2000) and CFQ-R (Quittner 2009) that had the same names (e.g. physical functioning, body image) and calculated SMDs with 95% CIs. For domains that could not obviously be combined with domains from other measures (e.g. career concerns, interpersonal relationships), we included these in separate data analyses and calculated MDs with 95% CIs. There was insufficient information available to calculate the change from baseline in five trials (Gur 2016; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017). Therefore, results are presented as post-intervention data for the eight trials that reported this outcome (Cottrell 1996; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022), except where otherwise specified (e.g. two trials also reported adjusted data (Hind 2017; Wildman 2022)).

Up to three months

One trial (20 participants) assessed the mean score on the Quality of Wellbeing scale (Kaplan 1989) at up to three months (Cottrell 1996). A further trial (35 participants) assessed the mean scores on all nine domains of the CFQoL (Gee 2000) at up to three months using an intention-to-treat analysis (Quinn 2004). A third trial (five participants) assessed QoL using only the treatment burden domain of the CFQ-R (Shakkottai 2017).

There was no evidence of a difference between intervention and control groups in the mean score on the Quality of Wellbeing scale (MD -0.02, 95% CI -0.09 to 0.05; Analysis 1.13). The trial authors highlighted a possible ceiling effect, with participants scoring 0.7 or higher at baseline (on a scale of 0 to 1, where 0 is 'death' and 1 is 'perfect health'), suggesting that participants were already experiencing a relatively high QoL pre-intervention (Cottrell 1996).

There was no evidence of a difference between groups at three months for the following domains: physical functioning (Analysis 1.14); emotional functioning (Analysis 1.16); social functioning (Analysis 1.18); treatment burden (Analysis 1.20); respiratory or chest symptoms (Analysis 1.32); treatment issues (Analysis 1.38); career concerns (Analysis 1.39); interpersonal relationships (Analysis 1.40); or concerns for the future (Analysis 1.41). However, results favoured the intervention for body image (SMD 0.69, 95% CI 0.00 to 1.38; Analysis 1.24). The authors of the Quinn trial highlighted that mean scores were higher in the intervention group compared to usual care on most subscales at three months (excluding treatment issues and concerns for the future) (Quinn 2004).

Over three months and up to six months

Two trials (87 to 89 participants) assessed the mean scores on all 12 domains of the CFQ-R (Quittner 2009) at this time point (Hind 2017; Knudsen 2016). There was no evidence of a difference between groups on any of the following QoL domains: physical functioning (Analysis 1.14); emotional functioning (Analysis 1.16); social functioning (Analysis 1.18); treatment burden (Analysis 1.20); role limitations (Analysis 1.22); body image (Analysis 1.24); vitality (Analysis 1.26); eating disturbance (Analysis 1.28); weight problems (Analysis 1.30); respiratory symptoms (Analysis 1.32); digestive symptoms (Analysis 1.34); or health perceptions (Analysis 1.36) (Hind 2017; Knudsen 2016).

In addition to the endpoint data, one trial also reported the adjusted MD between groups (Hind 2017). These results also showed no evidence of a difference in any of the following QoL domains: physical functioning (Analysis 1.15); emotional functioning (Analysis 1.17); social functioning (Analysis 1.19); treatment burden (Analysis 1.21); role limitations (Analysis 1.23); body image (Analysis 1.25); vitality (Analysis 1.27); eating

disturbance (Analysis 1.29); weight problems (Analysis 1.31); respiratory symptoms (Analysis 1.33); digestive symptoms (Analysis 1.35); and health perceptions (Analysis 1.37).

One trial calculated an average CFQ-R score for each group (rather than reporting results for each domain separately), so we could not analyse the data (Gur 2016). Mean (SD) overall CFQ-R score post-intervention was 62.39 (14.33) in the intervention group compared with 65.91 (18.09) in the control group.

Over six months and up to 12 months

Three trials assessed QoL at this time point: two reported mean scores for all 12 domains of the CFQ-R (Knudsen 2016; Quittner 2019), while the third trial used mean score on eight domains of the CFQ-R (physical functioning, emotional functioning, social functioning, eating disturbance, body image, treatment burden, respiratory symptoms and digestive symptoms) (Wildman 2022).

There was no evidence of a difference between groups in any of the following CFQ-R domains: physical functioning (1089 participants) (Analysis 1.14); emotional functioning (1089 participants) (Analysis 1.16); social functioning (1089 participants) (Analysis 1.18); treatment burden (1090 participants) (Analysis 1.20); role limitations (412 participants) (Analysis 1.22); body image (1089 participants) (Analysis 1.24); vitality (413 participants) (Analysis 1.26); eating disturbances (1089 participants) (Analysis 1.28); weight problems (413 participants) (Analysis 1.30); respiratory symptoms (1085 participants) (Analysis 1.32); digestive symptoms (1084 participants) (Analysis 1.34); or health perceptions (413 participants) (Analysis 1.36). Only one trial found a difference between groups in one domain of the CFQ-R (treatment burden) at this time point, SMD 0.26 (95% CI 0.09 to 0.43; Analysis 1.20) (Wildman 2022).

In addition to the endpoint data, one trial also reported the adjusted MDs (Wildman 2022). These results showed no evidence of a difference between groups in any of the following QoL domains: physical functioning (Analysis 1.15); emotional functioning (Analysis 1.17); social functioning (Analysis 1.19); body image (Analysis 1.25); eating disturbance (Analysis 1.29); respiratory symptoms (low-certainty evidence; Analysis 1.33); or digestive symptoms (Analysis 1.35) (Wildman 2022). However, results did favour the intervention for the treatment burden domain (MD 3.90, 95% CI 1.20 to 6.60; low-certainty evidence; Analysis 1.21).

Over 12 months

Lastly, one trial (22 to 24 participants) assessed QoL using all 12 domains of the CFQ-R at over 12 months (Knudsen 2016). There was no evidence of a difference between groups in any of the following QoL domains: physical functioning (Analysis 1.14); emotional functioning (Analysis 1.16); social functioning (Analysis 1.18); treatment burden (Analysis 1.20); role limitations (Analysis 1.22); body image (Analysis 1.24); vitality (Analysis 1.26); eating disturbances (Analysis 1.28); weight problems (Analysis 1.30); respiratory symptoms (Analysis 1.32); digestive symptoms (Analysis 1.34); or health perceptions (Analysis 1.36).

% predicted

Five trials reported analysable data (Hind 2017; Knudsen 2016; Quinn 2004; Shakkottai 2017; Wildman 2022). There was insufficient information available to calculate the change from baseline in three trials (Knudsen 2016; Quinn 2004; Shakkottai 2017). Therefore, we present results as endpoint (i.e. post-intervention) data for the five trials (Hind 2017; Knudsen 2016; Quinn 2004; Shakkottai 2017; Wildman 2022). In addition to the endpoint data, two trials also reported the adjusted MD for FEV_1 % predicted (Hind 2017; Wildman 2022). Additionally, one trial reported means and SDs for this outcome at baseline only, meaning we could not include the data from this trial in the analysis (Quittner 2019). However, the authors report that no significant intervention effects were found for any of the secondary outcomes in this trial, compared to usual care (and FEV_1% predicted was a secondary outcome in this trial) (Quittner 2019).

Up to three months

Two trials assessed FEV_1 % predicted at up to three months (Quinn 2004; Shakkottai 2017). There was no evidence of a difference between groups (MD -3.25, 95% CI -18.13 to 11.64; 2 trials, 40 participants; Analysis 1.42).

Over three months and up to six months

Two trials reported FEV_1 % predicted at over three months and up to six months (Hind 2017; Knudsen 2016); results showed no evidence of a difference between treatment and control (MD -2.98, 95% CI -12.50 to 6.55; 2 trials, 95 participants; Analysis 1.42). Adjusted results from one trial also showed no evidence of a difference between groups (MD 5.00, 95% CI -2.00 to 12.00; Analysis 1.43) (Hind 2017).

Over six months and up to 12 months

Two trials (593 participants) reported FEV_1 % predicted at over six months and up to 12 months (Knudsen 2016; Wildman 2022); results showed no evidence of a difference between groups (MD 3.20, 95% CI -0.59 to 6.99; 2 trials, 593 participants; Analysis 1.42). Adjusted results from one trial also showed no evidence of a difference between groups at over six months and up to 12 months (MD 1.40, 95% CI -0.20 to 3.00; moderate-certainty evidence; Analysis 1.43) (Wildman 2022).

Over 12 months

One trial assessed this outcome (Knudsen 2016), finding no evidence of an effect at over 12 months (MD -4.20, 95% CI -19.31 to 10.91; 1 trial, 36 participants; Analysis 1.42).

3. Pulmonary exacerbations

Up to three months

It was not possible to analyse the results of one trial (five participants) for this outcome (Shakkottai 2017), as the authors do not report the means, SDs or ratio data. Investigators reported the total number of pulmonary exacerbations per group in the three-month duration of the trial, rather than the number of people experiencing an exacerbation. There were two exacerbations in the intervention group compared with one in the control group (Shakkottai 2017). The trial reports that there was no change in the average number of pulmonary exacerbations in either group.

Over three months and up to six months

One trial (60 participants) reported the total (and the mean (SD) and median (IQR)) number of exacerbations per group at over three months and up to six months (Hind 2017). There were a total of

35 exacerbations in the intervention group (mean (SD) 1.1 (1.1); median (range) 1 (0 to 2); 32 participants) compared with 25 (mean (SD) 0.9 (1.1); median (range) 0.5 (0 to 2); 28 participants) in the control arm over the six-month trial. Analysed data showed no evidence of a difference in the mean number of exacerbations between groups (MD 0.20, 95% CI -0.36 to 0.76; Analysis 1.44) (Hind 2017). The authors reported unadjusted data showing no evidence of a difference between groups (rate ratio 1.22, 95% CI 0.69 to 2.16; Analysis 1.45); the adjusted data also did not show a difference in exacerbation rates between groups at over three months and up to six months (rate ratio 1.12, 95% CI 0.66 to 1.90; Analysis 1.46).

This trial also reported the number of participants per group who experienced one or more exacerbations over the six-month trial (60 participants) (Hind 2017). A total of 19 out of 32 participants (59%) in the intervention group and 14 out of 28 participants (50%) in the control group experienced at least one exacerbation.

Over six months and up to 12 months

One trial (607 participants) reported the number of exacerbations at over six months and up to 12 months, with no evidence of a difference in exacerbations between treatment or control arms (P = 0.64) (Wildman 2022). Over the 12-month trial duration, there were 526 pulmonary exacerbations in the 303 participants in the usual care arm compared with 482 exacerbations in the 304 participants in the intervention arm. Analysis of the unadjusted data at over six months and up to 12 months generated the rate ratio 0.92 (95% CI 0.77 to 1.10; Analysis 1.45). When the adjusted data were analysed (adjusted rate 1.77/year in the usual care arm compared with an adjusted rate of 1.63/year in the intervention arm), there was also no evidence of a difference between groups, rate ratio 0.96 (95% CI 0.83 to 1.11; low-certainty evidence; Analysis 1.46).

One 12-month trial measured pulmonary exacerbations as 'IV antibiotic treatment', but it was unclear how this outcome was defined, and investigators only reported the percentage of participants receiving '1+ course of IV antibiotics in the past year' at baseline (Quittner 2019). The authors of this trial did, however, report that they did not find any intervention effect for pulmonary exacerbations.

Psychological intervention (MI) versus active comparator (EPS)

One trial (128 participants) compared MI with an active comparator control arm (EPS) (Riekert 2013). However, this trial only reported medians and IQRs, so we were not able to analyse data for this comparison and we describe results narratively below. We have graded the certainty of the evidence for those outcomes at the 'over six months and up to 12 months' time point (Summary of findings 2).

Primary outcomes

1. Adherence to inhaled therapies

b. Objective count measures

The included trial measured adherence to inhaled therapies using a cMPR measure, which included inhaled therapies (dornase alfa, hypertonic saline, inhaled tobramycin, and aztreonam), as well as one non-inhaled treatment (azithromycin) (Riekert 2013). At 12 months (95 participants), median (IQR) cMPR was 54 (37 to 73) in the MI group, compared with 51 (17 to 71) in the EPS group. The trial authors also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that no intervention effects were found for cMPR (P = 0.763; no effect size reported or calculable) or any of the individual drugs (very low-certainty evidence).

Secondary outcomes

1. QoL

Riekert assessed this outcome using three domains of the CFQ-R (Quittner 2009) (respiratory, physical functioning, and treatment burden). At six months (112 participants), median (IQR) score was 67 (56 to 78) in the MI group and 64 (50 to 78) in the EPS group (respiratory); 81 (63 to 96) in the MI group and 77 (58 to 96) in the EPS group (physical functioning); and 56 (44 to 67) in the MI group and 56 (44 to 67) in the EPS group (treatment burden). At 12 months (95 participants), median (IQR) score was 67 (50 to 83) in the MI group and 67 (50 to 72) in the EPS group (respiratory); 79 (60 to 96) in the MI group and 79 (54 to 96) in the EPS group (physical functioning); and 56 (44 to 67) in the MI group and 56 (44 to 78) in the EPS group (treatment burden).

The trialists assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months). They reported that no intervention effects were found for QoL, with the exception of the treatment burden domain where the MI group had an increase from baseline at six months relative to the EPS group (P = 0.006; no effect size reported or calculable; very low-certainty evidence) (Riekert 2013).

2. Lung function

At 12 months (125 participants), median (IQR) FEV_1 % predicted was 66% (48% to 85%) in the MI group and 64% (49% to 84%) in the EPS group. The authors of the included trial also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that the intervention had no effect on lung function (P = 0.773; no effect size reported or calculable; very low-certainty evidence).

3. Pulmonary exacerbations

a. Number of exacerbations

The included trial reported exacerbations as 'pulmonary exacerbations (1+ in past year)' as a percentage for each group. Using these percentages and the total number of participants in each group, we calculated that in the MI group, 12 out of 63 participants (19%) experienced an exacerbation over the 12-month trial period compared with 12 out of 65 (18%) in the EPS group. The trial authors also assessed whether there was an effect of the intervention between groups (MI and EPS) over time (baseline and 12 months); they reported that the intervention had no effect on pulmonary exacerbations (P = 0.929; no effect size reported or calculable; very low-certainty evidence).

DISCUSSION

Summary of main results

We systematically reviewed available evidence comparing the efficacy of psychological interventions for improving adherence to inhaled therapies in people with CF. We included 10 trials (1642 participants) published between 1996 and 2021; four trials included children and adolescents (and their parents or caregivers) (Cottrell

1996; Downs 2006; Quittner 2019; Shakkottai 2017), five trials included adults (Hind 2017; Knudsen 2016; Quinn 2004; Riekert 2013; Wildman 2022), and one trial included children and adults (Gur 2016). No interventions specifically targeted the families of people with CF or MDTs. Nine trials compared a psychological intervention with a usual care control group (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Quittner 2019; Shakkottai 2017; Wildman 2022), and one compared a psychological intervention (MI) with an active comparator (EPS) (Riekert 2013).

Given the heterogeneity of the participants, interventions, and outcome measures, statistical analysis was limited, and we have summarised the main outcomes at the 'over six months and up to 12 months' time point in the summary of findings tables (Summary of findings 1; Summary of findings 2). Due to the limited number of included trials and the variety of the interventions, we were unable to investigate the most effective components, or BCTs, for improving adherence. We have, however, identified a hierarchy of the most common BCTs that feature in these studies (Table 1). Psychological interventions were generally multi-component and complex, containing an average of 9.6 BCTs; the most frequently used BCTs were 'problem solving' and 'instruction on how to perform the behaviour' (Michie 2013). The 10 trials differed in the outcomes and the time points assessed (ranging from six to eight weeks post-intervention (Cottrell 1996) to 23 months post-intervention (Knudsen 2016)).

Psychological interventions versus usual care

All nine trials included in this comparison reported on our primary outcome of adherence, using a variety of outcome measures. Only three trials suggested evidence of an effect of psychological interventions for improving adherence to inhaled therapies in people with CF. When measured objectively, using data-logging nebulisers, results from one large, 19-centre trial (607 participants) showed that a digital intervention (CFHealthHub) combined with behaviour change sessions with trained interventionists, can increase adherence to inhaled therapies in adults with CF by 18% (9.5% increase from baseline) at 12 months, compared with usual care (Wildman 2022). This trial used 23 BCTs, the joint second highest of all included trials (see 'Table 1').

A further two trials showed an increase in adherence between groups, but these were assessed using subjective measures (e.g. standardised questionnaires or participant diaries) (Downs 2006; Knudsen 2016). One of these trials (n = 51) assessed a 10-week self-management paper-based workbook exercise completed by children with CF and their parents/caregivers at home (Downs 2006). Results demonstrated that post-intervention, adherence to aerosol treatments was 16.6% greater in the intervention group compared with usual care, but this was not sustained at six months and 12 months. This trial used 28 BCTs, the largest number of all included trials (see 'Table 1'). Results from the second trial suggested that, compared with usual care, a life-coaching intervention improved adherence to dornase alfa in adults with CF (n = 28) at one year-post intervention (Knudsen 2016). This trial used the fewest BCTs of all included trials (n = 1; Table 1). There was a difference of 1.72 in favour of the intervention on the MMAS-8 (Morisky 2008); however, it is unclear if the differences are of any clinical significance, as the scores on this measure would still meet the cut-off for 'low adherence'. There was also no evidence of an effect of the intervention at any other reported time point, or for the other treatment measured (inhaled antibiotics).

For our second primary outcome, treatment-related adverse events, no trial found a difference between groups on anxiety or depression at any time point.

For our secondary outcomes, there was no evidence of a difference between groups in terms of pulmonary exacerbations or lung function (measured using FEV_1% predicted), although one trial found the rate of decline in FEV_1 over 12 months was less among intervention participants (0.1%) compared with usual care (1.4%) (Wildman 2022). In terms of QoL, the adjusted data from the Wildman 2022 trial demonstrated a difference in favour of the CFHealthHub intervention on treatment burden at 12 months compared with usual care (MD 3.90, 95% CI 1.20 to 6.60; Analysis 1.21). A further trial found behaviour change counselling had a greater effect on body image at three months than usual care (Analysis 1.24; Quinn 2004). No other trial reported a difference on any QoL domain.

In summary, psychological interventions probably improve our primary outcome of adherence to inhaled therapies in people with CF at over six months and up to 12 months (one trial; 588 participants; moderate-certainty evidence). There was no evidence to suggest they may have an effect on treatment-related adverse events, anxiety or depression, at the same time point (one trial; 534 to 535 participants; low-certainty evidence). For our secondary outcomes, psychological interventions probably make little or no difference to lung function measured by FEV_1 % predicted (one trial; 556 participants; moderate-certainty evidence), pulmonary exacerbations (one trial; 607 participants; moderate-certainty evidence), or the QoL domain of respiratory symptoms (one trial; 534 participants; low-certainty evidence). There is, however, low-certainty evidence to suggest that psychological interventions may improve the QoL domain of treatment burden (one trial; 539 participants) (Summary of findings 1).

Psychological intervention (MI) versus active comparator (EPS)

For our second comparison, we identified one trial involving 128 participants which compared an MI intervention with EPS (Riekert 2013). The authors reported medians and IQR, so we were unable to analyse the data in our review. The original paper reported that no intervention effects were found for adherence (cMPR), QoL, lung function, or pulmonary exacerbations at the 'over six months and up to 12 months' time point. The authors reported that the MI group had an improvement in treatment burden compared with the EPS group at six months (P = 0.006; no effect size reported; Riekert 2013), but this was not sustained at 12 months. We found that the overall certainty of the evidence from this single trial was very low across outcomes. We are therefore uncertain whether an MI intervention (compared with EPS) improves adherence to inhaled therapies, lung function, or QoL in people with CF. We are also uncertain whether there is an effect on pulmonary exacerbations. The included trial for this comparison did not report on treatment-related adverse events (anxiety and depression) (Summary of findings 2).

Overall completeness and applicability of evidence

Many of the included trials had small sample sizes and were heterogenous in terms of participants (age), interventions (content and mode of delivery), and outcomes (measures, number and range of assessment time points). For these reasons, it was not possible to identify an overall intervention effect using meta-analysis, which therefore limits the overall completeness and, ultimately, the generalisation of the evidence to the wider CF population at present. The results of five trials are awaited (Jirasek 2022; O'Hayer 2019; Phan 2021; Thee 2021; White 2017). We will report on these trials in the next update of the review.

Our planned subgroup analyses by types of participants (e.g. children and adolescents with CF; adults with CF; families of people with CF; or MDTs) or to compare trials assessing adherence to multiple CF treatments versus those that focused on inhaled therapies only were not possible due to the limited data available (Subgroup analysis and investigation of heterogeneity). Although children and adolescents were included in four trials in this review (Cottrell 1996; Downs 2006; Quittner 2019; Shakkottai 2017), two trials assessed short-term outcomes (less than three months) (Cottrell 1996; Shakkottai 2017); one trial assessed only one of our outcomes, adherence (Downs 2006); and the results of one large, multicentre trial were difficult to interpret due to post-intervention means (and SDs) not being reported for most outcomes (Quittner 2019). It is likely that an intervention will work in slightly different ways for children and adolescents (who may have high parent/caregiver involvement), compared with adults with CF. The overall completeness and applicability of evidence to children and adolescents with CF may therefore be limited.

We had also planned to investigate which BCTs are most effective for improving adherence, and whether the number of BCTs used in an intervention can affect adherence. From the current available evidence, this was not possible.

Many of the interventions were complex and multi-component, and included a range of BCTs, and there was also variety in the types of psychological intervention delivered (Included studies). It should be noted that some of the interventions were non-specific and focused on either adherence to CF treatments in general (Cottrell 1996; Gur 2016; Knudsen 2016; Quittner 2019; Riekert 2013), or multiple CF treatments (Downs 2006; Shakkottai 2017); only three were focused on improving adherence to inhaled therapies only (Hind 2017; Quinn 2004; Wildman 2022). This makes it challenging to draw conclusions on the efficacy of an intervention in relation to the primary or secondary outcomes of the review.

Interventions were delivered in a variety of modes, and included individual; face-to-face; telephone- or paper-based interventions; or the use of digital technology (e.g. website; mobile application or 'app'; device such as home spirometer). The oldest study in this review delivered the intervention in a group, face-to-face setting (Cottrell 1996), but face-to-face group interventions are no longer recommended for people with CF due to infection control guidelines (Conway 2008).

A previous Cochrane Review highlighted likely inclusion bias in adherence trials, with participants having higher than average adherence at baseline (Nieuwlaat 2014). Some of our included trials reported relatively large numbers of participants who had declined to take part (Cottrell 1996; Knudsen 2016; Wildman 2022); whilst others did not report this information at all. Some trials also highlighted a possible ceiling effect (Quinn 2004; Wildman 2022), as their recruited participants had baseline adherence rates already higher than 'real world' adherence (Daniels 2011; Hoo 2019; Hoo 2020; Hoo 2021). If people with higher adherence at baseline are recruited, this reduces the statistical power of trials to detect a difference post-intervention (as the intervention and control groups will be more similar). This could therefore influence the applicability of the evidence.

Lastly, it should be noted that the included trials were conducted prior to the availability of highly-effective CF transmembrane conductance regulator (CFTR) modulator treatments for many people with CF (e.g. ivacaftor-tezacaftor-elexacaftor). These treatments have changed the landscape of CF care, including the relationship that people with CF (and their families) may have with their condition and treatments, their patterns of adherence, as well as clinician views and prescribing practices (Granger 2022). An ongoing observational study in the UK, the National Efficacy-Effectiveness Modulator Optimisation (NEEMO) programme, is exploring adherence to inhaled therapies in people with CF before and after commencing modulator treatments, and in those not prescribed modulator treatments (NCT05519020). It will also look at the relationship between adherence to inhaled therapies and outcomes (e.g. lung function) among adults with CF who are prescribed modulator treatments. Another observational study, the Home-Reported Outcomes (HERO-2) study, is taking place in the USA to investigate the changes in lung function among individuals who have made treatment changes after initiating ivacaftor-tezacaftor-elexacaftor treatment (NCT04798014). Additionally, there are ongoing trials investigating the withdrawal of mucolytic treatments following the introduction of CFTR modulator therapy, including CF STORM in the UK (ISRCTN14081521) and SIMPLIFY in the USA (NCT04378153).

Quality of the evidence

This review draws on data from 10 trials (1642 participants) which include children and adolescents with CF (and their parents or caregivers) or adults with CF. We have concerns regarding risk of bias in several domains in the included trials (Risk of bias in included studies; Figure 2). The generation of allocation sequence was unclear in three trials (Cottrell 1996; Riekert 2013; Shakkottai 2017) and high in one trial (Gur 2016), while allocation concealment was at high risk of bias in two trials (Downs 2006; Gur 2016) and unclear in five trials (Cottrell 1996; Knudsen 2016; Quittner 2019; Riekert 2013; Shakkottai 2017). Blinding of outcome assessors was unclear in six trials (Cottrell 1996; Downs 2006; Knudsen 2016; Quinn 2004; Quittner 2019; Riekert 2013) and high risk in four trials (Gur 2016; Hind 2017; Shakkottai 2017; Wildman 2022). Only three trials had a low risk of bias from incomplete outcome data (Hind 2017; Quinn 2004; Wildman 2022), three trials had an unclear risk (Gur 2016; Riekert 2013; Shakkottai 2017), and four trials had a high risk of bias (Cottrell 1996; Downs 2006; Knudsen 2016; Quittner 2019). We judged only two trials to have a low risk of bias from selective reporting (Hind 2017; Wildman 2022); the remainder of studies had an unclear (Cottrell 1996; Downs 2006; Gur 2016; Quinn 2004; Riekert 2013; Shakkottai 2017) or high (Knudsen 2016; Quittner 2019) risk of bias on this domain. We judged three studies to have a high risk of bias from other potential sources (Cottrell 1996; Quittner 2019; Riekert 2013), and one had an unclear risk (Gur 2016).

Treatment arms (both intervention and control) were not always described in sufficient detail in terms of the frequency, scheduling, duration, and content of the sessions. Additionally, nine out of 10 included trials reported that participants in the control or comparison group received 'treatment as usual' or 'usual care', but they did not describe what this consisted of, and this is known to vary across countries, across CF centres within countries, and even across individuals within the same CF centre.

Most included trials had small sample sizes; seven trials had fewer than 100 participants and many stated they were underpowered (Cottrell 1996; Downs 2006; Gur 2016; Hind 2017; Knudsen 2016; Quinn 2004; Shakkottai 2017). Underpowered trials are more likely to miss a meaningful difference in adherence, even when improving adherence substantially, and showing an effect on clinical outcomes is likely even harder (Nieuwlaat 2014). Some trials were feasibility studies but no larger, follow-on RCT was conducted. Even the largest trial in this review was underpowered to find a difference in medication adherence, due to missing data and attrition (Quittner 2019).

Lastly, in some trials, the intervention that was delivered deviated from what was planned in the protocol, e.g. in one trial, most participants only completed 2.5 of the planned four sessions (Quittner 2019); in another trial, the average use of the daily medication reminder feature of the intervention was only 50.23% (Shakkottai 2017); and in two trials, the number of cancelled sessions meant it was not possible to follow the original schedule of intervals between intervention sessions and the programmes had to be extended (Gur 2016; Knudsen 2016). One trial also reported some challenges with recruitment, with some participants not wanting to commit to Skype video calls or WhatsApp messages (Gur 2016). In trials that reported intervention fidelity assessments, scores ranged from 67% (covering a 51% to 80% range across different CF centres) (Quittner 2019) to 93-97% (Wildman 2022). This variation could influence the effectiveness of the intervention, as well as the reliability and validity of conclusions drawn.

Using GRADE, we found that the overall certainty of the evidence for the comparison of psychological interventions versus usual care at the 'over six months and up to 12 months' time point ranged from low to moderate (Summary of findings 1). We deemed the outcomes, adherence to inhaled therapies, lung function, and pulmonary exacerbations to provide moderate-certainty evidence, downgraded only for indirectness as there was only one trial included at this time point which exclusively included adults (aged 16 years and over), whereas our review question was broader and focused on people with CF of all ages. We deemed the certainty of evidence for treatment-related adverse events (anxiety and depression) and QoL (treatment burden and respiratory symptoms) to be low, downgraded due to indirectness (as above) and an unclear risk of detection bias.

For our second comparison of a psychological intervention (MI) versus an active comparator arm (EPS), we found that the overall certainty of the evidence from a single trial was very low across outcomes at the 'over six months and up to 12 months' time point (Summary of findings 2). The outcomes adherence to inhaled therapies, QoL, lung function and pulmonary exacerbations were downgraded due to: imprecision stemming from low participant numbers; indirectness because the trial included only adults (aged 16 years and above); and an unclear risk of selection and attrition bias (and detection bias for QoL, due to outcome assessors not being blinded). The trial did not measure our primary outcome of treatment-related adverse events (anxiety and depression).

Potential biases in the review process

Any deviations from our published protocol (Dawson 2020) are noted with reasons in 'Differences between protocol and review'.

We are confident that our search strategies have identified all relevant trials. The selection of trials, data extraction, risk of bias assessment and BCT coding were independently conducted by at least two authors. Disagreements were resolved by discussion or by consultation with a third review author as necessary. Two review authors who are or were involved with a wider programme of work linked to two included trials, though not the trials themselves, were not involved in the selection, data extraction, risk of bias assessments or BCT coding for these trials (Hind 2017; Wildman 2022).

While we were successful in obtaining additional information from the authors of five trials (Downs 2006; Gur 2016; Hind 2017; Quinn 2004; Wildman 2022), some trials were excluded due to a lack of available information and no response from investigators to our queries. We were unable to obtain additional information or data for some outcomes, e.g. MPR data for individual drugs, or results for participants on inhaled therapies only in trials that reported a composite adherence measure.

A strength of the review is the use of the BCT taxonomy to code the 'active ingredients' or components of the interventions. The taxonomy aims to standardise terminology across research and so was useful in categorising the components of the interventions. Previous Cochrane Reviews on adherence (Nieuwlaat 2014) and CF-specific reviews (Goldbeck 2014; Savage 2014) have not used a coding framework, so this review has improved on existing methodologies. Understanding the 'active ingredients' of promising interventions will make it easier to replicate effective interventions; will reduce the potential waste of time and resources on trials of ineffective techniques (Michie 2009); and will inform adherence research in the future (Nieuwlaat 2014).

However, the coding of BCTs is limited to information reported in the included trials. We contacted all trial authors to request further information (e.g. protocols); only two provided intervention manuals (Hind 2017; Wildman 2022), and the lead author of one trial provided the intervention worksheets which could be coded (Downs 2006). Consequently, we could not code some potential BCTs in the included trials due to there being insufficient details reported. This might mean that some BCTs were used in the interventions but have not been described in this review. This highlights the need for more clarity and transparency in the reporting of interventions (Michie 2009).

Agreements and disagreements with other studies or reviews

To our knowledge, this is the only systematic review to investigate the effectiveness of psychological interventions for improving adherence to inhaled therapies in people with CF. This is also the first review to examine the BCTs used in interventions with people with CF.

Three of our included trials were also included in two other Cochrane Reviews. Two trials (Cottrell 1996; Downs 2006) were

included in a review of self-management education for CF (Savage 2014). In contrast to the Savage 2014 review, we judged these two studies to have a high risk of bias from incomplete outcome data (attrition bias), whereas Savage 2014 judged them to have an unclear risk of bias for this domain. We also assessed treatment-related adverse events (anxiety and depression) in our review, which Savage 2014 did not. The Quinn 2004 trial was included in a review of psychological interventions for individuals with CF and their families (Goldbeck 2014). The Goldbeck 2014 review judged the Quinn trial to have an unclear risk of bias from allocation concealment (selection bias), and a low risk of bias from blinding (performance bias and detection bias). In contrast, we judged this trial to have a low risk of bias in relation to allocation concealment, and an unclear risk of bias from blinding of outcome assessors (Quinn 2004). These discrepancies might be explained by us being able to obtain additional information from unpublished data (thesis), in addition to the conference abstract for this trial (Quinn 2004).

This review is in agreement with other, CF-related reviews and general adherence reviews, which have highlighted the limitations of many included trials in terms of having small sample sizes and being underpowered to detect a meaningful difference in adherence (Goldbeck 2014; Nieuwlaat 2014).

Our review was more specific and focused on adherence to inhaled therapies in CF in particular, more so than the Cochrane Review of psychological interventions for individuals with CF and their families (Goldbeck 2014). The Goldbeck 2014 review was more general and, although adherence to treatment was assessed as a secondary outcome, interventions were focused on a range of outcomes, e.g. well-being and functioning, lung function, weight and height or body mass index (BMI), adherence to treatment etc. (Goldbeck 2014). The authors in that review categorised the different types of interventions into 1. Cognitive behavioural; 2. Cognitive; 3. Family systems or systemic; 4. Psychodynamic; or 5. Other interventions. We did not predefine the eligible types of psychological interventions in our protocol (Dawson 2020), as psychological interventions are often wide-ranging and varied, and we did not want to limit the scope of the review. We did, however, look beyond psychological interventions in the traditional sense (such as cognitive behavioural therapy) and included psychological interventions delivered via therapy, as well as those focused more specifically on behaviour change.

AUTHORS' CONCLUSIONS

Implications for practice

Due to the limited quantity of trials included in this review, as well as their clinical and methodological heterogeneity, there is insufficient evidence to clearly recommend or refute the use of psychological interventions for improving adherence to inhaled therapies for people with cystic fibrosis (CF) in clinical practice. There is some moderate-certainty evidence to suggest that psychological interventions probably improve adherence to inhaled therapies in adults with CF compared with usual care, and may have little or no effect on treatment-related adverse events such as anxiety and depression (low-certainty evidence). Psychological interventions may also improve treatment burden (low-certainty evidence). In addition, based on the very low-certainty evidence from one relatively small trial, we are uncertain whether a psychological intervention (motivational interviewing (MI)) improves adherence to inhaled therapies, lung function or quality of life (QoL), or reduces pulmonary exacerbations in people with CF when compared with an active comparator intervention (education plus problem-solving (EPS)).

It is promising that one included trial showed that a psychological intervention focused on supporting adults with CF to build habits for treatment-taking can increase adherence to inhaled therapies whilst reducing perceived treatment burden (Wildman 2022). This is an area of importance amongst the CF community, since “simplifying the treatment burden” and "improving and sustaining adherence to treatment" have been identified as two of the top 10 CF research priorities in the James Lind Alliance Priority Setting Partnership (Davies 2020; Rowbotham 2018). While it is often assumed that simplifying treatment regimens reduces perceived burden and thereby increases adherence (Schultz 2022), the results of the included trial suggest that there are other ways of reducing perceived treatment burden other than withdrawing treatments or replacing treatments with those perceived to be less burdensome (Rowbotham 2022). This may be consistent with previous research highlighting the role of habit on adherence to inhaled therapies in people with CF (Arden 2019; Ball 2013; Hoo 2017; Hoo 2019a), and the suggestion that habit (i.e. "automatically experiencing an urge to use a nebuliser" (Hoo 2019a)) may attenuate the relationship between treatment complexity and perceived treatment burden (Hoo 2017). However, adherence seems to be particularly challenging during adolescence and the transition to adult care (Sawicki 2018). This is the age group with the greatest risk of lung function decline (VandenBranden 2012). It is therefore likely that an intervention will work in slightly different ways for children and adolescents (who may have high parent/caregiver involvement), compared with adults with CF.

Despite previous research highlighting the discrepancy between objective and subjective methods of measuring adherence to inhaled therapies in people with CF (Daniels 2011; Thorton 2013; Warnock 2020), objective measures are rarely used in practice (Robinson 2020). An ongoing observational study ('CFHealthHub Data Observatory') (ISRCTN14464661), being conducted in parallel with one of the included trials in this review (Wildman 2022), aims to address this by integrating objective adherence measurement (available from data-logging nebulisers) into routine CF care, using learning from the randomised controlled trial (RCT) and quality improvement cycles. Over 50% of UK adult CF centres are now involved in the digital learning health system, which also serves as a Trials within Cohorts (TWICs) platform, collecting data from a large number of people with CF as part of routine care with the aim of overcoming some of the challenges associated with conducting trials in rare conditions like CF (e.g. high costs and small sample sizes) (Wildman 2022).

A previous Cochrane Review highlighted that CF teams need training in mental health in order to integrate manualised psychological interventions, including those aimed at supporting adherence, into CF care (Goldbeck 2014). We would argue that non-adherence should be viewed as "the norm" rather than the exception (NICE 2009), and as a "problem of humans" (Wildman 2014), akin to other health behaviours (e.g. physical inactivity, low fruit and vegetable intake) (WHO 2021). Adherence is a skillset that can be developed, and whilst mental health training and expertise within CF teams is undoubtedly important, healthcare professionals also need training and expertise in facilitating

'normal' human behaviour change, which includes supporting adherence. As highlighted in one of the included studies in this review, the competing clinical demands of healthcare professionals can influence the extent to which an intervention can be implemented in practice (e.g. limiting the amount of training and supervision that can be provided) (Quittner 2019). The implementation of psychological interventions for improving adherence to inhaled therapies in practice may therefore require specially trained interventionists (Goldbeck 2014), and thus, it may be necessary to develop roles for health psychologists, with expertise in behaviour change, or to increase the behavioural expertise of other healthcare professionals (e.g. physiotherapists, nurses).

Finally, despite healthcare professionals being trained to deliver interventions in the included trials, the fidelity of interventions varied (and even across CF centres involved in multicentre trials), and this is likely to be even more of a problem outside the carefully managed and controlled environment of an RCT. It is therefore important to consider how intervention fidelity can be assessed and improved, where necessary, in practice (e.g. through direct observation, audits, coaching and supervision, refresher training (Breitenstein 2010)), to ensure that the 'active ingredients' of interventions are delivered.

Implications for research

Protocol deviations such as those seen in the included trials in this review may influence results, and the reasons for them should be taken into account when planning future trials (e.g. they can inform about trial feasibility and acceptability).

In future trials, investigators should use the most objective measures of adherence available to accurately determine intervention effects. With the development of data-logging nebulisers (e.g. Philips I-neb AAD system and PARI eTrack®), which record time- and date-stamped usage data, measuring adherence to inhaled therapies using this method should be the 'gold-standard', particularly in countries where such devices are available (e.g. the UK). In the absence of objective 'recorded' methods (e.g. data-logging nebulisers), measuring adherence using pharmacy refill data or medication possession ratio (MPR) (i.e. objective 'count' methods) should be the next best alternative. However, MPR is less granular than electronic data capture and, as an indirect measure, tends to overestimate adherence, with recent research highlighting the gap between the supply of inhaled therapies and actual usage in adults with CF (Bevan 2022a; Bevan 2022b). Indeed, increases in adherence may not be detected using MPR, as people with CF could be using up their existing supplies of medicines rather than collecting or requesting new supplies. Subjective measures of adherence (e.g. participant diaries and self-report questionnaires such as the MMAS-8 (Morisky 2008)) appear to be less widely used in more recent trials. This is promising as it shows that the methodology is advancing alongside evidence that highlights the discrepancy between objective and subjective measures of adherence (Daniels 2011; Thorton 2013; Warnock 2020).

When adherence is measured, there is often a lack of consistency in the assessment time periods. It is important for investigators to allow time for a 'run-in' period to overcome issues of increased adherence due to a novelty effect (Shin 2018), or 'white coat adherence', which are often short-lived (Apter 1998; Modi 2012; Podsadecki 2008). Adherence is complex and varies across times and situations, and so measuring adherence over a longer period of time where possible is important in order to gain a more accurate assessment of adherence, although there is no consensus on how long adherence should be monitored for.

The reporting of interventions could be improved, for example, when reporting a composite MPR (cMPR), the MPRs for individual treatments should be reported alongside cMPR data where possible to allow the differentiation between MPRs for individual treatments. Investigators should also clearly report the time intervals for the data collection and, where multiple versions of a measure are available, e.g. the CFQ-R (Quittner 2009), investigators should specify which version has been used (e.g. Teen/Adult or Older child 12 to 13 years or Young child 6 to 11 years or Parent/caregiver 6 to 13 years) and whether different versions have been used with different participants in the trial, to facilitate data analysis where appropriate.

Furthermore, details of intervention mode of delivery, duration and intensity (e.g. number and duration of sessions) should be provided in order to better understand how interventions could be implemented in clinical practice (Hoffmann 2014). It would also be helpful if investigators provided more details on the content of interventions, including the care provided to the control group (whether that is an active comparator or usual care (Michie 2009)), and described the BCTs used. This would help to create a shared language and more easily enable the comparison of interventions (e.g. using meta-regression to investigate the impact of type and number of BCTs on intervention effectiveness).

In this review, outcomes were assessed using a variety of measures, which makes it difficult to compare and combine the results. Depression, for example, was measured using four different scales: eight-item Patient Health Questionnaire depression scale (PHQ-8) (Kroenke 2009); Major Depression Inventory (MDI) (Bech 2001); Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977); and Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983); anxiety using three: HADS (Zigmond 1983), State-Trait Anxiety Inventory (STAI)-short form (Marteau 1992), and Generalised Anxiety Disorder (GAD)-7 (Spitzer 2006); and two trials even used multiple measures to assess one outcome. This highlights the need for a 'core' outcome set in CF (Dwan 2013), an agreed, standardised set of outcomes that should be measured to improve the comparability of trials (Williamson 2017).

In addition, participants should be recruited to adherence trials because their adherence is low, not just because they are willing to participate. It is not only important to consider attrition and withdrawals, but who is volunteering to take part in adherence trials in the first place (and who is declining). Given the issues with adherence during adolescence and the transition to adult care which are highlighted above (Implications for practice), more research is needed to assess the possible differences in the BCTs used in different populations (e.g. whether some BCTs are more effective when used in paediatrics compared to adult care). More research is also needed to understand how to support adherence in 'under-served' or 'harder to reach' CF populations.

Lastly, when designing RCTs, it is important that intervention designers, researchers and clinicians consider how interventions will be embedded into practice. Of the trials included in this review, many interventions were delivered by healthcare professionals rather than researchers (e.g. registered nurses,

physiotherapists, psychologists etc.), which is promising and suggests that healthcare professionals can be trained to deliver such interventions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cottrell 1996

Study characteristics	
Methods	Parallel, 2-arm RCT conducted at a single CF centre in the USA.
Participants	**Eligibility criteria** People with CF Aged between the ages of 8 and 18 years Being treated at the CF Clinic, a regional CF centre for both treatment and research, at Children's Hospital in Columbus, Ohio, USA. **Number invited to participate (met eligibility criteria)**: (all families with CF child aged 8 - 18 years old from regional CF centre): n = 112 families with a total of 120 children or adolescents with CF. **Number of invited participants who declined**: n = 68 families (n = 39 declined as too busy or too far away from study site; n = 29 were already involved or on waiting-list for ongoing medication study). **Number of participants enrolled**: n = 34 (of these, 4 withdrew and 10 did not return diaries despite telephone reminders - unsure if these withdrawals occurred pre- or post-randomisation). **Number of participants analysed (n = 20, in 18 families)**: intervention arm n = 10, control arm n = 10. **Number of participants who received intended treatment**: not reported. **Demographic details** **Age, mean**: 13.5 years. **Sex**: intervention group 4 females, 6 males; control group 6 females, 4 males. **Ethnicity**: not reported. **Socioeconomic status** 95% of parents were high school graduates; 2% were college graduates. 4 mothers (2 in each group) were full-time homemakers. 6 families had annual incomes above USD 50,000, and two had incomes below USD 15,000.

Cottrell 1996 *(Continued)*

	intervention group had 4 single-parent families and the control group had 1. 1 family in each group had 2 children with CF; both children participated in the study. 2 families in the intervention group had experienced a child dying of CF. **Disease status**: to assess severity in the 2 groups, the 3 CF centre physicians independently rated each participant's degree of disease involvement on a 1 to 10 point scale with 1 being very severe and 10 being no involvement. The mean (SD) severity ratings for pulmonary system involvement was 7.03 (1.614) in the intervention group and 7.08 (2.162) in the control group. These differences were not statistically significant.
Interventions	**Intervention arm**: 2 x 6-hour self-management training sessions delivered face-to-face by psychologists or registered nurses. No details were provided on the scheduling of these sessions so the intervention duration and gap between sessions is unclear. Each session consisted of teaching participants about the nature of CF, principles of self-management, identification of early warning signs of illness exacerbations, appropriate self-management steps, types of medications and their appropriate use etc). Report states that "parents and patients met together during discussion of the nature of CF and self-management principles". During the remainder of the training sessions, parents, adolescents, and children met in separate groups. **Control arm**: presume usual care (no details reported).
Outcomes	**Outcomes included (not reported as primary and secondary outcomes)** 1. Knowledge of CF (measured by the percentage of questions answered correctly on the CF knowledge survey). 2. Compliance with medical regimen (assessed by comparing the medication and treatment schedule recorded on a physician record with the medication and treatment schedule reported by the participants on the CF diary. % compliance was computed separately by medications aerosols, and chest physiotherapy. Medication compliance was computed by dividing the total number of medication doses recorded by the participants by the total number prescribed by physicians. Aerosol and CPT compliance was computed in the same manner). 3. Self-management behaviours. Two aspects of self-management behaviours were considered. The first was the total number of self-management behaviours each participant used on a regular basis. This was measured by counting the number of self-management items the participant reported engaging in at least "sometimes" as recorded on the self-management behaviours form. The second was the frequency of self-management behaviours with which participants performed each of the self-management behaviours. This was measured by assigning each response item a score as follows: 0 = never, 1 = rarely, 2 = sometimes, 3 = usually, and 4 = always. Overall frequency was assessed by averaging the responses on items on the self-management behaviours form. 4. Weight (in pounds, was measured weekly by each participant and recorded on the CF diary). 5. Quality of Well-Being score (Kaplan 1989) (scale assesses functioning on three subscales (mobility, physical activity, social activity), and 22 problems or symptoms that could impair functioning); total score ranges from zero (i.e. death) to one (i.e. optimal functioning, equal to perfect health). 6. Pulmonary function. Peak flow meters were used to measure PEFR or the degree of airway obstruction recorded by each participant. **Assessment time points** Baseline 6 to 8 weeks post assessment
Funding source	Not reported.
Declaration of interest among the primary researchers	Not reported.
Notes	Contacted lead study author who was unable to provide further information on the study (e.g. protocol, intervention manual, participant invitation letter, participant information sheet etc).

Cottrell 1996 *(Continued)*

	Unable to access dissertation and lead study author confirmed this is no longer available. Intervention fidelity: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Report states: “At the end of the 2-week baseline period, subjects were randomly assigned to one of two groups.” No further information reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Report states: "Of the 34 subjects enrolled in the study, 2 withdrew due to illness of a family member, 2 withdrew because of family vacations, and 10 did not return diaries despite repeated telephone reminders”. It is unclear if the four withdrawals occurred pre- or post-randomisation. It is unclear which trial arms the 10 families who did not return diaries were allocated to. The trial authors provide no further information on why 10 families dropped out. Not analysed as intention-to-treat.
Selective reporting (reporting bias)	Unclear risk	Contacted study author but unable to access trial protocol to assess reporting bias.
Other bias	High risk	The mean (SD) baseline weight measurement for participants in the intervention group was 89.15 (29.29) lb and for children in the control group was 101.4 (32.17) lb. This difference indicates a clinically important baseline imbalance in the case of CF.

Downs 2006

Study characteristics

Methods	Parallel, 2-arm RCT conducted at 3 public hospital CF clinics in Australia.
Participants	**Eligibility criteria** Children with CF aged 6 to 11 years and their primary caregivers (if the child currently performed ACT as part of home management programme). Fluent in English No learning difficulties Not currently exposed to other CF self-management programmes **Number of participants recruitment discussed with**: n = 86 eligible families. **Number of participants randomised (n = 65 families (caregiver/child dyads))**: intervention arm n = 33, control arm n = 29.

Downs 2006 *(Continued)*

Number of participants who received intended treatment: intervention arm n = 18, control arm n = 25.

Number of participants analysed (per-protocol; n = 43): intervention arm n = 18, control arm n = 25.

Number of participants analysed (intention-to-treat; n = 51): intervention arm n = 26, control arm n = 25.

Demographic details

Age, mean (SD): intervention group 8.4 (1.8) years, control group 8.4 (1.5) years.

Sex: intervention group (8 males, 10 females) control group (16 males, 9 females).

Ethnicity: not reported.

Socioeconomic status: not reported.

Disease status: not reported.

Aerosols, mean (SD) doses/day (P = 0.844): intervention group (n = 16) 3.8 (2.1) doses, control group (n = 24) 3.9 (2.4) doses.

Aerosols, mean (SD) minutes/day (P = 0.837): intervention group (n = 16) 29.9 (15.6) minutes, control group (n = 24) 28.6 (22.8) minutes

Interventions

Intervention arm: self-management education programme focused on improving adherence to aerosol treatments and ACT in children with CF. Pen and paper programme was completed by the caregiver and child over a 10-week period, with each of the 10 chapters taking approximately 20 minutes to complete. Caregivers participating in the programme were telephoned at the end of weeks 3, 6 and 9 to support participation and answer questions.

Control arm: usual care (confirmed in email by first author).

Outcomes

Outcomes included (not reported as primary and secondary outcomes)

1. Adherence to aerosol and ACT regimens (measured using 1-week diary card developed for the study where parents/caregivers-child dyads recorded the days and times the children started taking a nebuliser treatment).
2. Caregiver self-management behaviours (measured using 1-week diary card developed for the study).
3. Responsiveness of ACT performance when the child was unwell (if the caregiver recorded performing longer ACT or additional treatments on the diary cards on an unwell day, then self-management behaviours on that day were considered to be responsive to the child's treatment needs. For each child, a mean responsiveness score for all pre-intervention unwell days and all post-intervention unwell days was calculated).
4. Child knowledge of ACT (measured using Child Knowledge of ACT Questionnaire developed for the study).
5. Child feelings about regular performance of aerosol and ACT (treatment regimens (measured using single item question, 'How do you feel about doing chest treatments in your day?', with the response indicated by the child on the Faces Pain Scale).
6. Caregiver self-efficacy to manage aerosol and ACT treatment regimens (measured using the Self-efficacy Scale).

Assessment time points

Pre-intervention.

Post-intervention (took place 3 to 4 months after pre-intervention assessment for control group and immediately after completion of 'Airways' for intervention group).

6-month follow-up (took place 6 months after post-intervention assessment - involved completion of adherence and self-management diary cards, and caregiver Self-efficacy Scale).

Downs 2006 *(Continued)*

	12-month follow-up (took place 6 months after 6-month follow-up assessment - all measures completed pre- and post-intervention completed again).
Funding source	The authors report that the study was supported by the Physiotherapy Research Foundation, Australia, and the Australian Cystic Fibrosis Research Trust.
Declaration of interest among the primary researchers	Not reported.
Notes	**Intervention fidelity**: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Report states: “Following recruitment at each participating centre, participants were stratified according to the child's age (six to eight and nine to 11 years) and allocated to the control or intervention group using randomized permuted blocks”
Allocation concealment (selection bias)	High risk	No details are provided in the published report. Information provided by the lead author on request states that allocation was not concealed.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	No details are provided in the published report on blinding of outcome assessors. Information provided by the lead author on request states that "most outcomes were child or parent report - they cannot be blinded. The clinical measures were blinded". It is unclear if outcome assessors were blinded from knowing which group participants were randomised to.
Incomplete outcome data (attrition bias) All outcomes	High risk	Report states: "There was significant attrition from this study and the potential for bias. Withdrawals from the study prior to the intervention phase occurred in both groups and related to lack of completion of assessments. However, later attrition occurred only in the intervention group and was mainly due to time pressures. In some cases, attrition related to the nature of the intervention (i.e., the need for consistent effort from child and caregiver) and sometimes to characteristics of the participants.” The report also states that "the gender, age and FEV_1 of children completing the study were not significantly different to those who withdrew from the study". Intention-to-treat analysis was conducted which included data from participants in the intervention group who commenced the intervention and later withdrew (n = 8). 7 intervention and 4 control arm participants did not complete pre-test assessments or withdrew from study prior to commencing intervention (so not included in intention-to-treat analysis).
Selective reporting (reporting bias)	Unclear risk	Contacted study author but unable to access trial protocol to assess reporting bias.
Other bias	Low risk	No other potential source of bias identified.

Gur 2016

Study characteristics

Gur 2016 *(Continued)*

Methods	Parallel, 2-arm, pilot study conducted at a single CF centre (Paediatric Pulmonology Institute, Ruth Rappaport Children's Hospital) in Northern Israel.
Participants	**Number of participants analysed (n = 18)** Intervention arm: n = 9 Control arm: n = 9 NB. 3 participants who were originally assigned to the study group by consecutive order were later assigned to the control group (2 participants were not interested in performing Skype video chats due to busy schedules, and 1 participant did not have an Internet connection). **Inclusion criteria** (from protocol provided by the study authors) Aged over 8 years Documented diagnosis of CF by a physician for at least the prior year No major comorbid diagnoses (e.g. cerebral palsy, cancer), able to complete the pre- and post-treatment assessments. **Demographic details** (recorded from participant medical records) **Age, mean (SD), median (range)**: intervention group 21.2 (6.2) years, 21.2 (12.7 to 32.5) years; control group 24.8 (11) years, 13 (14.2 to 50.7) years. **Sex**: intervention group 5 females (56%); control group 5 females (56%). **Ethnicity**: unclear. **Socioeconomic status**: not reported.
Interventions	**Intervention arm**: telehealth intervention comprising Skype-based online video chats conducted with a member of the multidisciplinary CF team (e.g. doctor, nurse, dietician, physiotherapist, psychologist or social worker) and twice-weekly WhatsApp messages. Each Skype video chat session was performed by a different member of the CF team. Team members were instructed to use supportive, non-judgemental language. Adherence was evaluated during the chats, with an effort to address barriers and solve them. After each chat, the staff member was asked to submit to the principal investigator a free-text description of his/her experience, which was kept with the questionnaires filled in by the subjects. Different issues were raised by people with CF (e.g. inhalation therapies (n = 9); cleaning of devices (n = 7) and members of the CF team (medication adherence; assess adherence; barriers to adherence)). The focus of the chats varied and included a range of topics and treatments, not just inhaled therapies or adherence. WhatsApp messages regarded the importance of adherence to the treatment regimen, nutritional support, physical activity and diabetes control (e.g. 'Do your physiotherapy, get it off your chest'; 'Keep your belly calm, take creon'; 'Gaining weight = gaining health'). Participants had a median of five (range 4 to 6) Skype video chats, and received 22 to 45 WhatsApp messages during the intervention period. The authors report that the intervention period was longer than originally planned due to difficulties in scheduling the Skype video chats (each chat required 2 to 3 attempts). The authors report some challenges with recruitment (some participants did not want to commit to the Skype video chats). 1 participant asked to stop the WhatsApp messages but continued with the Skype chats. Another participant was interested in performing more Skype chats than planned, and began communicating with the team members with WhatsApp messages. **Control arm:** presume usual care (no details reported).
Outcomes	**Outcomes included (not reported as primary and secondary outcomes)**

Gur 2016 *(Continued)*

	1. Age-appropriate versions of the CFQ-R (Quittner 2009) (measure assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL) 2. Knowledge questionnaire (33 questions in 4 domains: lung disease, nutrition, general health and treatment in CF; each question was scored 1 for a wrong answer and 2 for a right answer) 3. Adherence: self-report questionnaire describing the type and frequency of 12 types of common CF therapies scored on a 5-point Likert scale (where 1 = never and 5 = a few times a day, with a higher score indicating higher adherence) 4. Satisfaction with relations with CF team (graded on a scale of 1 to 10) **Assessment time points** Participants in the intervention group completed the questionnaires before and after the intervention Control participants completed the questionnaires in 2 routine visits, 3 to 5 months apart.
Funding source	Report states that the study was supported by an investigator-initiated grant from Novartis.
Declaration of interest among the primary researchers	None declared.
Notes	Contacted the study authors who provided further information (e.g. baseline data results, study protocol) on the method and results of the study. **Intervention fidelity:** not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were consecutively assigned to the intervention or control group by one of the physicians during a routine clinic visit. No other details on the randomisation process provided. Contacted the study author who reported that the participants were assigned by order of recruitment.
Allocation concealment (selection bias)	High risk	Allocation concealment not blinded. Participants were consecutively assigned to the intervention or control group by 1 of the physicians during a routine clinic visit.
Blinding (performance bias and detection bias) Outcome Assessors	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Contacted the study authors who provided a copy of the unpublished study protocol. The authors confirmed that they did not have any dropouts, although 3 participants who were originally assigned to the intervention group said they would prefer to be in the control group (2 were not interested in performing Skype video chats due to busy schedules, and 1 did not have an Internet connection), so were transferred to the control group.
Selective reporting (reporting bias)	Unclear risk	Adherence results not reported in the published report, but were provided by the study authors after contact.
Other bias	Unclear risk	Unpublished protocol states they had planned to recruit 66 participants, whereas only 18 participants were recruited according to the published report.

Hind 2017

Study characteristics	
Methods	Parallel, 2-arm, feasibility RCT conducted at 2 adult CF centres (Nottingham and Southampton) in England (CFHealthHub pilot study).
Participants	**Eligibility criteria** Diagnosed with CF and with data within the CF registry. Aged 16 years and above. Taking inhaled mucolytics or antibiotics via a chipped nebuliser (e.g. PARI eFlow® rapid nebuliser system and eTrack® controller or BiNeb) or able and willing to take via eTrack or Bi-Neb. **Exclusion criteria** Post-lung transplant. On the active lung transplant list. Receiving palliative care. Lacking in capacity to give informed consent. Using dry powder devices to take antibiotics or mucolytics. **Population of interest (reviewed for eligibility)**: n = 430. **Number who met eligibility criteria**: n = 135. **Number successfully contacted**: n = 95. **Number of participants randomised (n = 64)**: intervention arm n = 33; control arm n = 31. **Number of participants who completed study (at 5 (+/-1) month follow-up) (n = 59)**: intervention arm n = 31, control arm n = 28. **Number of participants analysed at study completion (n = 64)**: intervention arm n = 33, control arm n = 31. **Demographic details (intervention group n = 33, control group n = 31)** **Age, mean (SD), median (IQR), range**: intervention group 31.6 (13.3) years, 28 (21 to 37) years, 16 to 69 years; control group 27.8 (8.9) years, 26 (20 to 34) years, 16 to 50 years. **Sex**: intervention group 18 males (54.5%) and 15 females (45.5%), control group (n = 31) 18 males (58.1%) and 13 females (41.9%). **Ethnicity**: not reported. **Socioeconomic status** Intervention group (n = 33): Most deprived n = 6 (18.2%); High deprivation n = 4 (12.1%); Average n = 8 (24.2%); Low deprivation n = 6 (18.2%); Least deprived n = 9 (27.3%). Control group (n = 31): Most deprived n = 1 (3.2%); High deprivation n = 7 (22.6%); Average n = 8 (25.8%); Low deprivation n = 9 (29%); Least deprived n = 6 (19.4%). **Disease status**: not reported.
Interventions	**Intervention arm**: complex intervention comprising 3 main components: 1. a microchipped device (nebuliser) for delivering inhaled medications;

Hind 2017 *(Continued)*

2. information technology infrastructure to capture and store adherence data from the nebulisers and display it to participants and the CF team, and;
3. the behaviour change intervention, comprising a software platform ('CFHealthHub' mobile app and website) offering adherence feedback and tailored modules of content and tools used by the health professional (interventionist) in interactions with participants and accessed independently by participants via CFHealthHub.

Mean (SD) number of intervention sessions/participant (n = 33): 3 (1.6) sessions.

Mean (SD) duration of sessions: 36.1 (23.9) minutes.

Mean number of review sessions/participant (n = 33): 1 (0.5) sessions.

Median number of clinic visits: 2 visits.

Dose/frequency of intervention: initial visit and at least 1 additional review visit from a trained interventionist who delivered face-to-face behaviour change content.

Control arm: usual care (heterogeneous within and between centres, based on the needs of individuals and the skills and interests of CF centre staff). Participants in the control arm used a microchipped nebuliser but were not able to access adherence data or other content and tools through CFHealthHub, neither did they receive the structured CFHealthHub intervention as described in the intervention manual. Control arm participants using Bi-neb nebulisers might have had access to their data as part of routine care, but this was not in the user-friendly format provided by the intervention. This trial assessed possible leakage from intervention to controls via a process evaluation.

Outcomes

Primary outcome

1. Number of pulmonary exacerbations in 5 (+/-1) month post-baseline follow-up period, defined according to the Fuchs criteria. An exacerbation of respiratory symptoms was said to have occurred when a participant was treated with parenteral antibiotics for any 1 of the following 12 signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38 °C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest, derived from notes by site staff; decrease in pulmonary function by 10% or more from a previously recorded value, derived from notes by site staff; radiographic changes indicative of pulmonary infection, derived from notes by site staff. The trial interventionist or prescribing clinician/nurse collected data on the "exacerbations" form at the point of a participant starting a course of IV antibiotics.

Secondary outcomes

1. BMI
2. FEV_1
3. EuroQol EQ-5D-5L: generic health status measure for health economic analysis
4. Patient Activation Measure (PAM-13) (Health Style Assessment): assessment of patient knowledge, skill, and confidence for self-management
5. Assessment of routine: measure of life chaos
6. Self-Report Behavioural Automaticity Index: automaticity-specific subscale of the Self Report Habit index to capture habit-based behaviour patterns
7. CFQ-R: disease specific HRQoL instrument (Quittner 2009) (measure assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL)
8. PHQ-8: severity measure for depressive disorders
9. Medication adherence data - 3 items
10. GAD-7: severity measure for anxiety (scores range from 0 to 21, and cut-off scores of 5, 10, and 15 indicate mild, moderate, and severe levels of anxiety, respectively)

Hind 2017 *(Continued)*

11. Capability Opportunity Motivation Behaviour Beliefs Questionnaire: incorporating The Beliefs about Medicines Questionnaire (specific nebuliser adherence) and project-specific items (1 additional belief item, 1 intention item, 1 confidence item, and a list of barriers).
12. Subjective adherence/self-report estimate of adherence as a percentage. Self-reported problems include the identification of capability and opportunity barriers to nebuliser adherence.
13. Concomitant medications.
14. Resource-use form: data collected from a combination of hospital notes and the NHS patient electronic system to determine inpatient IV days, routine clinic visits, unscheduled outpatient contacts and unscheduled inpatient stays.
15. Exploratory analysis of habit formation using the objective nebuliser data.
16. Monthly prescription check to both check for data transfer to CFHealthHub and review for an indication that the prescription has changed or indication of microorganism e.g. Pseudomonas.
17. Adherence to prescribed medication defined in several ways, including unadjusted adherence, simple normative adherence (without numerator adjustment), sophisticated normative adherence (without numerator adjustment), simple normative adherence (with numerator adjustment) and sophisticated normative adherence (with numerator adjustment).
18. Any treatment with IV antibiotics.

Assessment time points

Baseline

5 months +/-1 post-randomisation

Funding source	Research funded by the NIHR under its Grants for Applied Research Programme (Grant Reference Number RP-PG1212-20015).
Declaration of interest among the primary researchers	Last author received funding from Zambon and support from Philips Respironics for the early intervention development work. In addition, last author has worked with PARI to carry out studies using the e-Track (authors report this had not had any direct influence on the feasibility study reported here). The University of Manchester software team received funding from PARI to create a medication reporting component within the CFHealthHub software (authors report this had not had any direct influence on the feasibility study reported here). The other authors declared no competing interests.
Notes	**Clinical trial register**: isrctn.com/ISRCTN13076797 **Intervention fidelity**: report states that structured interventionist fidelity assessments were conducted on all three interventionists. Audio-recordings of intervention sessions were coded using a fidelity scoring system which assessed whether each component of the intervention was delivered according to the manual and the quality of that delivery. Based on fidelity assessment of intervention session recordings, the 'content' fidelity of face-to-face interactions was excellent (100%) - with all aspects delivered as per the manual. 'Delivery quality' fidelity was more variable (60% to 92%). "The generation of goals and action plans was sometimes too directive rather than negotiated and supportive. Fidelity assessment of recordings identified that, in interactions with the adequately motivated, the focus was not always on the most active ingredients - goal-setting, action planning (habit formation) and problem solving/ coping planning."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Report states: "Randomisation in a 1:1 ratio through computer-generated pseudo-random list and random permuted blocks of varying sizes (2, 4 and 6), stratified by site and number of IV antibiotic days in previous 12 months".
Allocation concealment (selection bias)	Low risk	Report states: "Study researchers accessed the allocation for each participant by logging into the remote, secure internet-based randomisation system. Once participant consent was gained, the researcher entered participant demo-

Hind 2017 *(Continued)*

		graphic information into the system upon which the allocation was then revealed to the researcher".
Blinding (performance bias and detection bias) Outcome Assessors	High risk	Outcome assessor (i.e. researcher/interventionist) was non-blinded after allocation revealed following consent visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed as intention-to-treat with all participants entering the trial.
Selective reporting (reporting bias)	Low risk	All outcomes listed in protocol reported in trial paper.
Other bias	Low risk	Trial statisticians remained blind to treatment allocation until database freeze (the point where all data had been input and all known queries resolved).

Knudsen 2016

Study characteristics	
Methods	Parallel, 2-arm, feasibility RCT conducted at a single outpatient CF clinic in Denmark for young adults with CF (Coach to Cope).
Participants	**Eligibility criteria** Diagnosed with CF, confirmed by clinical findings, identification of two disease-causing CFTR mutations, and a positive sweat chloride test. Attending the Copenhagen CF Centre. **Exclusion criteria** Severe intellectual impairment or insufficient mastery of the Danish language, determined by incapacity to independently complete the questionnaires. **Population of interest:** n = 92. **Number invited to participate (met eligibility criteria):** n = 85. **Number of invited participants who declined**: n = 15 (n = 30 never responded). **Number of participants randomised (n = 40)**: intervention arm n = 20, control arm n = 20. **Number of participants who received intended treatment** 1 session (n = 18) 2 sessions (n = 17) 3 sessions (n = 16) 4 sessions (n = 13) 5 sessions (n = 12) 6 sessions (n = 9) 7 sessions (n = 9) 8 sessions (n = 9)

Knudsen 2016 *(Continued)*

	9 sessions (n = 9) 10 sessions (n = 9) **Number of participants analysed at midway (5 months) time point (n = 31)**: intervention arm (n = 12), control arm (n = 19). **Number of participants analysed at post-intervention (11 months) time point (n = 28)**: intervention arm (n = 9), control arm (n = 19). **Number of participants analysed at 1-year post-intervention time point (n = 24)**: intervention arm (n = 12), control arm (n = 12). **Demographic details** **Age, mean (range)**: 23.7 years (18 to 30). **Sex**: 27/38 (71%) female. **Ethnicity**: not reported. **Socioeconomic status**: lower education, n = 11 (29%); high school, n = 12 (32%); college/university, n = 15 (39%); employed or studying, n = 33 (87%). **Disease status**: 50% of participants had average FEV_1 values above 70% of predicted. More than 25% of participants (total group) had elevated symptoms of depression at baseline (26.2%). There were more participants with CF-related diabetes in the intervention group (44%) versus the control group (20%) and clinical parameters like FEV_1, BMI, and HbA1C were slightly, but not significantly, worse in the intervention group.
Interventions	**Intervention arm:** up to 10 individual, face-to-face or telephone (according to participant preferences) life coaching sessions (up to 60 minutes in duration) with a certified coach. The first and last coaching sessions were intended to be face-to-face and last up to 90 minutes. Participants attended an average of 6 coaching sessions (range 1 to 10), which were scheduled to be every 1 to 2 weeks early in the program and every 2 to 4 weeks later on. The entire coaching intervention was planned to last 6 to 9 months (although this was extended due to cancellations). The number of same-day cancellations was 38 (31%); five (6%) were no-shows. Planned telephone coaching calls were not answered 10 times (25%). Individuals who cancelled or were no-shows for in-person or telephone sessions were offered new appointments. Due to the number of cancellations, it was not possible to adhere to the original schedule of intervals between coaching sessions and the time frame for completion of the coaching program varied; however, those who participated in all 10 sessions completed in 8 – 15 months. 121 coaching sessions were delivered in total. Coaching was primarily face-to-face (n = 82; 68%) and lasted, on average, 57 minutes (range 20 to 110 minutes). Telephone coaching (n = 39; 32%) was shorter and lasted, on average, 28 minutes (range 5 to 60 minutes). Coaching took place either in a quiet room at the hospital outside the Department of Infectious Diseases or at a location close to the hospital. **Control arm:** usual care.
Outcomes	**Primary outcome** 1. Feasibility of the intervention (measured at 12 months) - willingness of eligible participants to be recruited and randomised, adherence to the intervention, and attrition rates **Secondary outcomes**

Knudsen 2016 *(Continued)*

1. HRQoL - special focus on the domains Social and Emotional functioning on the CFQ-R (measured at up to 21 months - for the intervention group at baseline, after 5 coaching sessions, after 10 coaching sessions and at 12 months post intervention; for the control group at baseline, after 4 months, after 9 months and at 12 months post intervention)
2. Self-reported adherence using MMAS-8 (measured at baseline and 4, 9 and 21 months) where scores range from 0 to 8 and cut-off scores include 0 to less than 6 (low adherence), 6 to less than 8 (medium adherence), and 8 (high adherence)
3. Adherence through pharmacy refill histories (data collected for 4 months prior to the intervention and 4 months at the end of the intervention (for the intervention group 2 months prior to end of study and 2 months after for the intervention group; for the control group 7 to 11 months after baseline))
4. Self-efficacy - GSE questionnaires (at baseline, 4, 9 and 21 months after baseline)
5. Clinical data (at baseline, 4, 9 and 21 months after baseline)
   a. Lung function test (spirometry, FEV_1)
   b. BMI
   c. Haemoglobin A1C (HbA1C)

Other outcome measures:

1. Experiences with and acceptability of the intervention through in-depth interviews with participants from the intervention arm after their last coaching session (12 months)

Assessment time points

Baseline

Midway (5 months)

Post-intervention (11 months)

Follow-up (1-year post-intervention)

Funding source	**Funding:** supported by an unconditional grant by Gilead.
Declaration of interest among the primary researchers	Authors report no conflict of interest.
Notes	**Clinical trial register**: clinicaltrials.gov/ct2/show/NCT02110914. **Intervention fidelity**: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized 1:1 in computer-generated blocks of 4, to obtain equal numbers in both arms.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates - retention rates after 5 and 10 coaching sessions were 67% and 50%, respectively. Reasons for stopping the intervention included lack of time (n = 1), poor health (n = 1), coaching not being helpful (n = 2), lack of motivation (n = 1), no need for further coaching (n = 2), and unknown reasons (n = 2). Those who stopped because of "no need for further coaching" were not

Knudsen 2016 *(Continued)*

		considered dropouts, as they had achieved what they wanted from the coaching intervention in less than 10 sessions. Thus, the dropout rate overall was reported as 39%. Not analysed as intention-to-treat.
Selective reporting (reporting bias)	High risk	Clinicaltrials.gov mentions an additional secondary outcome that is not reported in the published paper (unsure if this was not examined as part of the trial or is due to selective reporting): "Pharmacy Refill Histories [Time Frame: up to 1 year]: Data from the pharmacy database will be collected for two four-month periods: four months prior to the intervention and four months at the end of the intervention. The last four months will be two months prior to end of study and two months after for the intervention group, and seven to eleven month after baseline for the control group".
Other bias	Low risk	No other potential sources of bias identified.

Quinn 2004

Study characteristics	
Methods	Parallel, 2-arm RCT conducted at a single CF centre (Leeds) in England.
Participants	**Eligibility criteria** Males and females with a diagnosis of CF confirmed by either 2 positive sweat tests or recognised CF genotypes, prior to the onset of the trial. Aged 18 and over. Taking nebulised colistin for CF via a Prodose nebuliser. Able to use a nebuliser mouthpiece. **Exclusion criteria** FVC below 30% predicted (i.e. eligible for lung transplant assessment). Participation in other ongoing therapeutic trials for CF. Pregnant. **Withdrawal criteria** Participants who become pregnant during the trial. Choose to withdraw for any reason at any time throughout the trial. Participants who experience adverse effects whereby an independent physician deems that the patient be withdrawn for their own safety. **Population of interest (prescribed nebulised colistimethate)**: n = 102 **Number invited to participate (met eligibility criteria)**: n = 47 **Number of invited participants who declined**: n = 8 **Number of participants randomised**: n = 39 (3 participants dropped out after the start of the trial: n = 1 was withdrawn due to possible side effects of the medication and n = 2 dropped out because they

Quinn 2004 *(Continued)*

	preferred their previous nebulisers to the Prodose). The study sample therefore consisted of 36 participants. Unclear which group participants who dropped out were assigned to). **Number of participants in each group pre-intervention (n = 36)**: intervention arm n = 17, control arm n = 19. **Number of participants receiving intended treatment (n = 31)**: intervention arm (received minimum 3 intervention sessions) n = 12, control arm n = 19. **Number of participants analysed at post-intervention (intention-to-treat analysis; n = 35)**: intervention arm n = 16 (1 participant was transferred for heart-lung transplantation), control arm n = 19. **Number of participants analysed at post-intervention (per-protocol; n = 31)**: intervention arm n = 12 (1 participant was transferred for heart-lung transplantation; 4 participants did not receive the minimum 3 intervention sessions), control arm n = 19. **Demographic details (overall n = 36, intervention group n = 17, control arm n = 19)** **Age, mean (SD)**: overall 24.28 (5.15) years, intervention arm 23.94 (3.88) years, control arm 24.58 (6.16) years - there was no significant difference between groups. **Sex**: overall 19 males (52.78%) and 17 females (47.22%), intervention arm 5 males (29.41%) and 12 females (70.59%), control arm 14 males (73.68%) and 5 females (26.32%) - there was a significantly larger proportion of males in the control group and a larger proportion of females in the intervention group (Fisher's exact test, P = 0.010). **Ethnicity**: overall 33 participants (91.67%) were white European and 3 participants (8.33%) were of Asian (India/Pakistan) origin. The intervention group had 14 white Europeans and three participants of Asian origin (Fisher's exact test, P = 0.095); all 19 participants in the control group were white European. **Socioeconomic status** There were no differences between the intervention and control groups on marital status, accommodation, occupation, time known to the unit, time known to the physiotherapists, and the length of time participants had been using a nebuliser. 22 participants (61.11%) were single; five (13.89%) participants cohabited; and nine (25%) were married. 19 participants (52.78%) lived at home with their parents, whereas six (16.67%) lived on their own; five (13.89%) lived with their spouse; five (13.89%) with their partner; and one (2.78%) lived in university halls of residence. 12 participants (33.33%) were in full-time employment and six participants (16.67%) in part-time employment; seven (19.44%) were unemployed; six (16.67%) claimed sick/ benefit support; and five (13.89%) were students. **Disease status**: participants had been using a nebuliser for a mean (SD) of 120.19 (79.06) months.
Interventions	**Intervention arm:** brief telephone MI intervention. Up to 6 telephone sessions of MI delivered over 3 months by a trainee clinical psychologist (study investigator), focused on increasing adherence and enhancing self-efficacy. Sessions were fortnightly, lasting approximately 15 - 30 minutes each. **Control arm:** usual care (the investigator made no contact with participants in this arm of the trial until the end of the intervention, when they were required to complete the battery of questionnaires and submit their Prodose device so that their adherence data could be collected).
Outcomes	**Primary outcomes** 1. Difference in adherence pre- and post-intervention (measured using the ProDose Adaptive Aerosol Delivery System, which records usage data) reported as mean % of prescribed inhaled therapies taken (including values above 100% if device was being used more than prescribed); mean % days participants totally adhered to prescribed inhaled therapies (0 to 100%); mean % of days the device has

Quinn 2004 *(Continued)*

been used at least once for prescribed treatments (0 to 100%); and mean % of days the device has been used at least twice for prescribed treatments (0 to 100%);
2. Relationship between adherence and other variables (e.g. items from the IPQ and the TPBQ) to identify predictors of adherence behaviour (for separate multiple regression study)

Other outcomes

1. STAI–short form (possible scores range from 6 to 24 to indicate low to high anxiety)
2. HADS (possible scores range from 0 to 21 on each subscale to indicate low to high anxiety or depression)
3. CFQOL (52 items to assesses 9 domains (physical functioning, social functioning, treatment issues, chest symptoms, emotional functioning, concerns for the future, interpersonal relationships, body image, and career concerns); scores on each subscale range from 0 to 100, with higher scores indicating better QoL)
4. IPQ - Revised
5. URICA
6. TPBQ

Assessment time points

Questionnaires administered at: baseline (pre-intervention) and post-intervention (3 months after pre-intervention).

Adherence measured for the periods: baseline: 0 to 3 months (pre-intervention; designed so that all participants could become accustomed to their new nebuliser device prior to their allocation in the second phase); post-intervention: 3 to 6 months.

Funding source	Not reported.
Declaration of interest among the primary researchers	Not reported.
Notes	Contacted lead study author and supervisor who provided digital copy of thesis, but no further information was available (e.g. protocol, intervention manual, participant invitation letter, participant information sheet etc). During data extraction, we noted some discrepancies between the information reported in the thesis and conference abstract for this study (e.g. mean age; participant numbers; results). We extracted information from both references but used the thesis as our primary reference (as this was more detailed and will likely have been reviewed by internal and external examiners). **Intervention fidelity**: the authors reported that audiotapes of the consultations were used in supervision, and were checked by the supervisor to ensure treatment fidelity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Thesis reports that the randomisation procedure was generated using a pseudo-random number generation technique (which allocates a given number of participants at random to 1 of 2 independent groups (i.e. intervention and control)). The procedure was carried out by a member of staff who was independent to the study.
Allocation concealment (selection bias)	Low risk	Thesis reports that the investigator remained blinded to the details regarding the allocation of participants to the treatment groups (intervention and control) until the participant was ready for Phase 2 of the trial. A psychologist in clinical training, independent to the trial, held the details of each allocation until they were to commence to Phase 2 (on completion of assessments

Quinn 2004 *(Continued)*

		at 3 months). At this time, the investigator was given the participant's allocation and was able to contact them if they were allocated into the 'intervention' group. Participants in the 'usual care' condition were not contacted.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	Thesis states that physiotherapists administering the assessments were blinded to participants' treatment allocation. At the end of the trial, physiotherapists were asked to state their knowledge of each participant's allocation in an attempt to evaluate the success of the blindness. 1 of the physiotherapists was aware of 2 allocations into the intervention arm but both had completed their telephone contact with the investigator by this time.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Thesis reports that subsequent to the onset of the trial, 1 participant was withdrawn due to possible side effects of the medication and 2 dropped out because they preferred their previous nebulisers to the Prodose. The study sample therefore, consisted of 36 participants. Intention to treat analyses were conducted with 35 participants (1 participant was removed because she was transferred for heart-lung transplantation).
Selective reporting (reporting bias)	Unclear risk	Contacted study author but unable to access trial protocol to assess reporting bias.
Other bias	Low risk	Thesis states that the staff on the CF unit, including physicians in charge of prescribing medication and admitting participants for additional/emergency treatment were not informed of participants' treatment allocation. Efforts were made to maintain their blindness throughout the study by asking participants not to inform staff of contacts with the investigator during their time in the study.

Quittner 2019

Study characteristics	
Methods	Pragmatic, parallel, clustered 2-arm RCT conducted at 18 CF centres in the USA (iCARE; I Change Adherence and Raise Expectations).
Participants	**Eligibility criteria** Males or females aged 11 to 20 years old. Diagnosis of CF. Attending the accredited care centre for regularly scheduled clinic visits. Prescribed at least 1 of the following medications for at least 6 months prior to signing the informed consent: azithromycin; hypertonic saline; Pulmozyme®; TOBI®; inhaled compounded tobramycin. Consented to provide data to the CF Foundation Registry prior to conversion to PORTCFv2. **Exclusion criteria** Planning to change care teams within the next 2 years. Seen at a satellite clinic. On the lung transplant list. **Number of CF centres randomised (n = 18)**: intervention arm n = 9, control arm n = 9. **Number of participants consented (n = 641)**: intervention arm n = 321, control arm n = 320.

Quittner 2019 *(Continued)*

Number of invited participants who declined: not reported.

Number of participants receiving intended treatment (completed intervention delivery)

4+ sessions: n = 63 (21%)

3 sessions: n = 91 (30%)

2 sessions: n = 90 (30%)

1 session: n = 40 (13%)

0 sessions: n = 16 (5%)

Number of participants analysed at 12 months (post-intervention)

Survey: intervention arm n = 246 (82%), control arm n = 279 (91%)

Analysable pharmacy data*: intervention arm n = 205 (68%), control arm n = 231 (75%)

*there were challenges in obtaining pharmacy records which resulted in significant amounts of missing adherence data, particularly at baseline.

Demographic details (overall n = 607, intervention arm n = 300, control arm n = 307)

Age, mean (SD): overall 14.7 (2.6) years, intervention arm 14.7 (2.6) years, control arm 14.7 (2.6) years (P = 0.98).

Sex: overall 52.9% females, intervention arm 55.7% females, control arm 50.2% females (P = 0.17).

Ethnicity: overall 91.4% Caucasian, intervention arm 90.6% Caucasian, control arm 92.2% Caucasian (P = 0.49).

Socioeconomic status

Family-reported income (P = 0.52 reported but unclear what this relates to):

Below USD 20K: overall 12.0%, intervention arm 11.7%, control arm 12.4%;

USD 20 to 39K: overall 15.7%, intervention arm 15.7%, control arm 15.6%;

USD 40 to 59K: overall 12.9%, intervention arm 14.7%, control arm 10.7%;

USD 60 to 79K: overall 17.0%, intervention arm 17.3%, control arm 16.6%;

USD 80 to 99K: overall 11.9%, intervention arm 13.3%, control arm 10.4%;

Over USD 100K: overall 24.7%, intervention arm 22.3%, control arm 27.0%;

Refused/missing: overall 6.1%, intervention arm 5.0%, control arm 7.2%.

Public or no health insurance (%): overall 36.5%, intervention arm 36.9%, control arm 36.2% (P = 0.86).

Disease status

Pancreatic insufficient: overall 95.4%, intervention arm 95.4%, control arm 95.4 (P = 0.99).

Prior year IV days (1+ course of IV antibiotics in past year): overall 42.0%, intervention arm 48.1%, control arm 36.9% (P = 0.006).

Interventions	**Intervention arm**: clinic-based problem-solving intervention. Face-to-face, during clinic visits, delivered by trained interventionists, including 30 social workers (63%), 8 nurses (16%), 6 research coordinators (12%), 3 physicians (7%) and 1 respiratory therapist/ dietician (2%). Report states: “Interventionists had competing clinical demands, which limited the amount of IMPACT training and supervision that could be provided”.

Quittner 2019 *(Continued)*

	The goal was to implement 4 x 10 to 15-minute problem-solving sessions during regular clinic visits with each family over Year 1. Overall, 745 problem-solving sessions were delivered across the 9 intervention sites, with 95% of adolescents completing at least 1 session (mean (SD) sessions/participant 2.5 (1.1)). Trial has a pragmatic design; participants could choose to focus on any aspect of CF care and receive intervention for that (i.e. intervention was not necessarily focused on improving adherence to inhaled therapies). Report states: "Fifty-eight percent of problem-solving sessions targeted barriers to airway clearance, exercise or nutrition, while 18% addressed pulmonary medications." **Control arm**: usual care.
Outcomes	**Primary outcome** 1. MPR derived from pharmacy refill records (measured at 12 months)* **Secondary outcomes** 1. CF knowledge (measured at 24 months) 2. Skills associated with CF treatments (measured at 24 months) 3. HRQOL (measured at 24 months) using CFQ-R (Quittner 2009) (measure assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL) 4. FEV_1% predicted (abstracted from CF Registry and measured at 24 months) 5. Pulmonary exacerbation as IV antibiotic treatment (abstracted from CF Registry and measured at 24 months) 6. CF hospitalisations (measured at 24 months) 7. Clinic report of pulmonary hospitalisation (abstracted from CF Registry) **Assessment time points** Baseline 12 months *Baseline interval for cMPR was the baseline date back one year; and the 12-month interval was the baseline date plus one year.
Funding source	The work was supported by The Cystic Fibrosis Foundation, Genentech, Inc., & Novartis Pharmaceuticals Corp.
Declaration of interest among the primary researchers	ALQ – Served on industry advisory committees to consult on use of patient-reported outcome measures (Bayer Schering, Vertex Pharmaceuticals) and made presentations on adherence and disease management (Vertex Pharmaceuticals). MNE – speaker presentation on adherence (Praxis Pharmaceuticals). ANA – performed consulting activities for Abbvie Pharmaceuticals. No conflicts exist for AKR, KAM, ALB, KKC, and SC. KAR - Served on advisory committees for transition (Gilead) and adherence promotion (Genentech) and presented on adherence (Vertex Pharmaceuticals).
Notes	**Clinical trial register**: clinicaltrials.gov/ct2/show/NCT01232478. **Intervention fidelity**: fidelity assessment was conducted for first session - "Each participant's first session was videotaped and supervisors provided tailored feedback. A 35-item fidelity checklist was used

Quittner 2019 *(Continued)*

to rate videos on provider implementation of the problem-solving steps and converted to a percent correct score (e.g. achieving a score of 35/35 = 100%)".

Report states: "Videotapes were received for 198 (66%) of intervention participants; submissions ranged from 9% to 94% of participants enrolled at a site. The average session fidelity score was 67% (SD=14%; Range = 26–100%). Fidelity varied by site, with mean site scores ranging from 51 to 80%. Most interventionists allowed the teen to choose the treatment for the problem-solving session (84%); however, only 65% asked the teen to identify the barrier for that treatment, and only 50% operationalized how to implement the solution (e.g. who, what, where, when you will start)".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Centre" was unit of randomisation. Report states that "a clustered design was critical given that clinicians, not research staff, implemented the intervention; thus, within-site randomization posed cross-contamination risks. Randomization was completed by the study statistician, with centers stratified by size to account for differences in staffing and resources. Three strata were included: <100 patients (7 centers), 100-200 patients (6 centers) and >200 patients (5 centers)".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	Report states that "Pharmacy and health records were collected by data coordinating centre staff blinded to intervention allocation". Unclear how other outcomes (i.e. QoL survey) assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Report states: "Of the 641 families who consented to participate (321 in intervention group and 320 in control group), 300 (93%; Mean=33/site) in intervention and 307 (95%; Mean=34/site) in the control group completed the baseline survey ... Of those, 589 (97%) had CF Foundation Patient Registry data, 308 (51%) had analysable pharmacy records at baseline (n=156 intervention; n=152 control), 436 (72%) had analysable pharmacy records at 12 months (n=205 intervention; n=231 control). Availability of a baseline cMPR score did not differ by patient characteristics." From CONSORT flow diagram (p 891 of publication), 20 participants (7%) withdrew and 1 died from the intervention group between consenting and completing baseline survey; 13 participants (4%) withdrew from the control group between consenting and completing baseline survey. In the intervention group, a further 20 participants (6%) withdrew and 2 died (1%) between completing baseline and 12 month follow up surveys, and an additional 32 (11%) did not complete the 12-month survey. In the control group, a further 13 participants (4%) withdrew and 1 died (<1%) between completing the baseline and 12 month follow-up surveys, and an additional 14 (5%) did not complete the 12-month survey. Report does not provide additional information on reasons for withdrawal or surveys not being completed. Report states: "Intervention effects were evaluated based on the intent-to-treat (ITT) principle", but unclear whether this included all participants entering the trial or whether some were excluded.

Quittner 2019 *(Continued)*

		Additionally, there were challenges obtaining pharmacy records during the study, which resulted in a significant amount of missing data (and meant the study was underpowered to find differences in medication adherence). Report states that: “Initially, pharmacy records were intended to be obtained from a third party vendor; however, the accuracy of these records was suboptimal and therefore none of the data from this source was used in the analyses. Thus, halfway through the study, procedures were changed to obtain all records directly from participants' pharmacies for the entirety of the study duration. Pharmacy record release authorizations, signed by each participant/parent were obtained. Releases could not be obtained if the family had withdrawn from the study or did not return to clinic. Some pharmacies did not retain records >12 months, resulting in missing baseline data for some participants enrolled before this protocol change”.
Selective reporting (reporting bias)	High risk	The following secondary outcome was listed on clinical trial register but not reported in full trial paper: "CF hospitalizations [Time Frame: 24 Months] - Clinic report of pulmonary hospitalization (abstracted from CF Registry)."
Other bias	High risk	Report states: “To increase feasibility, centers interested in adherence-promoting strategies were invited to participate. The first 18 centers signing a contract and obtaining Institutional Review Board (IRB) approval were enrolled. No other center eligibility criteria were applied.” In addition, participants enrolled in the intervention were compensated USD 50/session up to 4 intervention sessions. Assessment included a patient-completed survey and skills assessment; participants were compensated USD 50 for each assessment. Report states: "selecting CF Centers interested in addressing adherence, randomizing CF Centers prior to participant enrollment, not collecting data on nonparticipants, and paying participants for completing PS sessions, may have led to biases and affected generalizability of the findings".

Riekert 2013

Study characteristics	
Methods	Parallel, 2-arm, RCT conducted at a single CF centre in the USA - 'Building Adherence to Live And Navigate my CF Experience (BALANCE)' study.
Participants	**Eligibility criteria** Confirmed diagnosis of CF by a doctor. Aged 16 years or older. Prescribed an inhaled mucolytic, inhaled antibiotic therapy, chronic macrolide therapy and/or hypertonic saline therapy for the previous 12 months. Scheduled for a regular visit at either the paediatric or the adult CF clinic at Johns Hopkins Hospital. **Exclusion criteria** *Burkholderia cepacia* complex isolated from the respiratory tract within the past 2 years. Post lung transplant. Participated in NA_00008649 'A pilot study of Motivational Interviewing for adults with CF'.

Riekert 2013 *(Continued)*

	Number of participants randomised (n = 128): intervention arm n = 63, control arm n = 65. **Demographic details (overall n = 128, intervention arm n = 63, control arm n = 65)** **Age, mean (SD)**: 29 (11) years. **Sex:** 60 (47%) females. **Ethnicity**: 119 (93%) were Caucasian. **Socioeconomic status**: 100 (78%) had private insurance. **Disease status** **Pancreatic sufficiency**: 105 (82%) were pancreatic insufficient. **CFRD**: 19 (15%) had CFRD.
Interventions	**Intervention arm**: MI designed to motivate and assist participants to improve their adherence to CF pulmonary medications (e.g. by providing personal feedback to participants on their adherence (pharmacy refill data) and health outcomes (e.g. trajectory of lung function values, frequency of exacerbations), as well as clinic-level figures showing the association between adherence and health outcomes). **Control arm**: EPS (attention control group), designed to increase knowledge and enhance the skills needed to optimise CF-management. The strategies used to improve adherence include providing didactic education and skills training, and proscriptively using behavioural modification strategies, such as positive reinforcement for desired behaviours, and problem-solving training to overcome barriers. **Duration of intervention/control arm sessions**: not reported. **Number of intervention/control arm sessions**: unclear (report describes an intervention consisting of 1 clinic session and 8 phone sessions, but it was unclear if this referred to the MI intervention or active comparator intervention (EPS), or both).
Outcomes	**Primary outcome** 1. MPR calculated for each prescribed drug monitored for adherence (dornase alfa, inhaled tobramycin, hypertonic saline, aztreonam lysine, and/or azithromycin) (measured at 12 months) Note: cMPR only reported in the symposium summary, not MPR for individual drugs. Also, pharmacy refill records were collected and a baseline and 12-month annual MPR was calculated for each prescribed treatment. **Secondary outcome** 1. Change in FEV_1% predicted (measured at 12 months) Note: 2 additional outcomes were not listed on clinical trial register but are reported in symposium summary (e.g. QoL, pulmonary exacerbations). **Assessment time points** Baseline: cMPR, FEV_1% predicted, pulmonary exacerbations (1+ in past year), CFQ-R. 6 months: CFQ-R (Quittner 2009) (measure assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3 domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL). 12 months: cMPR, FEV_1% predicted, pulmonary exacerbations (1+ in past year), CFQ-R.
Funding source	Report states that the study was funded by NIH NHLBI R01HL087997.

Riekert 2013 *(Continued)*

Declaration of interest among the primary researchers	Not reported.
Notes	**Clinical trial register**: clinicaltrials.gov/ct2/show/NCT01013896. **Intervention fidelity**: report states that sessions were audiotaped for supervision and fidelity coding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Report states that participants were randomised (stratified by age < 25 or ≥ 25 years) to either the MI (n = 63) or EPS (n = 65) intervention, but no further details provided on method used to generate allocation.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome Assessors	Unclear risk	Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Report states: "98% of participants completed the initial face-to-face session while 80% completed all 9 intervention sessions. Eighty-eight percent and 74% completed the 6- and 12-month surveys, respectively and thus far, 12-month pharmacy records are available for 72% of the sample. There were 3 deaths post-randomization (n=2 EPS and n=1 MI), none were related to study participation." Withdrawals and dropouts are not described or explained. Unclear when the 3 deaths occurred (e.g. before baseline assessment or post treatment). It is unclear what happened to the 20% of participants who did not complete all 9 intervention sessions, and which group these were from.
Selective reporting (reporting bias)	Unclear risk	Additional outcomes not listed on clinical trial register but reported in symposium summary (e.g. QoL, pulmonary exacerbations).
Other bias	High risk	Report states: "At baseline, there was a trend for the MI group to have higher Composite MPR scores than the EPS group (p=.07) and to have greater perceived Treatment Burden (p<.01)".

Shakkottai 2017

Study characteristics

Methods	Parallel, 2-arm, pilot RCT conducted at a single paediatric CF centre in the USA.
Participants	**Eligibility criteria** Aged 10 to 21 years. Confirmed diagnosis of CF either by a sweat chloride ≥ 60mEq/L or the presence of 2 disease-causing mutations. Clinically stable with at least 1 month from their last hospitalisation or use of oral antibiotics for a pulmonary exacerbation.

Shakkottai 2017 *(Continued)*

	Signed informed consent from the participant and/or from the parent/legal guardian, if younger than 18 years. **Exclusion criteria** Aged less than 10 years or greater than 21 years. Clinically unstable. **Number of invited participants who declined**: not reported. **Number of participants (n = 5)**: intervention arm n = 3, control arm n = 2. **Demographic details (overall n = 5, intervention arm n = 3, control arm n = 2)** **Age, mean (SD) (range)**: overall 11.67 (0.82) years (10 to 14 years), intervention arm 11.50 (0.64) years, control arm 11.93 (1.29) years. **Sex**: overall 4 females and 1 male, intervention arm 3 females and no males, control arm 1 female and 1 male. **Ethnicity**: not reported. **Socioeconomic status**: not reported. **Disease status** **Lung function**: intervention group had a lower mean FEV_1 and FEF25-75 % predicted compared to control group. **BMI percentile, mean (SD)**: intervention arm 64.33 (19.14), control arm 41.50 (16.26). **Sweat chloride (mmol/L), mean (SD)**: intervention arm 100.00 (5.66), control arm 95.00 (1.41). **Homozygous delF508**: intervention arm 2 participants (66%), control arm 1 participant (50%). **Heterozygous delF508**: intervention arm 1 participant (33%), control arm 1 participant (50%).
Interventions	**Intervention arm**: participants given a personal spirometer device that provides medication reminders and allows for lung function monitoring at home. **Control arm**: usual care.
Outcomes	**Primary outcome** 1. Overall % medication adherence to inhaled hypertonic saline, dornase alfa and CF multivitamins based on prescription refill data (actual number of prescriptions filled divided by the number prescribed as a percentage) (measured at 3 months)* **Secondary outcomes** 1. CFQ-R** Treatment Burden domain score (Child) (measured at 3 months) 2. CFQ-R** Treatment Burden domain score (Parent) (measured at 3 months) **Assessment time points** Baseline 3 months *It is unclear over which time periods the baseline and 3-month cMPR data were calculated. The trial register states that pharmacies were contacted for prescription refill data during the 3-month trial duration.

Shakkottai 2017 *(Continued)*

	**CFQ-R assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL.
Funding source	Study authors report that this was funded by the Second Year Fellowship Training Grant through the Cystic Fibrosis Foundation (SHAKKO13B0) and the Charles Woodson Fund for Clinical Research.
Declaration of interest among the primary researchers	No conflict of interest declared.
Notes	Contacted corresponding study author who replied to say she was unable to provide further information on the study (e.g. protocol, intervention manual, participant invitation letter, participant information sheet etc). **Clinical trial register**: clinicaltrials.gov/ct2/show/NCT02301377. **Intervention fidelity**: mean adherence to the weekly spirometry was 94.67%. Report states that average use of the medication reminder feature was 50.23%, largely due to alarms not being audible enough and/or finding it too cumbersome to repeatedly change alarm times to suit changing schedules.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Clinical trial register and published report states random assignment but no further details provided.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome Assessors	High risk	Report states that participants were trained on the proper use of their device at enrollment by a respiratory therapist who also contacted them once a week via telephone to record their lung function result and address any questions about the device, so outcome assessors not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Small sample (n=5). Withdrawals not described.
Selective reporting (reporting bias)	Unclear risk	All outcomes listed in clinical trial register were reported in the full trial paper. However, this study was planned to be 12 months in duration according to the clinical trial register, but the intervention duration was subsequently changed to 3 months with no details provided.
Other bias	Low risk	No other potential source of bias identified.

Wildman 2022

Study characteristics	
Methods	Parallel, 2-arm RCT conducted at 19 adult CF centres in the UK (CFHealthHub).
Participants	**Eligibility criteria**

Wildman 2022 *(Continued)*

	Diagnosed with CF and with data within the CF Registry. Aged 16 years and above. Willing and able to take inhaled mucolytics or antibiotics via a chipped nebuliser (e.g. PARI eFlow® rapid nebuliser system and eTrack® controller). **Exclusion criteria** Post lung transplant. On the active lung transplant list. Receiving palliative care. Lacking in capacity to give informed consent. Using dry powder devices to take antibiotics or mucolytics. **Number of people screened**: n = 3510. **Number who were excluded (met exclusion criteria)**: n = 1279. **Number who were not contacted**: n = 1056. **Number of invited participants who declined**: n = 556 (n = 11 expressed an interest initially but did not consent). **Number of participants randomised (n = 608)**: intervention arm n = 305, control arm n = 303. **Number of participants who completed 12-month follow-up (n = 534)**: intervention arm n = 265, control arm n = 269. **Number of participants analysed (intention-to-treat)**: Pulmonary exacerbations (primary study outcome; n = 608): intervention arm n = 304, control arm n = 303; Adherence (n = 588): intervention arm n = 293, control arm n = 295). **Demographic details (intervention n = 304, control n = 303)** **Age, mean (SD)**: intervention arm 31.1 (10.6) years, control arm 30.3 (10.8) years. **Sex**: intervention arm 156 (51.3%) females, control 154 (50.8%) females. **Ethnicity**: not reported. **Socioeconomic status** **Deprivation quintiles (intervention arm (n = 302), control arm (n = 302))** 1 (least deprived): intervention arm 50 (16.6%), control arm 51 (16.9%) 2: intervention arm 59 (19.5%), control arm 71 (23.5%) 3: intervention arm 63 (20.9%), control arm 66 (21.9%) 4: intervention arm 63 (20.9%), control arm 67 (22.2%) 5 (most deprived): intervention arm 67 (22.2%), control arm 47 (15.6%)
Interventions	**Intervention arm:** complex intervention comprising 3 main components: 1. a microchipped nebuliser for delivering inhaled medications;

Wildman 2022 *(Continued)*

2. information technology infrastructure to capture and store adherence data from the nebulisers and display it to participants and the CF team, and;
3. the behaviour change intervention, comprising a software platform ('CFHealthHub' mobile app and website) offering adherence feedback and tailored modules of content and tools used by the health professional (interventionist) in interactions with participants and accessed independently by participants via CFHealthHub.

Frequency of administration of the intervention was dependent upon level of objectively measured adherence at baseline:

1. participants with a baseline adherence of 80% or less, followed a 'normal' pathway of 6 sessions (1x first intervention visit of 40 to 60 minutes, 2 x intermediate reviews of 5 to 15 minutes, 2 x reviews of 30 to 45 minutes and 1 x phase review of 20 to 30 minutes) over 12 weeks, with phase reviews every 12 weeks thereafter, or every 6 weeks for participants with low baseline adherence of 25% of lower;
2. participants with a baseline adherence of over 80%, followed a less intensive pathway of 3 sessions (1 x first intervention visit, 1 x intermediate review and 1 x phase review), with phase reviews every 12 weeks thereafter.

Following the initial pathways above, additional sessions were offered upon request of the participant for further support if participants adherence decreased by at least 20% in a 4-week period, or if a participant received IV antibiotics for an exacerbation.

Report states that the median (IQR) number of interventionist sessions per participant was 7.0 (6.0 to 10.0). The median (IQR) total interventionist delivery time per participant (including contact time and preparation outside of sessions) was 185 (126 to 263) minutes.

Control arm: usual care (heterogeneous within and between centres, based on the needs of participants and the skills and interests of CF unit staff). Participants in the control group used a micro-chipped nebuliser but could not access adherence data or other content and tools through CFHealthHub, nor did they receive the structured CFHealthHub intervention as described in the intervention manual. Members of the MDT did not have access to the graphs or data generated by CFHealthHub for control arm participants although they did, centrally, follow participants up for troubleshooting missing data or data errors).

Outcomes

Primary outcome

1. Number of pulmonary exacerbations in the 12 month post-baseline follow-up period, defined according to the modified Fuchs criteria* and noted at the point of a participant starting a course of IV antibiotics (whether these are planned or unscheduled)

Secondary outcomes

1. BMI
2. FEV_1
3. EuroQol EQ-5D-5L
4. Patient Activation Measure (PAM-13)
5. Assessment of routine: measure of life chaos
6. Self-Report Behavioural Automaticity Index (automaticity-specific subscale of the Self Report Habit)
7. CFQ-R (Quittner 2009) (measure assesses 9 function domains (physical functioning, vitality, emotional functioning, eating disturbances, treatment burden, health perceptions, social functioning, body image, and role functioning) and symptoms across 3domains (weight, respiratory symptoms, and digestive symptoms); scores range from 0 to 100, with higher scores indicating better QoL)
8. PHQ-8
9. MAD
10. GAD-7 (scores range from 0 to 21, and cut-off scores of 5, 10, and 15 indicate mild, moderate, and severe levels of anxiety, respectively)
11. The Capability Opportunity Motivation Behaviour Beliefs Questionnaire (COM-BMQ) including the Beliefs about Medicines Questionnaire - specifically nebuliser adherence - and one additional belief item, one intention item, one confidence item, and a list of barriers
12. Self-report estimate of adherence as a percentage

Wildman 2022 *(Continued)*

13.Resource-use form comprised of a combination of hospital notes and the NHS patient electronic system to determine inpatient IV days, routine clinic visits, unscheduled outpatient contacts and unscheduled inpatient stays
14.Habit formation
15.Monthly prescription check to both check for data transfer to CFHealthHub and review for an indication that the prescription has changed or indication of microorganism e.g. Pseudomonas
16.Adherence to prescribed medication, defined in several ways including unadjusted adherence, simple normative adherence (without numerator adjustment), sophisticated normative adherence (without numerator adjustment), simple normative adherence (with numerator adjustment) and sophisticated normative adherence (with numerator adjustment)
17.any treatment with IV antibiotics
18.acceptability of intervention (11-item questionnaire)

Assessment time points

Baseline (pre-intervention)

12 months (post-intervention)

*An exacerbation of respiratory symptoms will be said to have occurred when a participant was treated with parenteral antibiotics for any one of the following 12 signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38 °C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest, derived from notes by site staff; decrease in pulmonary function by 10% or more from a previously recorded value, derived from notes by site staff; or radiographic changes indicative of pulmonary infection, derived from notes by site staff.

Funding source	Research funded by the NIHR under its Grants for Applied Research Programme (RP- PG-1212-20015) and NHS England Commissioning for Quality and Innovation (IM2 Cystic Fibrosis Patient Adherence).
Declaration of interest among the primary researchers	Report states: "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no direct influence of any competing interest on the submitted work; support for MJW from Philips Respironics for early data transfer experience; support for the University of Manchester software team from PARI Pharma to create a medication reporting component within the CFHealthHub software; funding for MJW from Zambon; funding for IB from Microsoft Research; SJW is an NIHR Senior Investigator; IB became Chief Data Scientist (advisory) for AstraZeneca in September 2019; no other financial relationships that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work".
Notes	**Intervention fidelity**: report states that fidelity of intervention delivery was assessed throughout the study with 2 reviewers independently assessing a sample of audio- recording and worksheets from sessions (first intervention session, review, phase review) using a scoring sheet (further details provided in Appendix A of published report). Fidelity of intervention delivery median (IQR) scores were 97.2% (92.3 to 100.0), 92.6% (87.0 to 98.1) and 94.4% (91.7 to 97.2) at the first intervention visits, reviews and phase reviews, respectively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Report states that 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.
Allocation concealment (selection bias)	Low risk	Report states that the allocation sequence was hosted by Sheffield Clinical Trials Unit, with the sequence created by a statistician (not otherwise involved in

Wildman 2022 *(Continued)*

		the trial). Allocation only revealed to interventionist upon entering participant demographic data into the secure server.
Blinding (performance bias and detection bias) Outcome Assessors	High risk	Outcome assessor (i.e. researcher/ interventionist) was non-blinded after allocation revealed following consent visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis reported (all participants entering trial).
Selective reporting (reporting bias)	Low risk	All outcomes listed in protocol reported in trial paper.
Other bias	Low risk	Trial statistician remained blind to treatment allocation until database freeze.

ACT: airway clearance techniques
BMI: body mass index
CF: cystic fibrosis
CFQ-R: Cystic Fibrosis Questionnaire-Revised (Quittner 2009)
CFQOL: Cystic Fibrosis Quality of Life Scale
CFRD: cystic fibrosis-related diabetes
CFTR: cystic fibrosis transmembrane conductance regulator
cMPR: composite medication possession ratio
CPT: chest physiotherapy
EPS: education plus problem-solving
FEF25-75: mid-expiratory flow
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GAD-7: General Anxiety Disorder 7-item anxiety scale (Spitzer 2006)
GSE: General Self-Efficacy Scale
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
IPQ: Illness Perception Questionnaire
IQR: interquartile range
IV: intravenous
MMAS-8: Morisky Medication Adherence Scale (Morisky 2008)
MDT: multidisciplinary team
MI: motivational interviewing
MPR: medication possession ratio
NIHR: National Institute for Health Research
PEFR: peak expiratory flow rate
PHQ-8: Patient Health Questionnaire depression scale (Kroenke 2009)
QoL: quality of life
RCT: randomised controlled trial
SD: standard deviation
STAI: State-Trait Anxiety Inventory
TPBQ: Theory of Planned Behaviour Questionnaire
URICA: University of Rhode Island Change Assessment
USD: US dollars

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 2015	This is not a study - it is an editorial focused on adherence to Ivacaftor in cystic fibrosis.

Study	Reason for exclusion
ACTRN12607000234415	This RCT aims to evaluate the use of mentoring to improve the self-efficacy and self-management of adolescents and adults with CF, it is not focused on improving adherence to inhaled therapies.
ACTRN12619001730190	This study aims to implement an adherence protocol in clinical practice, but it is not an RCT (no control group).
Betz 2019	This RCT aimed to assess the feasibility, acceptability, and fidelity of an intervention to decrease spiritual struggles of parents of children with CF (i.e. it is a spiritual intervention delivered by chaplains and is not a psychological intervention).
Bingham 2012	This is a cross-over trial on breath biofeedback and was not focused on psychological interventions for improving adherence to inhaled therapies.
Bryon 2000	Contacted lead author for clarification on methods and results, but they were unable to provide any further publications or information.
Cannon 1999	This study explored the feasibility and benefit of in-home videoconferencing and is not a psychological intervention study.
Chadelat 2005	Unable to access thesis or find contact details of thesis author or supervisor. Attempted contact with a co-author from another study in 2005 but no response to email.
Chan 2013	This study aimed to examine the value of a pharmacist in identifying drug-therapy problems among people with CF, and was not an intervention study aimed at improving adherence.
Cummings 2011	This RCT aimed to assess the effectiveness of a digital intervention to improve self-management in adolescents and adults with CF, but adherence was not one of the outcomes and the intervention was not focused on improving adherence to inhaled therapies.
Czajkowski 1985	Unable to contact author to request copy of thesis, and not able to access online, so study excluded.
Daniels 2013	This is not a study - it is a Cochrane Review focused on nebuliser systems for drug delivery in CF.
Davis 2004	This is an RCT to assess the effectiveness of an educational tool for children and adolescents with CF for improving knowledge and coping skills (i.e. wrong outcomes).
Dodd 2000	This is not a study - it is an editorial focused on understanding treatment adherence in adults with CF.
DRKS00027569	This RCT aims to evaluate a self-help manual ('MukoHelp') for improving psychological symptoms and adherence to therapy, it is not focused on improving adherence to inhaled therapies in CF.
Duff 2014	This is not a study - it is a commentary on adherence in CF.
Elkins 2006	This study compared three methods of monitoring adherence in a clinical trial and is not a psychological intervention study.
Fischer 2003	Contacted lead author for clarification on methods and results, but they confirmed that the results of this study were never published, and they were unable to provide any further information.
Geirhos 2022	This is a feasibility RCT of a guided internet- and mobile-based CBT intervention for adolescents and young adults with chronic medical conditions (e.g. CF) and comorbid depression or anxiety symptoms (youthCOACH$_{CD}$). It is not focused on improving adherence to inhaled therapies in CF.

Study	Reason for exclusion
Geller 2011	This is not a study - it is a review of the literature on technological and behavioral strategies to reduce treatment burden and improve adherence to inhaled antibiotics in CF.
Goldbeck 2013	This study examined a multi-component education and counselling program coordinated by a case manager, but it is a non-randomised study.
Goodill 2005	This is an intervention study focused on adherence to exercise and nutrition regimens in CF, not inhaled therapies.
Grossoehme 2020	This is a mixed-methods study which examines the relationship between treatment adherence, exercise and spirituality in adults with CF, and is not an intervention study.
Hagelberg 2008	The intervention described is not psychological. The abstract describes 'direct dispensing' as an adherence-improving intervention.
Hatziagorou 2017	This study investigates the effectiveness of a home care program compared to a telephone communication programme among people with CF, and did not assess the effectiveness of a psychological intervention for improving adherence to inhaled therapies.
Hawkins 2002	This is not an intervention study or RCT. The dissertation includes a review paper and empirical study focused on illness perceptions and treatment beliefs in relation to adherence.
Hebestreit 2010	This RCT evaluates the effects of physical conditioning program on health status and physical activity in youths and young adults with CF, and is not focused on improving adherence to inhaled therapies.
Hebestreit 2022	This RCT evaluates an exercise intervention in CF and is not focused on improving adherence to inhaled therapies.
Hlela 2018	This study aims to evaluate the feasibility and usefulness of an educational book for children with CF, focused on increasing knowledge (e.g. of the cause of CF and the importance of treatment adherence), but did not measure adherence as an outcome.
Huang 2014	This study aims to test a text message and internet-based intervention for improving health-related self-efficacy and frequency of adolescent-conducted healthcare interactions among adolescents and young adults with CF, type 1 diabetes, or inflammatory bowel disease (i.e. it is not focused on improving adherence to inhaled therapies).
Jackson 2017	Attempted contact with study authors on several occasions for clarification on methods and results, but received no reply.
Landau 2021	This study aims to evaluate a 12-month problem-solving intervention to improve adherence in adolescents and adults with CF, but it is not an RCT (no control group).
Marciel 2010	Attempted contact with study authors on several occasions for clarification on methods and results, but received no reply. Unclear if the focus of the intervention is on improving adherence to inhaled therapies.
Martinez 2017	This study aims to assess a pulmonary rehabilitation program to increase adherence to airway clearance techniques (ACT) in CF; it is not focused on improving adherence to inhaled therapies. Contacted first author who clarified that ACT included "active cycle breathing technique, autogenic drainage, chest physiotherapy, positive expiratory pressure (PEP), and oscillating devices for airway clearance".
McDonald 2007	Attempted contact with study authors for clarification on methods and results, but one author was unable to provide additional information, and we received no reply from the other study authors.

Study	Reason for exclusion
Meyers 1975	This is not an intervention study - it describes a study to determine the relationship between degree of compliance to antibiotics and severity of CF.
Modi 2010	This study describes an RCT comparing three airway secretion clearance therapies in CF: 1) postural drainage and percussion, 2) flutter device or 3) high frequency chest wall oscillation - i.e. it is not focused on improving adherence to inhaled therapies.
Montero-Ruiz 2020	This RCT aims to evaluate the effects of music therapy as an adjunct to chest physiotherapy (airway clearance techniques) in children with CF, and does not evaluate a psychological intervention for improving adherence to inhaled therapies.
NCT00688051	This study aimed to assess changes in adherence in adolescents with CF after using a simulation game "My Life with CF", but it is not an RCT - no control group.
NCT01025258	This study aimed to assess the impact of an intervention on improving adherence to chronic medications and improve clinical outcomes in CF patients, but it is not an RCT - no control group.
NCT02286050	This study aimed to assess the effect of a nursing programme on patient satisfaction, adherence and self-efficacy, but it is not an RCT - no control group.
NCT02501369	This study aims to investigate the use of a positive parenting programme to improve treatment adherence in CF, but it is not an RCT (no control group).
NCT02906826	This is a non-randomised study and is focused on adherence to airway clearance techniques (i.e. PEP mask), not inhaled therapies.
NCT03052231	This RCT aims to evaluate the feasibility of interactive mobile health information to enhance patient care at a CF centre. Attempted contact with Principal Investigator listed on clinical trial register on several occasions for clarification on methods and results, but received no reply.
NCT03226795	This study aims to assess an intervention comprising medication reminders, coaching and behavioural skills for improving adherence to treatments in adults with CF, but it is not an RCT (no control group).
NCT03304028	This study is focused on the early detection of pulmonary exacerbations and does not assess a psychological intervention for improving adherence to inhaled therapies in people with CF.
NCT03518697	This is a non-randomised study which aims to evaluate the effects of a partially supervised exercise program on different aspects of physical fitness, and is not focused on improving adherence to inhaled therapies.
NCT03938324	This RCT aims to evaluate a peer support coaching intervention to improve activated chronic illness self-management among adolescents and young adults with childhood onset chronic conditions (e.g. CF along with many other conditions). It is not focused on improving adherence to inhaled therapies.
NCT03992027	This RCT aims to evaluate a CF-specific CBT intervention for preventing depression and anxiety among adults with CF; it is not focused on improving adherence to inhaled therapies.
NCT04017559	This study aims to assess the clinical impact of a motivational interviewing intervention on inhaled antibiotic adherence in adults with CF, but is not an RCT (no control group).
NCT04096664	This study aims to evaluate the efficiency and acceptability of a medical device for bronchial clearance in patients with CF, it is not focused on improving adherence to inhaled therapies and does not assess a psychological intervention.

Study	Reason for exclusion
NCT04217889	This is an observational study that aims to assess the factors that influence adherence to chest physiotherapy adherence in adults with CF; it is not an RCT.
NCT04453358	This trial is focused on improving adherence to airway clearance techniques (i.e. vest therapy), not inhaled therapies.
NCT04696484	This study aims to assess the feasibility of a brief intervention for informing conversations between patients and physicians in routine tele-health and in-person adult CF care, but it is not an RCT (no control group).
O'Hayer 2021	This feasibility study examined whether Acceptance and Commitment Therapy (ACT) is a feasible and potentially effective treatment for people with CF and symptoms of anxiety and/or depression, but it is not an RCT (no control group).
Ohn 2018	This is not a study - it is a review focused on discussing treatment adherence with people with CF.
Parkins 2008	This is a study assessing the effect of an intervention to increase knowledge of CF for postgraduate medical trainees (i.e. not focused on improving adherence to inhaled therapies in people with CF).
Pendleton 2000	This is not a study - it is a commentary on adherence in CF.
Petzel 1991	This abstract describes a study which aims to evaluate adherence to medical/ behavioral interventions through an intervention targeting parents of children with CF. However, the adherence referred to includes completion of worksheets or home diaries by participants rather than adherence to treatments (i.e. wrong outcomes).
Polineni 2017	This is a pilot trial to explore the feasibility of tele-coaching as an intervention to improve adherence to treatments (using data collected from vest photo capture and eTrack nebulisers) in people with CF, but it is not an RCT (no control group).
Quittner 1998	Attempted contact with study authors on several occasions to access the study results, but received no reply.
Rode 2008	Contacted study author who provided digital copy of thesis. Thesis describes a study which aimed to assess the impact of providing patients with a new nebuliser (associated with a decrease in treatment times) on quality of life and adherence amongst a cohort of 17 people with CF (i.e. it did not investigate a psychological intervention for improving adherence to inhaled therapies in CF).
Ruddy 2015	This RCT aimed to evaluate the safety of a standardised yoga program among young people with CF. Contacted first author who confirmed that adherence to inhaled therapies was not evaluated in the study.
Sadprasid 2021	This paper presents Percussion Hero, a game designed to improve adherence to chest physical therapy for people with CF. It is not focused on improving adherence to inhaled therapies and does not describe a study.
Schandevyl 2021	This study aims to evaluate a medication adherence– enhancing simulation intervention in children with CF, but it is not an RCT (no control group).
Strawhacker 2004	This is not a study - it is a review focused on a collaborative clinical and school approach to caring for children with CF.
Trapp 1998	This is a parallel CCT of 2 interventions with a convenience control group sample to assess whether self-administration of drugs leads to greater knowledge about medications. This is a non-randomised study and is not focused on psychological interventions for improving adherence to inhaled therapies.

Study	Reason for exclusion
Viviani 2006	This is a trial aimed at assessing whether adults with CF could benefit from a telemonitoring system that enables them to test their spirometry and oximetry at home. It is not focused on inhaled therapies.
Wood 2020	This is an RCT aimed at evaluating a smartphone application for reporting symptoms in adults with CF (which is intended to facilitate the early identification of symptoms suggestive of a respiratory exacerbation), and does not describe a psychological intervention for improving adherence to inhaled therapies in people with CF.

ACT: airway clearance techniques OR Acceptance and Commitment Therapy
CBT: cognitive behavioural therapy
CCT: controlled clinical trial
CF: cystic fibrosis
PEP: positive expiratory pressure
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Jirasek 2022

Study name	'CF Hero' application as a motivational and therapeutic tool for kids and teenagers with cystic fibrosis
Methods	Multicentre, randomised, prospective cross-over trial conducted in the Czech Republic.
Participants	Children and adolescents with CF (eligibility criteria not reported).
Interventions	**Intervention arm**: use of motivational (reward-based) mobile phone application ('CF Hero') for guided inhalation for 3 months. **Control arm**: unguided inhalation (without 'CF Hero' app) for 3 months. Since this is a cross-over trial, participants were randomised to use the 'CF Hero' app for guided inhalation for 3 months. They were then switched to unguided inhalation (without app) for another 3 months.
Outcomes	**Primary outcome** 1. Inhalation drug consumption was checked after 3 and 6 months to evaluate adherence to inhaled therapy. The prescribed amount of medication was compared with the amount consumed by collecting containers with unused saline solution and empty dornase alfa containers. **Secondary outcomes** 1. Spirometry measured at baseline and after 3 and 6 months. 2. Quality of life (CFQ-R) measured at baseline and after 3 and 6 months. 3. Thoracic excursions are measured at baseline and after 3 and 6 months.
Starting date	Not stated.
Contact information	M Jirásek, Charles University, Second Faculty of Medicine, Prague, Czech Republic.
Funding source	Not stated.
Clinical trial register	Not available.
Notes	

O'Hayer 2019

Study name	Acceptance and Commitment Therapy vs. Supportive Psychotherapy With Cystic Fibrosis Patients
Methods	Parallel, 2-arm, non-blinded RCT being conducted at 7 sites in the USA.
Participants	**Target sample size:** 210 adults with CF **Eligibility criteria** Males and females aged 18 years and above. Able to read and understand English. Diagnosis of CF. PHQ-9 score > 4 or GAD-7 score > 4. **Exclusion criteria** History of suicidal attempts or acute suicidal ideation on clinical assessment. Presence of psychotic disorder or symptoms. Pregnant women. Presence of psychiatric disorders that interfere with the participation of the study, judged by the study or treating clinician. Presence of other medical conditions that interfere with participation in the study, judged by the study or treating clinician.
Interventions	**Intervention arm**: 6 sessions of Acceptance and Commitment Therapy (ACT) delivered via video call in which participants learn new ways to manage uncomfortable experiences and feelings and to engage in positive behaviours. Duration of intervention phase: 6 weeks (6x weekly sessions of ACT). **Control arm**: supportive psychotherapy in which participants talk about their experiences to date in a cohort of adults with CF.
Outcomes	**Primary outcomes** 1. Change from baseline in presence of anxiety disorder (GAD-7 score) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 2. Change from baseline in symptoms of depression (PHQ-9) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 3. Change from baseline in self-reported anxiety (BAI) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 4. Change from baseline in severity of depression (BDI-II) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) **Secondary outcomes** 1. Change in FEV_1/FVC ratio (measured at 3 months after the study) 2. Change from baseline in cognitive fusion (CFQ13) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 3. Change from baseline in acceptance measures (AAQ-II) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 4. Change from baseline in medication adherence (Self-Reported Medication Adherence Questionnaire) (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment) 5. Participant change in re-hospitalization and unscheduled office visits secondary to CF exacerbations (measured at 3 months after the study)

O'Hayer 2019 *(Continued)*

	6. Number of scheduled CF clinic visits kept (measured at 3 months after the study) 7. Change in BMI (measured at 3 months after the study) 8. Change in PRO measures, including quality of care questionnaire (measured after 6 weeks of treatment and 3 months after the end of 6 sessions of treatment)
Starting date	1 July 2019
Contact information	Dr C Virginia F O'Hayer, 919-943-6738 virginia.ohayer@jefferson.edu
Funding source	Supported by Boomer Esiason Foundation.
Clinical trial register	clinicaltrials.gov/ct2/show/NCT04114227
Notes	

Phan 2021

Study name	Feasibility of a Mobile Medication Plan Application in CF patient care (MAP)
Methods	Parallel, 2-arm, prospective, pilot RCT being conducted at 5 sites in the USA.
Participants	**Eligibility criteria** **Clinician participants** CF care team member from any discipline, designated by the site PI and CF team. Willing to use MAP as part of CF care. **Patient participants** Males or females aged 12 years of age and older at Study Visit 1. Documented CF diagnosis (physician diagnosed). Ability to understand verbal and written English. Access to mobile device such as a tablet or smartphone (iPhone/iPad/iTouch or Android device). Willingness to use the MAP application. Currently taking at least 1 of the following chronic medications and willing to use AdhereTech pill bottles for oral medications or eTrack nebuliser for nebulised medications listed below: nebulised agents, dornase alfa, hypertonic saline, inhaled tobramycin, inhaled aztreonam, inhaled colistimethate, oral agents, azithromycin. **Caregiver participants** (for patient participants age under 18 years) Child is consented to participate in the study. Ability to understand verbal and written English. **Exclusion criteria** **Clinician participants** Previous use of MAP (with people with CF or self) in the last 12 months - when used with people with CF, defined as use in 5 or more.

Phan 2021 *(Continued)*

	Patient participants Previous use of MAP in the last 12 months - defined as use for 4 weeks or longer in own care. Presence of a condition or abnormality that in the opinion of the PI would compromise the safety of the individual or the quality of the data including, but not limited to, diagnosis of intellectual or developmental disability (e.g. autism); and/or history of lung transplant. Planned or scheduled hospitalisation during study period of up to 36 weeks. **Caregiver participants** (for patient participants age under 18 years) Previous use of MAP in the last 12 months - defined as use for 4 weeks or longer in child's or own care **Actual enrollment**: 105 participants.
Interventions	**Intervention arm**: web-based, mobile medication management application (MedActionPlan® (MAP)) to encourage self-management by reinforcing adherence and education about treatment regimens and continued use of eTrack nebuliser with or without AdhereTech pill bottles as measures of adherence. **Control arm**: usual care and continued use of eTrack nebuliser with or without AdhereTech pill bottles as measures of adherence.
Outcomes	**Primary outcomes** 1. Mean score of iFAQ for participants assessed by 5-point Likert scale (strongly disagree/disagree/neither agree or disagree/agree/strongly agree) to assess engagement, usefulness, functionality or ease of use, aesthetics, information and satisfaction of the web portal and application (measured at week 24) 2. Mean score of iFAQ for clinicians assessed by 5-point Likert scale (strongly disagree/disagree/neither agree or disagree/agree/strongly agree) to assess engagement, usefulness, functionality or ease of use, aesthetics, information and satisfaction of the web portal and application (measured at up to 30 months) **Secondary outcomes** 1. Change from baseline in KDM-CF scores (knowledge of disease management for general health, lung health, nutrition, treatments) (measured at week 24) 2. Change from baseline in CF-MBQ scores to measure impact of interventions on specific social cognitive beliefs across 5 domains (motivation, self-efficacy, perceived importance of medication, and decisional balance to take or miss medications) (measured at week 24) 3. Mean change from baseline in adherence from data collected from AdhereTech pill bottles and eTrack nebulizers (scored as a 'per drug analysis' of adherence and a composite score based on prescribed medications and medication/doses taken) (measured at week 24) 4. Change from baseline in CF-MQ scores assessing knowledge about prescribed CF medications (medication purpose, administration, dose, and dosing frequency based on own prescribed regimen) (measured at week 24)
Starting date	5 September 2018
Contact information	Dr Gregory Sawicki, Boston Children's Hospital, USA Gregory.Sawicki@childrens.harvard.edu
Funding source	Not stated.
Clinical trial register	clinicaltrials.gov/ct2/show/NCT03637504
Notes	**Sponsor**: Boston Children's Hospital

Phan 2021 *(Continued)*

	Recruitment completed.

Thee 2021

Study name	A multicentre, randomised, controlled trial on coaching and telemonitoring in patients with cystic fibrosis: conneCT CF
Methods	Parallel, 2-arm, non-blinded RCT being conducted at four CF centres in Germany.
Participants	**Target sample size**: 402 participants with CF (391 participants required according to power calculations). **Eligibility criteria** Confirmed diagnosis of CF. Aged 12 years or older. Able to give written informed consent or assent. At least 1 pulmonary exacerbation in the year before enrolment (defined according to the Bilton criteria (modified Fuchs criteria) as an episode of decreased pulmonary function caused by infection and treated with additional antibiotic therapy for at least 2 of the following reasons: change in the amount of sputum or colour, increased cough, malaise, fatigue, lethargy, anorexia or weight loss, decrease in FEV_1 by 10% or more from the last previously recorded values and/or radiographic changes indicative of pulmonary infection or increased dyspnoea). FEV_1 below 90% predicted at the day of inclusion. If receiving a CFTR modulator therapy, participants must be stable on this treatment for the last 3 preceding months with no planned change in CFTR modulator treatment during the study period. **Exclusion criteria** An acute depressive or psychotic episode. Substantial immobility. No prescribed inhaled therapy. Insufficient knowledge of the German language. Lack of possession of a smartphone. Post lung transplant. Unable to perform lung function testing, or lung function testing is contraindicated (e.g., because of pneumothorax or lung surgery within the previous 3 months). Participation in other intervention studies unless it is an open-label study with the participation of already 3 or more months without planned cessation within our study duration. Sociodemographic and anthropometric data will be recorded.
Interventions	**Intervention arm**: objective, continuous monitoring of adherence to inhaled therapies, weekly home spirometry using electronic devices with data transmission to participants and physicians combined with video-conferencing, a self-management app and professional telephone coaching. Duration of intervention phase: 18 months (coaching will take place for first 12 months of the intervention).

Thee 2021 *(Continued)*

	Control arm: usual care (scheduled visits with the CF physician take place quarterly; further visits only occur at the participant's request if health status deteriorates). Control group also receives a telemedicine-capable nebuliser (data on adherence will be automatically tracked for final evaluation, but without any data access for participants or CF physicians in this group).
Outcomes	**Primary outcome** 1. Time to first protocol-defined pulmonary exacerbation after initiation of the intervention phase **Secondary outcomes** 1. Number of pulmonary exacerbations 2. Time between pulmonary exacerbations 3. Adherence to inhalation therapy 4. Changes in FEV_1 and FVC from baseline 5. Number of CF-associated hospital admissions 6. Changes in HRQoL (assessed by CFQ-R German version and EQ-5D-5L/EQ-5D-Y-5L) 7. Changes in non-somatic depression symptoms (Beck Depression Inventar-Fast Screen) 8. Number of days absent from work or school 9. CF-associated medical treatment and care 10.Healthcare-related costs
Starting date	1 March 2021
Contact information	Marcus Alexander Mall, Berlin Institute of Health, Berlin, Germany marcus.mall@charite.de
Funding source	Published protocol states: "Material support is provided by PARI Medical Holding GmbH, Starnberg, Germany. The design, management, analysis and reporting of the study are entirely independent of the funder."
Clinical trial register	drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00024642
Notes	Competing interests: "The authors declare that they have no competing interests."

White 2017

Study name	Randomised controlled trial of a web-based intervention for adherence in cystic fibrosis.
Methods	Parallel, 2-arm RCT conducted at a single adult CF centre in the UK (Leeds).
Participants	**Target sample size:** 100 adults with CF (recruitment completed: intervention arm = 49; control arm = 51). **Eligibility criteria** Diagnosis of CF and attending Leeds Adult CF unit for their complete care. Males or females aged 16 to 60 years old. Consecutive volunteers recruited at time of clinical stability (end of inpatient treatment or at outpatient clinic). Being prescribed a minimum of 3 specified medications for at least 6 months prior to signing the informed consent form: azithromycin, hypertonic saline, TOBI®, Pulmozyme®, pancreatic en-

White 2017 *(Continued)*

	zyme replacement therapy, oral antibiotics, fat-soluble vitamins, insulin, inhaled compounded tobramycin, oral nutritional supplements, insulin, AZLI. **Exclusion criteria** Pregnancy. Acceptance on the lung transplant list (note: participation in this study will not delay or exclude individuals from being placed on the transplant list in the future or receiving a transplant once enrolled in the study).
Interventions	**Intervention arm**: web-based intervention comprising 6 interactive online modules (Nutrition, Pancreatic enzyme replacement therapy, Vitamins, Liver disease, Antibiotics, and Respiratory) and incorporated interactive materials and patient video inserts. 1 to 3 treatments for improved adherence will be identified jointly with the clinician at the start of the study from 6 areas of focus: i.e. nutrition, enzymes, liver medications, airways treatments, vitamins and antibiotics. In the intervention arm, participants will be provided with online information for the identified treatments which shows how medications and treatments work, contains 'patient video stories' of their own treatment experiences and is interactive, asking participants to undertake specific tasks as they view the information and to provide feedback and post questions prior to their planned 2-monthly appointments. Feedback or questions can then be answered at the next 2-monthly appointment. **Control arm**: usual care (participants will receive information from clinicians in the usual way, through individual discussion, and fact sheets and clinician explanations). In total, participants will have 7 appointments according to existing defined standards of care at start, 2, 4, 6, 8, 10 and 12 months.
Outcomes	**Primary outcome** 1. Change from baseline in measures of adherence (MPR or by self-report (DMI-CF)) (recorded at 1 year) **Secondary outcomes** 1. Change from baseline in CF medication knowledge (measured at baseline, 6 months and 12 months) 2. HRQoL measured by the validated CF-QoL (measured at baseline and 12 months) 3. Change from baseline in lung function (FEV_1% predicted and FVC) (measured at baseline and 12 months) 4. BMI (measured at baseline, 6 months and 12 months) 5. Vitamin A, D, E levels (measured at baseline, 6 months and 12 months) 6. Coefficient of variation for lung function: for each measure, the coefficient of variation will be calculated from the variation of the highest and lowest values of lung function over the previous 6 months (measured at baseline, 6 months and 12 months) 7. Number of pulmonary exacerbations requiring intravenous therapy (from 1 year prior to baseline until start; and from baseline to 1 year) 8. CF hospitalisations (including IV treatment days) (from 1 year prior to baseline until start; and from baseline to 1 year) Participants will complete 2 questionnaires at the beginning and end of the study. The first asks about the medications and treatments currently taken and any reasons they may have difficulty in taking prescribed treatments. The second asks about their quality of life. A blood sample will be taken at the start, middle and end of the study, to check fat soluble vitamin levels A, D and E. At baseline and end (12 months), their pharmacist will be contacted to provide details on how many prescriptions have been collected within the previous 6 months. At the beginning and end of the 12-month period, participants will also complete a knowledge questionnaire for each of their individual and agreed areas of focus, to assess change in knowledge.

White 2017 *(Continued)*

Starting date	1 February 2016
Contact information	Dr Helen White, Nutrition and Dietetic Group, Leeds Beckett University, Leeds, LS1 3HE, UK +44 (0)113 812 4994 H.White@leedsbeckett.ac.uk
Funding source	Supported by a grant from Gilead UK.
Clinical trial register	trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN37959826
Notes	Recruitment completed. Contacted first author who confirmed they are writing up the results of the study.

AAQ-II: Acceptance and Action Questionnaire
ACT: Acceptance and Commitment Therapy
AZLI: aztreonam lysine
BAI: Beck Anxiety Inventory
BDI-II: Beck Depression Inventory-II
BMI: body mass index
CF: cystic fibrosis
CF-MBQ: CF Medication Belief Questionnaire
CF-MQ: CF Medication Questionnaire
CFQ13: Cognitive Fusion Questionnaire
CFQ-R: Cystic Fibrosis Questionnaire - Revised
CFRD: cystic fibrosis-related diabetes
CFTR: cystic fibrosis transmembrane conductance regulator
DMI-CF: Disease Management Interview - CF
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GAD-7: General Anxiety Disorder 7-item anxiety scale (Spitzer 2006)
HRQoL: health-related quality of life
iFAQ: Intervention Feasibility and Acceptability questionnaire
IV: intravenous
KDM-CF: Knowledge of Disease Management-CF questionnaire
MPR: medication possession ratio
PHQ-9: Patient Health Questionnaire 9
PI: principal investigator
PRO: patient rated outcome
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Psychological interventions versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Adherence - percentage of prescribed inhaled therapies taken (objective recorded measures)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1.2 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1.3 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2 Adherence - percentage of prescribed inhaled therapies taken (objective recorded measures - adjusted mean difference)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.1 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3 Adherence - percentage of prescribed inhaled therapies taken (subjective measures)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.2 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.3 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.4 Over 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Adherence to dornase alfa	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Over 3 months and up to 6 months	2	46	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.62, 0.67]
1.4.2 Over 6 months and up to 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.43 [-0.41, 1.27]
1.4.3 Over 12 months	1	21	Std. Mean Difference (IV, Random, 95% CI)	0.91 [-0.00, 1.81]
1.5 Adherence to inhaled antibiotics (mean score on MMAS-8)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Over 3 months and up to 6 months	2	43	Std. Mean Difference (IV, Random, 95% CI)	0.49 [-1.01, 1.98]
1.5.2 Over 6 months and up to 12 months	1	23	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.99, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.3 Over 12 months	1	19	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.91, 0.91]
1.6 Adherence to inhaled steroids (subjective measure)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Adherence to hypertonic saline (subjective measure)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Adherence to bronchodilators (subjective measure)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Anxiety (endpoint data)	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9.1 Up to 3 months	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9.2 Over 3 months and up to 6 months	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9.3 Over 6 months and up to 12 months	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10 Anxiety (adjusted mean difference)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11 Depression (endpoint data)	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.1 Up to 3 months	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.2 Over 3 months and up to 6 months	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.3 Over 6 months and up to 12 months	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.4 Over 12 months	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.12 Depression (adjusted mean difference)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.12.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.12.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13 QoL: Quality of Well-being scale (mean score)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14 QoL: Physical functioning (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 Up to 3 months	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.57, 0.76]
1.14.2 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.57, 0.26]
1.14.3 Over 6 months and up to 12 months	3	1089	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.04, 0.20]
1.14.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-1.10, 0.51]
1.15 QoL: Physical functioning (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.15.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.15.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.16 QoL: Emotional functioning (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.16.1 Up to 3 months	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.14, 1.22]
1.16.2 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.58, 0.25]
1.16.3 Over 6 months and up to 12 months	3	1089	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.11, 0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-1.23, 0.39]
1.17 QoL: Emotional functioning (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.17.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.17.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.18 QoL: Social functioning (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.18.1 Up to 3 months	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.45 [-0.22, 1.13]
1.18.2 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.43, 0.41]
1.18.3 Over 6 months and up to 12 months	3	1089	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.12, 0.11]
1.18.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.95, 0.65]
1.19 QoL: Social functioning (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.19.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.19.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.20 QoL: Treatment burden (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.20.1 Up to 3 months	1	5	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-1.50, 2.20]
1.20.2 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.44, 0.39]
1.20.3 Over 6 months and up to 12 months	3	1090	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.01, 0.28]
1.20.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.05, 0.56]
1.21 QoL: Treatment burden (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.21.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.22 QoL: Role limitations (endpoint data)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.22.1 Over 3 months and up to 6 months	2	87	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.54, 0.49]
1.22.2 Over 6 months and up to 12 months	2	412	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.21, 0.18]
1.22.3 Over 12 months	1	22	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-1.31, 0.38]
1.23 QoL: Role limitations (adjusted data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.23.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.24 QoL: Body image (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.24.1 Up to 3 months	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.00, 1.38]
1.24.2 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.56, 0.28]
1.24.3 Over 6 months and up to 12 months	3	1089	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.03, 0.20]
1.24.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-1.59, 0.08]
1.25 QoL: Body image (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.25.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.25.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.26 QoL: Vitality (endpoint data)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.26.1 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.77, 0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.26.2 Over 6 months and up to 12 months	2	413	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.99, 0.34]
1.26.3 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-1.28, 0.34]
1.27 QoL: Vitality (adjusted data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.27.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.28 QoL: Eating disturbance (endpoint data)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.28.1 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.38, 0.45]
1.28.2 Over 6 months and up to 12 months	3	1089	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.01, 0.23]
1.28.3 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.46 [-0.35, 1.27]
1.29 QoL: Eating disturbance (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.29.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.29.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.30 QoL: Weight problems (endpoint data)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.30.1 Over 3 months and up to 6 months	2	88	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.45, 0.40]
1.30.2 Over 6 months and up to 12 months	2	413	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.03, 0.36]
1.30.3 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.80, 0.80]
1.31 QoL: Weight problems (adjusted data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.31.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.32 QoL: Respiratory symptoms (endpoint data)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

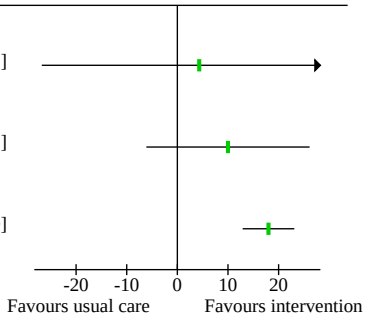
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.32.1 Up to 3 months	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.42, 0.92]
1.32.2 Over 3 months and up to 6 months	2	88	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.78, 0.07]
1.32.3 Over 6 months and up to 12 months	3	1085	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.10, 0.22]
1.32.4 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-1.27, 0.35]
1.33 QoL: Respiratory symptoms (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.33.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.33.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.34 QoL: Digestive symptoms (endpoint data)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.34.1 Over 3 months and up to 6 months	2	87	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.10, 0.22]
1.34.2 Over 6 months and up to 12 months	3	1084	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.08, 0.16]
1.34.3 Over 12 months	1	23	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.33, 0.34]
1.35 QoL: Digestive symptoms (adjusted data)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.35.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.35.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.36 QoL: Health perceptions (endpoint data)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.36.1 Over 3 months and up to 6 months	2	89	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.69, 0.17]
1.36.2 Over 6 months and up to 12 months	2	413	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.20, 0.19]
1.36.3 Over 12 months	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.16, 0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.37 QoL: Health perceptions (adjusted data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.37.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.38 QoL: Treatment issues (endpoint data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.38.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.39 QoL: Career concerns (endpoint data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.39.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.40 QoL: Interpersonal relationships (endpoint data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.40.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.41 QoL: Concerns for the future (endpoint data)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.41.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.42 FEV1 % predicted (endpoint data)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.42.1 Up to 3 months	2	40	Mean Difference (IV, Random, 95% CI)	-3.25 [-18.13, 11.64]
1.42.2 Over 3 months and up to 6 months	2	95	Mean Difference (IV, Random, 95% CI)	-2.98 [-12.50, 6.55]
1.42.3 Over 6 months and up to 12 months	2	593	Mean Difference (IV, Random, 95% CI)	3.20 [-0.59, 6.99]
1.42.4 Over 12 months	1	36	Mean Difference (IV, Random, 95% CI)	-4.20 [-19.31, 10.91]
1.43 FEV1 % predicted (adjusted mean difference)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.43.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.43.2 Over 6 months and up to 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.44 Number of pulmonary exacerbations	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.44.1 Over 3 months and up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.45 Pulmonary exacerbations incidence rate (unadjusted data)	2		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.45.1 Over 3 months and up to 6 months	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.45.2 Over 6 months and up to 12 months	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.46 Pulmonary exacerbations incidence rate (adjusted data)	2		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.46.1 Over 3 months and up to 6 months	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected
1.46.2 Over 6 months and up to 12 months	1		Rate Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Psychological interventions versus usual care, Outcome 1: Adherence - percentage of prescribed inhaled therapies taken (objective recorded measures)

	Intervention			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Up to 3 months								
Quinn 2004 (1)	48.8	47.44	16	44.48	45.93	19	4.32 [-26.77 , 35.41]	
1.1.2 Over 3 months and up to 6 months								
Hind 2017 (2)	47.7	33.8	29	37.7	27.1	26	10.00 [-6.12 , 26.12]	
1.1.3 Over 6 months and up to 12 months								
Wildman 2022 (3)	52.9	31.4	293	34.9	31.7	295	18.00 [12.90 , 23.10]	



Footnotes

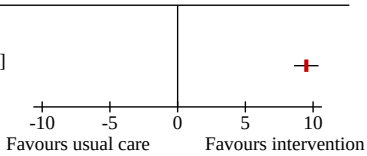
(1) Adherence to prescribed twice daily aerosolised antibiotics (ITT)

(2) Endpoint data

(3) Weekly objectively measured effective adherence (sum of doses taken/sum of doses prescribed) averaged over weeks 3–52 post-randomisation

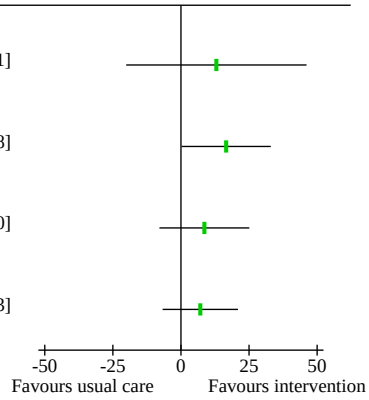
Analysis 1.2. Comparison 1: Psychological interventions versus usual care, Outcome 2: Adherence - percentage of prescribed inhaled therapies taken (objective recorded measures - adjusted mean difference)

Study or Subgroup	Mean Difference	SE	Intervention Total	Usual care Total	Mean Difference IV, Random, 95% CI
1.2.1 Over 6 months and up to 12 months					
Wildman 2022	9.5	0.4592	293	295	9.50 [8.60 , 10.40]



Analysis 1.3. Comparison 1: Psychological interventions versus usual care, Outcome 3: Adherence - percentage of prescribed inhaled therapies taken (subjective measures)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.3.1 Up to 3 months							
Cottrell 1996 (1)	74	33	10	61	42	10	13.00 [-20.11 , 46.11]
1.3.2 Over 3 months and up to 6 months							
Downs 2006 (2)	87.5	32.7	26	70.9	26.8	25	16.60 [0.22 , 32.98]
1.3.3 Over 6 months and up to 12 months							
Downs 2006 (2)	86.1	31.2	26	77.5	28.9	25	8.60 [-7.90 , 25.10]
1.3.4 Over 12 months							
Downs 2006 (3)	81.3	26.1	26	74.2	24.3	25	7.10 [-6.73 , 20.93]



Footnotes

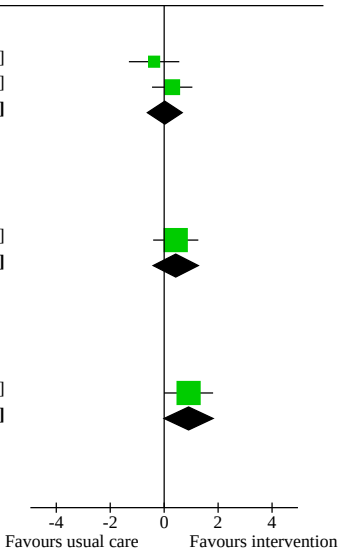
(1) Endpoint data

(2) Percentage of prescribed aerosol taken (measured using participant self-report diary card) (ITT) - endpoint data

(3) Percentage of prescribed aerosol taken (measured using participant self-report diary card) (ITT)

Analysis 1.4. Comparison 1: Psychological interventions versus usual care, Outcome 4: Adherence to dornase alfa

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Over 3 months and up to 6 months								
Gur 2016 (1)	4	1.32	9	4.44	0.88	9	40.9%	-0.37 [-1.31 , 0.56]
Knudsen 2016 (2)	4.45	2.44	13	3.72	2.33	15	59.1%	0.30 [-0.45 , 1.05]
Subtotal (95% CI)			**22**			**24**	**100.0%**	**0.02 [-0.62 , 0.67]**
Heterogeneity: Tau² = 0.04; Chi² = 1.21, df = 1 (P = 0.27); I² = 17%								
Test for overall effect: Z = 0.07 (P = 0.94)								
1.4.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	4.67	2.37	9	3.53	2.67	15	100.0%	0.43 [-0.41 , 1.27]
Subtotal (95% CI)			**9**			**15**	**100.0%**	**0.43 [-0.41 , 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.00 (P = 0.31)								
1.4.3 Over 12 months								
Knudsen 2016 (3)	4.7	1.87	11	2.98	1.77	10	100.0%	0.91 [-0.00 , 1.81]
Subtotal (95% CI)			**11**			**10**	**100.0%**	**0.91 [-0.00 , 1.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.95 (P = 0.05)								

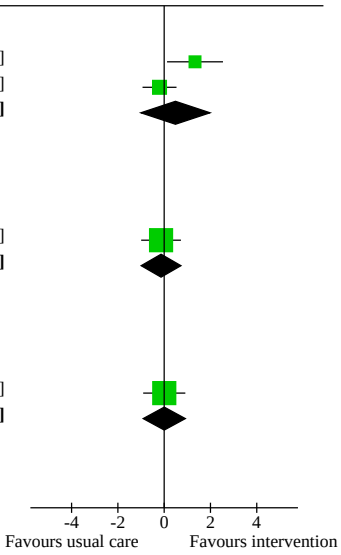


Footnotes

(1) Mean score on self-report adherence questionnaire - Endpoint data
(2) Mean score on MMAS-8 (Endpoint data)
(3) Mean score on MMAS-8 - Follow-up (one year post-intervention) endpoint data

Analysis 1.5. Comparison 1: Psychological interventions versus usual care, Outcome 5: Adherence to inhaled antibiotics (mean score on MMAS-8)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Over 3 months and up to 6 months								
Gur 2016	4.63	1.19	8	2.33	2.07	6	44.9%	1.33 [0.12 , 2.54]
Knudsen 2016 (1)	4.52	2.45	13	5.03	2.48	16	55.1%	-0.20 [-0.93 , 0.53]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**0.49 [-1.01 , 1.98]**
Heterogeneity: Tau² = 0.92; Chi² = 4.52, df = 1 (P = 0.03); I² = 78%								
Test for overall effect: Z = 0.64 (P = 0.52)								
1.5.2 Over 6 months and up to 12 months								
Knudsen 2016 (1)	4.97	2.47	8	5.3	2.31	15	100.0%	-0.13 [-0.99 , 0.72]
Subtotal (95% CI)			**8**			**15**	**100.0%**	**-0.13 [-0.99 , 0.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
1.5.3 Over 12 months								
Knudsen 2016 (2)	4.4	2.46	8	4.39	2.32	11	100.0%	0.00 [-0.91 , 0.91]
Subtotal (95% CI)			**8**			**11**	**100.0%**	**0.00 [-0.91 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.01 (P = 0.99)								

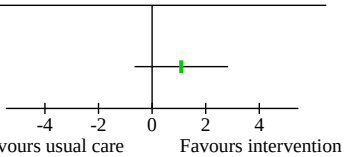


Footnotes

(1) Mean score on MMAS-8 (Endpoint data)
(2) Mean score on MMAS-8 (Follow-up (one year post-intervention) endpoint data)

Analysis 1.6. Comparison 1: Psychological interventions versus usual care, Outcome 6: Adherence to inhaled steroids (subjective measure)

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.6.1 Over 3 months and up to 6 months								
Gur 2016 (1)	3.22	2.11	9	2.13	1.55	8	1.09 [-0.66 , 2.84]	

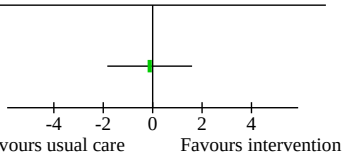


Footnotes

(1) Mean score on self-report adherence questionnaire - Endpoint data

Analysis 1.7. Comparison 1: Psychological interventions versus usual care, Outcome 7: Adherence to hypertonic saline (subjective measure)

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.7.1 Over 3 months and up to 6 months								
Gur 2016 (1)	3.88	1.46	8	4	2	8	-0.12 [-1.84 , 1.60]	

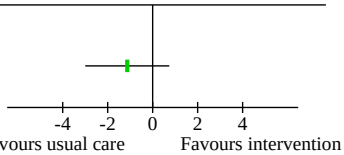


Footnotes

(1) Mean score on self-report adherence questionnaire - Endpoint data

Analysis 1.8. Comparison 1: Psychological interventions versus usual care, Outcome 8: Adherence to bronchodilators (subjective measure)

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.8.1 Over 3 months and up to 6 months								
Gur 2016 (1)	3	1.69	8	4.13	2.1	8	-1.13 [-3.00 , 0.74]	

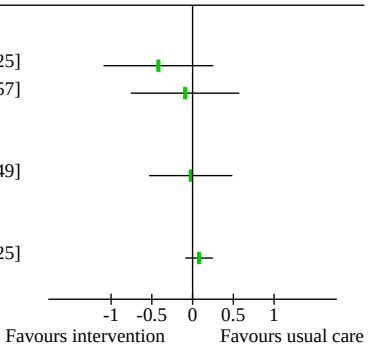


Footnotes

(1) Mean score on self-report adherence questionnaire - Endpoint data

Analysis 1.9. Comparison 1: Psychological interventions versus usual care, Outcome 9: Anxiety (endpoint data)

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Std. Mean Difference IV, Random, 95% CI
1.9.1 Up to 3 months							
Quinn 2004 (1)	32.94	9.78	16	37.37	10.75	19	-0.42 [-1.09 , 0.25]
Quinn 2004 (2)	4.59	3.24	16	4.9	3.36	19	-0.09 [-0.76 , 0.57]
1.9.2 Over 3 months and up to 6 months							
Hind 2017 (3)	4.1	4.1	31	4.2	4.4	28	-0.02 [-0.53 , 0.49]
1.9.3 Over 6 months and up to 12 months							
Wildman 2022	4.9	5.3	262	4.5	4.8	273	0.08 [-0.09 , 0.25]

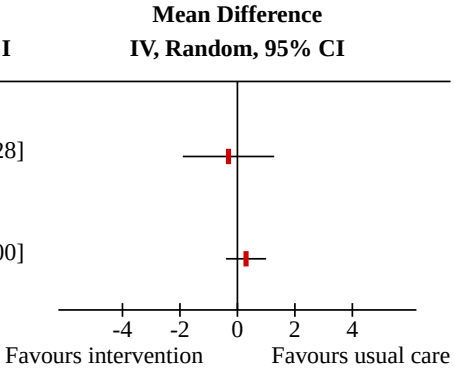


Footnotes

(1) Mean score on STAI-short form - endpoint data (ITT)
(2) Mean score on HADS - endpoint data (ITT)
(3) Mean score on GAD-7 - endpoint data

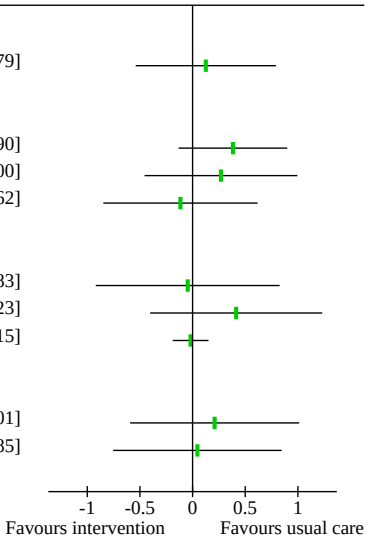
Analysis 1.10. Comparison 1: Psychological interventions versus usual care, Outcome 10: Anxiety (adjusted mean difference)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.10.1 Over 3 months and up to 6 months			
Hind 2017	-0.31	0.8112	-0.31 [-1.90 , 1.28]
1.10.2 Over 6 months and up to 12 months			
Wildman 2022	0.3	0.3571	0.30 [-0.40 , 1.00]



Analysis 1.11. Comparison 1: Psychological interventions versus usual care, Outcome 11: Depression (endpoint data)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
1.11.1 Up to 3 months							
Quinn 2004 (1)	2.71	2.71	16	2.37	2.59	19	0.13 [-0.54 , 0.79]
1.11.2 Over 3 months and up to 6 months							
Hind 2017 (2)	7.3	5.2	31	5.3	5.1	28	0.38 [-0.13 , 0.90]
Knudsen 2016 (3)	13.4	11.2	13	10.9	6.95	17	0.27 [-0.46 , 1.00]
Knudsen 2016 (4)	11.3	11.4	13	12.5	8.94	16	-0.12 [-0.85 , 0.62]
1.11.3 Over 6 months and up to 12 months							
Knudsen 2016 (5)	9.71	7.11	7	10.1	8.51	18	-0.05 [-0.92 , 0.83]
Knudsen 2016 (6)	11.9	7.03	9	9.18	6	17	0.41 [-0.40 , 1.23]
Wildman 2022 (2)	6.3	5.6	262	6.4	5	272	-0.02 [-0.19 , 0.15]
1.11.4 Over 12 months							
Knudsen 2016 (7)	12.9	8.67	12	10.9	9.76	12	0.21 [-0.59 , 1.01]
Knudsen 2016 (8)	13.3	10.3	12	12.8	10.8	12	0.05 [-0.75 , 0.85]

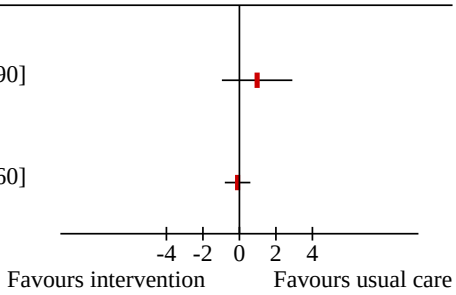


Footnotes

(1) Mean depression score on HADS - endpoint data (ITT)
(2) Mean score on PHQ-8 - endpoint data
(3) Mean score on MDI - endpoint data
(4) Mean score on CES-D - endpoint data
(5) Mean score on CES-D (Post-intervention: 11 months)
(6) Mean score on MDI (Post-intervention: 11 months)
(7) Mean score on MDI (Follow-up: one year post-intervention)
(8) Mean score on CES-D (Follow-up: one year post-intervention)

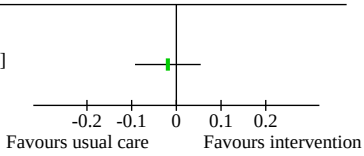
Analysis 1.12. Comparison 1: Psychological interventions versus usual care, Outcome 12: Depression (adjusted mean difference)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.12.1 Over 3 months and up to 6 months			
Hind 2017	0.97	0.9847	0.97 [-0.96 , 2.90]
1.12.2 Over 6 months and up to 12 months			
Wildman 2022	-0.1	0.3571	-0.10 [-0.80 , 0.60]



Analysis 1.13. Comparison 1: Psychological interventions versus usual care, Outcome 13: QoL: Quality of Well-being scale (mean score)

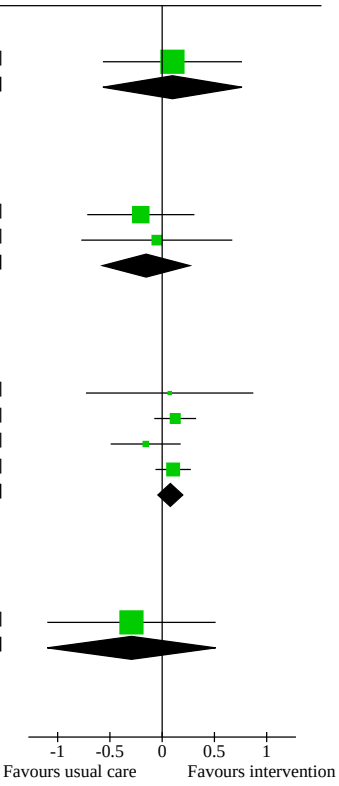
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.13.1 Up to 3 months								
Cottrell 1996 (1)	0.71	0.105	10	0.729	0.055	10	-0.02 [-0.09 , 0.05]	



Footnotes
(1) Endpoint data

Analysis 1.14. Comparison 1: Psychological interventions versus usual care, Outcome 14: QoL: Physical functioning (endpoint data)

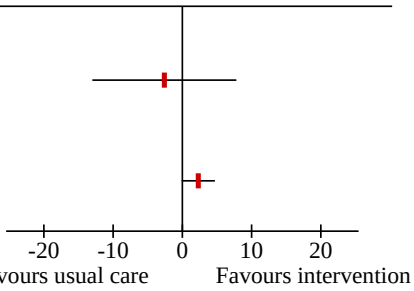
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
1.14.1 Up to 3 months									
Quinn 2004 (1)	76.59	14.07	16	75.37	10.2	19	100.0%	0.10 [-0.57 , 0.76]	
Subtotal (95% CI)			**16**			**19**	**100.0%**	**0.10 [-0.57 , 0.76]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.29 (P = 0.77)									
1.14.2 Over 3 months and up to 6 months									
Hind 2017 (2)	54.4	31.6	31	60.9	31.2	28	66.5%	-0.20 [-0.72 , 0.31]	
Knudsen 2016 (2)	74.4	35.1	13	76	26	17	33.5%	-0.05 [-0.77 , 0.67]	
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.15 [-0.57 , 0.26]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%									
Test for overall effect: Z = 0.72 (P = 0.47)									
1.14.3 Over 6 months and up to 12 months									
Knudsen 2016 (3)	81.9	23.1	9	80.3	21	18	2.2%	0.07 [-0.73 , 0.87]	
Quittner 2019 (2)	84	19.9	180	81.4	21.5	206	35.4%	0.12 [-0.08 , 0.33]	
Quittner 2019 (4)	79.1	20.3	66	82.4	21.3	72	12.7%	-0.16 [-0.49 , 0.18]	
Wildman 2022 (5)	55.8	30.2	264	52.6	30.6	274	49.6%	0.11 [-0.06 , 0.27]	
Subtotal (95% CI)			**519**			**570**	**100.0%**	**0.08 [-0.04 , 0.20]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 3 (P = 0.53); I² = 0%									
Test for overall effect: Z = 1.28 (P = 0.20)									
1.14.4 Over 12 months									
Knudsen 2016 (6)	68.2	36.8	12	78.5	30.6	12	100.0%	-0.29 [-1.10 , 0.51]	
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.29 [-1.10 , 0.51]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.72 (P = 0.47)									



Footnotes
(1) CFQoL endpoint data
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R post-intervention (11 months) - Teen/Adult version
(4) CFQ-R endpoint data (Child version)
(5) CFQ-R endpoint data (Teen/ Adult version)
(6) CFQ-R follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.15. Comparison 1: Psychological interventions versus usual care, Outcome 15: QoL: Physical functioning (adjusted data)

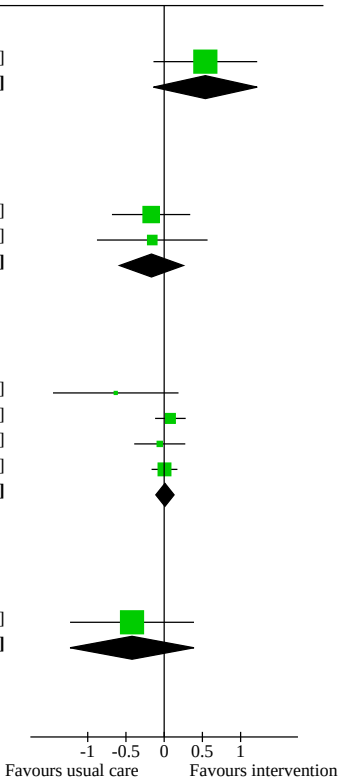
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.15.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-2.6	5.3062	-2.60 [-13.00 , 7.80]
1.15.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	2.3	1.2245	2.30 [-0.10 , 4.70]



Footnotes
(1) CFQ-R

Analysis 1.16. Comparison 1: Psychological interventions versus usual care, Outcome 16: QoL: Emotional functioning (endpoint data)

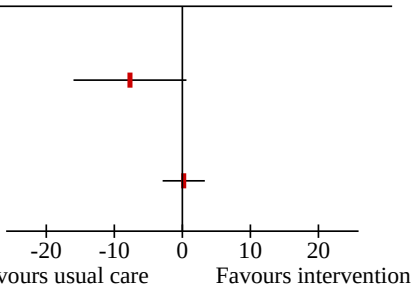
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.16.1 Up to 3 months								
Quinn 2004 (1)	90.88	10.38	16	83.68	14.94	19	100.0%	0.54 [-0.14 , 1.22]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**0.54 [-0.14 , 1.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.16.2 Over 3 months and up to 6 months								
Hind 2017 (2)	68.3	23.4	31	72.3	22.7	28	66.6%	-0.17 [-0.68 , 0.34]
Knudsen 2016 (2)	69.5	20.7	13	72.5	17.1	17	33.4%	-0.16 [-0.88 , 0.57]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.17 [-0.58 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.78 (P = 0.44)								
1.16.3 Over 6 months and up to 12 months								
Knudsen 2016 (3)	68.1	17.2	9	76.9	11.3	18	2.1%	-0.63 [-1.45 , 0.19]
Quittner 2019 (2)	80	18.4	180	78.5	18.4	206	35.5%	0.08 [-0.12 , 0.28]
Quittner 2019 (4)	77	12.8	66	77.8	14.6	72	12.8%	-0.06 [-0.39 , 0.28]
Wildman 2022 (2)	66.6	22.9	264	66.5	24.7	274	49.6%	0.00 [-0.16 , 0.17]
Subtotal (95% CI)			**519**			**570**	**100.0%**	**0.01 [-0.11 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 3.01, df = 3 (P = 0.39); I² = 0%								
Test for overall effect: Z = 0.17 (P = 0.87)								
1.16.4 Over 12 months								
Knudsen 2016 (5)	67.8	21.6	12	76.7	19.2	12	100.0%	-0.42 [-1.23 , 0.39]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.42 [-1.23 , 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								



Footnotes
(1) CFQoL
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R Post-intervention (11 months) - Teen/Adult version
(4) CFQ-R Endpoint data (Child version)
(5) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.17. Comparison 1: Psychological interventions versus usual care, Outcome 17: QoL: Emotional functioning (adjusted data)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.17.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-7.7	4.2348	-7.70 [-16.00 , 0.60]
1.17.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	0.2	1.5817	0.20 [-2.90 , 3.30]

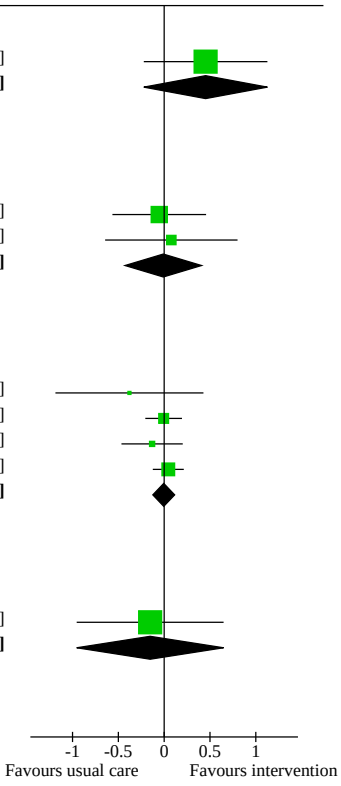


Footnotes

(1) CFQ-R

Analysis 1.18. Comparison 1: Psychological interventions versus usual care, Outcome 18: QoL: Social functioning (endpoint data)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.18.1 Up to 3 months								
Quinn 2004 (1)	91.77	13.34	16	84.47	17.55	19	100.0%	0.45 [-0.22 , 1.13]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**0.45 [-0.22 , 1.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.31 (P = 0.19)								
1.18.2 Over 3 months and up to 6 months								
Hind 2017 (2)	65.4	15.8	31	66.4	20.9	28	66.6%	-0.05 [-0.56 , 0.46]
Knudsen 2016 (3)	72.2	20.9	13	70.7	16.8	17	33.4%	0.08 [-0.64 , 0.80]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.01 [-0.43 , 0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
1.18.3 Over 6 months and up to 12 months								
Knudsen 2016 (4)	67.9	28.6	9	75.9	15.2	18	2.2%	-0.38 [-1.19 , 0.43]
Quittner 2019 (3)	73.9	17.6	180	74	16.9	206	35.5%	-0.01 [-0.21 , 0.19]
Quittner 2019 (5)	69.9	17.7	66	72.3	18.5	72	12.7%	-0.13 [-0.47 , 0.20]
Wildman 2022 (2)	60.5	20	264	59.6	20	274	49.7%	0.04 [-0.12 , 0.21]
Subtotal (95% CI)			**519**			**570**	**100.0%**	**-0.00 [-0.12 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 3 (P = 0.63); I² = 0%								
Test for overall effect: Z = 0.08 (P = 0.94)								
1.18.4 Over 12 months								
Knudsen 2016 (6)	67.1	22.2	12	70.8	24.4	12	100.0%	-0.15 [-0.95 , 0.65]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.15 [-0.95 , 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								

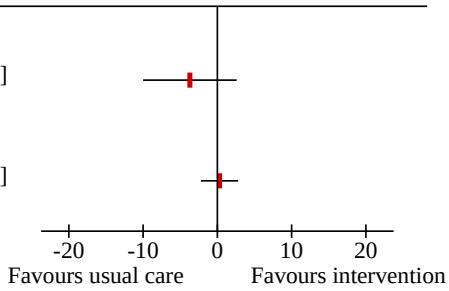


Footnotes

(1) CFQoL
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R Endpoint data (Teen/Adult version)
(4) CFQ-R Post-intervention (11 months) - Teen/Adult version
(5) CFQ-R Endpoint data (Child version)
(6) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.19. Comparison 1: Psychological interventions versus usual care, Outcome 19: QoL: Social functioning (adjusted data)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.19.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-3.7	3.2143	-3.70 [-10.00 , 2.60]
1.19.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	0.3	1.2755	0.30 [-2.20 , 2.80]

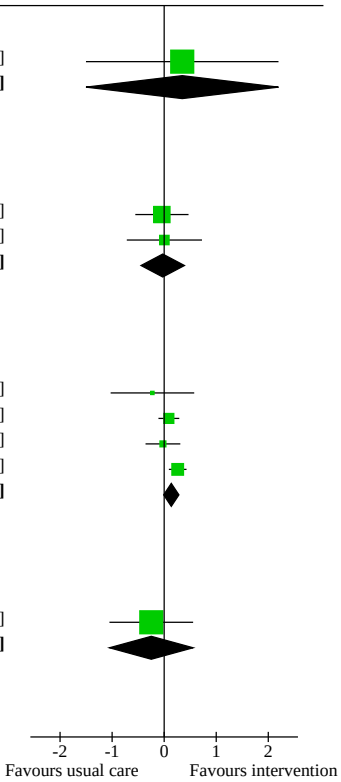


Footnotes

(1) CFQ-R

Analysis 1.20. Comparison 1: Psychological interventions versus usual care, Outcome 20: QoL: Treatment burden (endpoint data)

Study or Subgroup	Favours usual care Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.20.1 Up to 3 months								
Shakkottai 2017 (1)	81.67	16.8	3	72.5	23.33	2	100.0%	0.35 [-1.50 , 2.20]
Subtotal (95% CI)			**3**			**2**	**100.0%**	**0.35 [-1.50 , 2.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
1.20.2 Over 3 months and up to 6 months								
Hind 2017 (2)	56.5	16.6	31	57.3	19.9	28	66.6%	-0.04 [-0.55 , 0.47]
Knudsen 2016 (3)	52.4	24.8	13	52.3	22.5	17	33.4%	0.00 [-0.72 , 0.73]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.03 [-0.44 , 0.39]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.20.3 Over 6 months and up to 12 months								
Knudsen 2016 (4)	51.9	18.4	9	56.8	22.2	18	3.2%	-0.23 [-1.03 , 0.58]
Quittner 2019 (5)	58.5	17.5	180	56.8	19.9	206	36.0%	0.09 [-0.11 , 0.29]
Quittner 2019 (1)	73.7	21.6	66	74.2	19.9	72	16.3%	-0.02 [-0.36 , 0.31]
Wildman 2022 (5)	56.6	19.5	265	51.5	19.7	274	44.4%	0.26 [0.09 , 0.43]
Subtotal (95% CI)			**520**			**570**	**100.0%**	**0.14 [-0.01 , 0.28]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.84$, df = 3 (P = 0.28); $I^2 = 22\%$								
Test for overall effect: Z = 1.83 (P = 0.07)								
1.20.4 Over 12 months								
Knudsen 2016 (6)	51.9	16.6	12	57.4	25.4	12	100.0%	-0.25 [-1.05 , 0.56]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.25 [-1.05 , 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								

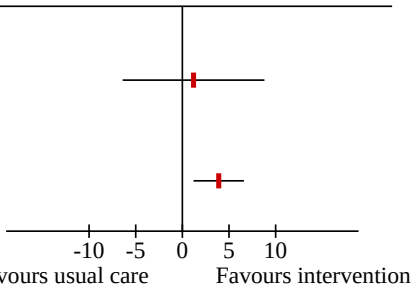


Footnotes

(1) CFQ-R Endpoint data (Child version)
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R Post-intervention (11 months) - Teen/adult version
(4) CFQ-R
(5) CFQ-R Endpoint data (Teen/adult version)
(6) CFQ-R Endpoint data (Teen/ adult version)

Analysis 1.21. Comparison 1: Psychological interventions versus usual care, Outcome 21: QoL: Treatment burden (adjusted data)

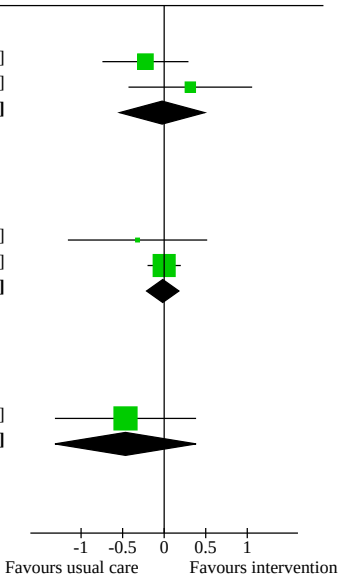
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.21.1 Over 3 months and up to 6 months			
Hind 2017 (1)	1.2	3.8776	1.20 [-6.40 , 8.80]
1.21.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	3.9	1.3776	3.90 [1.20 , 6.60]



Footnotes
(1) CFQ-R

Analysis 1.22. Comparison 1: Psychological interventions versus usual care, Outcome 22: QoL: Role limitations (endpoint data)

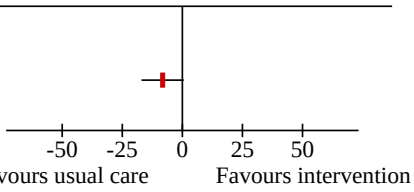
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.22.1 Over 3 months and up to 6 months								
Hind 2017 (1)	64.8	26.1	31	70.3	21.5	27	62.7%	-0.23 [-0.74 , 0.29]
Knudsen 2016 (1)	80.6	16.8	12	73.4	25.3	17	37.3%	0.31 [-0.43 , 1.06]
Subtotal (95% CI)			**43**			**44**	**100.0%**	**-0.02 [-0.54 , 0.49]**
Heterogeneity: Tau² = 0.04; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.22.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	78.1	19.9	8	83.8	16	18	5.4%	-0.32 [-1.16 , 0.52]
Quittner 2019 (1)	83.1	18.5	180	83.1	16.2	206	94.6%	0.00 [-0.20 , 0.20]
Subtotal (95% CI)			**188**			**224**	**100.0%**	**-0.02 [-0.21 , 0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%								
Test for overall effect: Z = 0.17 (P = 0.86)								
1.22.3 Over 12 months								
Knudsen 2016 (3)	81.1	13.5	11	87.9	14.6	11	100.0%	-0.47 [-1.31 , 0.38]
Subtotal (95% CI)			**11**			**11**	**100.0%**	**-0.47 [-1.31 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.28)								



Footnotes
(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.23. Comparison 1: Psychological interventions versus usual care, Outcome 23: QoL: Role limitations (adjusted data)

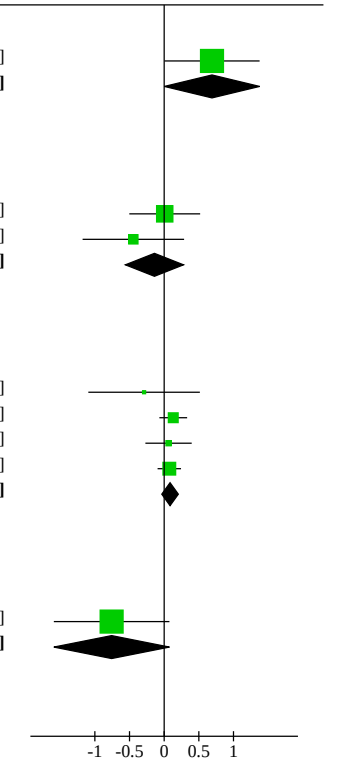
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.23.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-8.2	4.4899	-8.20 [-17.00 , 0.60]



Footnotes
(1) CFQ-R

Analysis 1.24. Comparison 1: Psychological interventions versus usual care, Outcome 24: QoL: Body image (endpoint data)

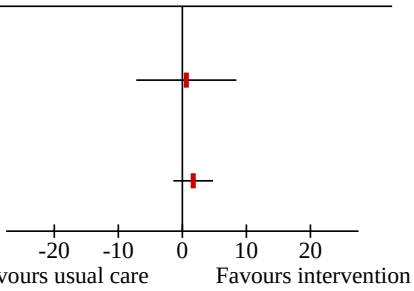
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.24.1 Up to 3 months								
Quinn 2004 (1)	77.26	19.87	16	63.16	20.05	19	100.0%	0.69 [0.00 , 1.38]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**0.69 [0.00 , 1.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.97 (P = 0.05)								
1.24.2 Over 3 months and up to 6 months								
Hind 2017 (2)	73.3	23.8	31	73.1	25.5	28	67.2%	0.01 [-0.50 , 0.52]
Knudsen 2016 (2)	75.4	18.6	13	84.3	20.1	17	32.8%	-0.44 [-1.18 , 0.29]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.14 [-0.56 , 0.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%								
Test for overall effect: Z = 0.66 (P = 0.51)								
1.24.3 Over 6 months and up to 12 months								
Knudsen 2016 (3)	72.8	26.1	9	79.6	21	18	2.2%	-0.29 [-1.09 , 0.51]
Quittner 2019 (2)	79.3	23.6	180	76.2	23.6	206	35.4%	0.13 [-0.07 , 0.33]
Quittner 2019 (4)	81.6	26.4	66	80.1	20.8	72	12.7%	0.06 [-0.27 , 0.40]
Wildman 2022 (2)	67.2	27.3	264	65.1	29.3	274	49.7%	0.07 [-0.10 , 0.24]
Subtotal (95% CI)			**519**			**570**	**100.0%**	**0.08 [-0.03 , 0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 3 (P = 0.78); I² = 0%								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.24.4 Over 12 months								
Knudsen 2016 (5)	69.4	25.6	12	86.1	15.8	12	100.0%	-0.76 [-1.59 , 0.08]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.76 [-1.59 , 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.78 (P = 0.07)								



Footnotes
(1) CFQoL
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R Post-intervention (11 months) - Teen/Adult version
(4) CFQ-R Endpoint data (Child version)
(5) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.25. Comparison 1: Psychological interventions versus usual care, Outcome 25: QoL: Body image (adjusted data)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.25.1 Over 3 months and up to 6 months			
Hind 2017 (1)	0.62	3.9899	0.62 [-7.20 , 8.44]
1.25.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	1.7	1.5817	1.70 [-1.40 , 4.80]

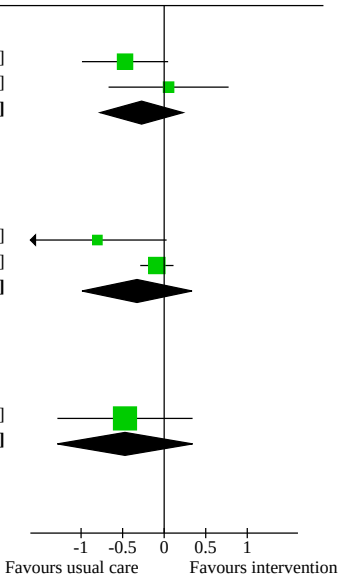


Footnotes

(1) CFQ-R

Analysis 1.26. Comparison 1: Psychological interventions versus usual care, Outcome 26: QoL: Vitality (endpoint data)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.26.1 Over 3 months and up to 6 months								
Hind 2017 (1)	38.5	19.8	31	48.7	23	28	62.0%	-0.47 [-0.99 , 0.05]
Knudsen 2016 (1)	51.8	21	13	50.8	16	17	38.0%	0.05 [-0.67 , 0.78]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.27 [-0.77 , 0.23]**
Heterogeneity: Tau² = 0.03; Chi² = 1.33, df = 1 (P = 0.25); I² = 25%								
Test for overall effect: Z = 1.07 (P = 0.29)								
1.26.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	49.1	16.4	9	63.9	18.5	18	33.4%	-0.80 [-1.64 , 0.03]
Quittner 2019 (1)	62	17.7	180	63.5	16.5	206	66.6%	-0.09 [-0.29 , 0.11]
Subtotal (95% CI)			**189**			**224**	**100.0%**	**-0.33 [-0.99 , 0.34]**
Heterogeneity: Tau² = 0.16; Chi² = 2.68, df = 1 (P = 0.10); I² = 63%								
Test for overall effect: Z = 0.97 (P = 0.33)								
1.26.3 Over 12 months								
Knudsen 2016 (3)	46.5	22.6	12	57.2	21.2	12	100.0%	-0.47 [-1.28 , 0.34]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.47 [-1.28 , 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.26)								

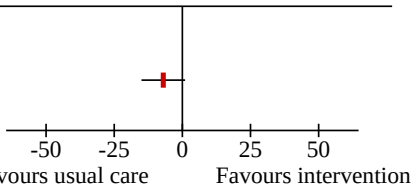


Footnotes

(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.27. Comparison 1: Psychological interventions versus usual care, Outcome 27: QoL: Vitality (adjusted data)

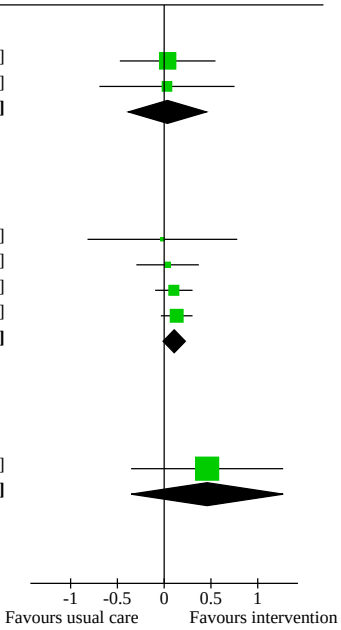
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.27.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-7	4.0817	-7.00 [-15.00 , 1.00]



Footnotes
(1) CFQ-R

Analysis 1.28. Comparison 1: Psychological interventions versus usual care, Outcome 28: QoL: Eating disturbance (endpoint data)

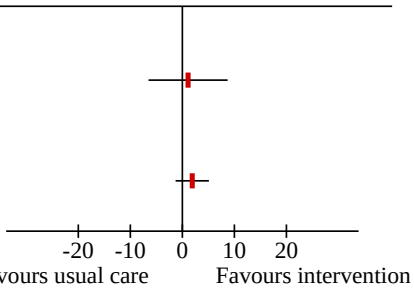
Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.28.1 Over 3 months and up to 6 months								
Hind 2017 (1)	80.7	21.6	31	79.9	20.7	28	66.6%	0.04 [-0.47 , 0.55]
Knudsen 2016 (1)	88.9	23.9	13	88.2	21.7	17	33.4%	0.03 [-0.69 , 0.75]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**0.03 [-0.38 , 0.45]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.16 (P = 0.87)								
1.28.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	90.1	15.2	9	90.4	15.2	18	2.2%	-0.02 [-0.82 , 0.78]
Quittner 2019 (3)	87	19.5	66	86.3	18.3	72	12.7%	0.04 [-0.30 , 0.37]
Quittner 2019 (1)	92	15	180	90.3	17.6	206	35.5%	0.10 [-0.10 , 0.30]
Wildman 2022 (1)	84	21.5	264	81	23.2	274	49.6%	0.13 [-0.04 , 0.30]
Subtotal (95% CI)			**519**			**570**	**100.0%**	**0.11 [-0.01 , 0.23]**
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 3 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.76 (P = 0.08)								
1.28.3 Over 12 months								
Knudsen 2016 (4)	93.5	11.1	12	86.1	19	12	100.0%	0.46 [-0.35 , 1.27]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.46 [-0.35 , 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								



Footnotes
(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Endpoint data (Child version)
(4) CFQ-R Follow-up (one year post-intervention) - Teen/Adult version

Analysis 1.29. Comparison 1: Psychological interventions versus usual care, Outcome 29: QoL: Eating disturbance (adjusted data)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.29.1 Over 3 months and up to 6 months			
Hind 2017 (1)	1.1	3.8776	1.10 [-6.50 , 8.70]
1.29.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	1.9	1.6327	1.90 [-1.30 , 5.10]

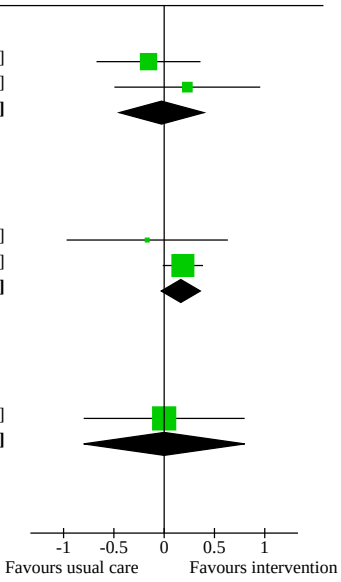


Footnotes

(1) CFQ-R

Analysis 1.30. Comparison 1: Psychological interventions versus usual care, Outcome 30: QoL: Weight problems (endpoint data)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.30.1 Over 3 months and up to 6 months								
Hind 2017 (1)	81.1	18.4	31	84.4	23.5	27	66.3%	-0.16 [-0.67 , 0.36]
Knudsen 2016 (1)	88.1	28.1	13	80.4	35.5	17	33.7%	0.23 [-0.49 , 0.96]
Subtotal (95% CI)			**44**			**44**	**100.0%**	**-0.03 [-0.45 , 0.40]**
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%								
Test for overall effect: Z = 0.12 (P = 0.91)								
1.30.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	77.8	33.3	9	83.3	30.8	18	5.9%	-0.17 [-0.97 , 0.63]
Quittner 2019 (1)	77.5	32.1	180	71.2	35.2	206	94.1%	0.19 [-0.01 , 0.39]
Subtotal (95% CI)			**189**			**224**	**100.0%**	**0.17 [-0.03 , 0.36]**
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%								
Test for overall effect: Z = 1.67 (P = 0.10)								
1.30.3 Over 12 months								
Knudsen 2016 (3)	80.6	26.4	12	80.6	38.8	12	100.0%	0.00 [-0.80 , 0.80]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.00 [-0.80 , 0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								

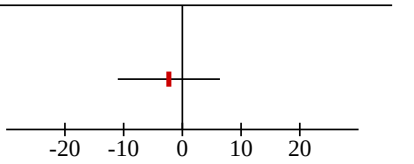


Footnotes

(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.31. Comparison 1: Psychological interventions versus usual care, Outcome 31: QoL: Weight problems (adjusted data)

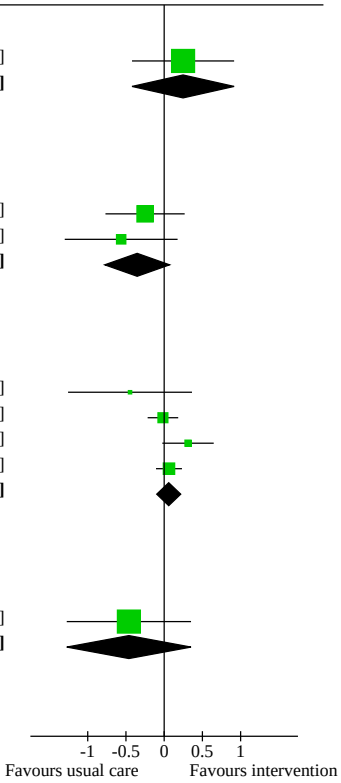
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.31.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-2.3	4.4389	-2.30 [-11.00 , 6.40]



Footnotes
(1) CFQ-R

Analysis 1.32. Comparison 1: Psychological interventions versus usual care, Outcome 32: QoL: Respiratory symptoms (endpoint data)

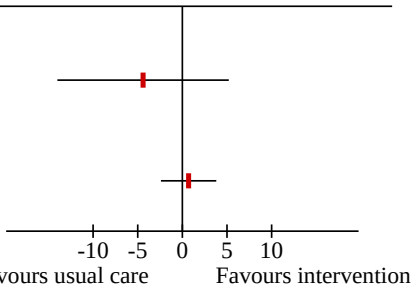
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.32.1 Up to 3 months								
Quinn 2004 (1)	82.35	14.16	16	78.42	16.59	19	100.0%	0.25 [-0.42 , 0.92]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**0.25 [-0.42 , 0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.32.2 Over 3 months and up to 6 months								
Hind 2017 (2)	59.5	25.2	31	65.6	22.7	27	67.0%	-0.25 [-0.77 , 0.27]
Knudsen 2016 (2)	61.5	18.7	13	73.3	21.6	17	33.0%	-0.56 [-1.30 , 0.18]
Subtotal (95% CI)			**44**			**44**	**100.0%**	**-0.35 [-0.78 , 0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 1 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 1.63 (P = 0.10)								
1.32.3 Over 6 months and up to 12 months								
Knudsen 2016 (3)	60.5	16.5	9	70.1	22.6	18	3.6%	-0.45 [-1.26 , 0.36]
Quittner 2019 (2)	72.2	19.2	180	72.5	17.5	206	36.0%	-0.02 [-0.22 , 0.18]
Quittner 2019 (4)	79.5	18.8	66	73.7	18.2	72	17.4%	0.31 [-0.02 , 0.65]
Wildman 2022 (2)	58	22.5	263	56.6	21.9	271	43.0%	0.06 [-0.11 , 0.23]
Subtotal (95% CI)			**518**			**567**	**100.0%**	**0.06 [-0.10 , 0.22]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.21$, df = 3 (P = 0.24); $I^2 = 29\%$								
Test for overall effect: Z = 0.74 (P = 0.46)								
1.32.4 Over 12 months								
Knudsen 2016 (2)	60.2	23.9	12	70.8	20.3	12	100.0%	-0.46 [-1.27 , 0.35]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.46 [-1.27 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								



Footnotes
(1) CFQoL (Chest symptoms domain)
(2) CFQ-R Endpoint data (Teen/ Adult version)
(3) CFQ-R Post-intervention (11 months) - Teen/Adult version
(4) CFQ-R Endpoint data (Child version)

Analysis 1.33. Comparison 1: Psychological interventions versus usual care, Outcome 33: QoL: Respiratory symptoms (adjusted data)

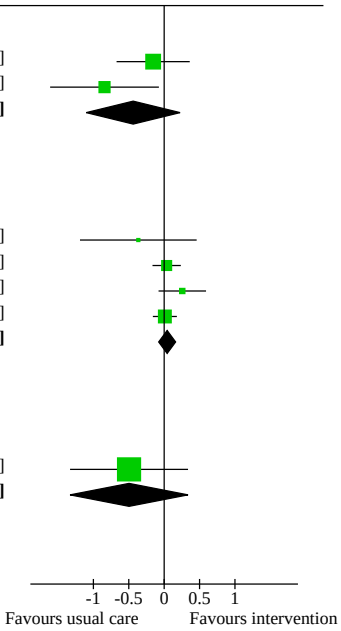
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.33.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-4.4	4.898	-4.40 [-14.00 , 5.20]
1.33.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	0.7	1.5817	0.70 [-2.40 , 3.80]



Footnotes
(1) CFQ-R

Analysis 1.34. Comparison 1: Psychological interventions versus usual care, Outcome 34: QoL: Digestive symptoms (endpoint data)

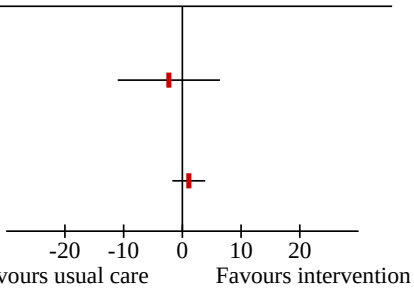
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.34.1 Over 3 months and up to 6 months								
Hind 2017 (1)	81.1	18.4	31	84.4	23.5	27	58.9%	-0.16 [-0.67 , 0.36]
Knudsen 2016 (1)	65.9	20.7	13	81.3	15	16	41.1%	-0.84 [-1.61 , -0.07]
Subtotal (95% CI)			**44**			**43**	**100.0%**	**-0.44 [-1.10 , 0.22]**
Heterogeneity: Tau² = 0.12; Chi² = 2.12, df = 1 (P = 0.15); I² = 53%								
Test for overall effect: Z = 1.30 (P = 0.20)								
1.34.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	67.9	23.9	9	75.7	18.7	16	2.1%	-0.37 [-1.19 , 0.46]
Quittner 2019 (1)	84	16.3	180	83.4	17.7	206	35.6%	0.04 [-0.16 , 0.24]
Quittner 2019 (3)	78.3	23.7	66	71.8	26.6	72	12.7%	0.26 [-0.08 , 0.59]
Wildman 2022 (1)	80.4	19.4	263	80.2	21.6	272	49.6%	0.01 [-0.16 , 0.18]
Subtotal (95% CI)			**518**			**566**	**100.0%**	**0.04 [-0.08 , 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 3 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.69 (P = 0.49)								
1.34.3 Over 12 months								
Knudsen 2016 (4)	61.1	23.5	12	73.7	25.5	11	100.0%	-0.50 [-1.33 , 0.34]
Subtotal (95% CI)			**12**			**11**	**100.0%**	**-0.50 [-1.33 , 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.17 (P = 0.24)								



Footnotes
(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Endpoint data (Child version)
(4) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.35. Comparison 1: Psychological interventions versus usual care, Outcome 35: QoL: Digestive symptoms (adjusted data)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.35.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-2.3	4.4389	-2.30 [-11.00 , 6.40]
1.35.2 Over 6 months and up to 12 months			
Wildman 2022 (1)	1.1	1.4286	1.10 [-1.70 , 3.90]

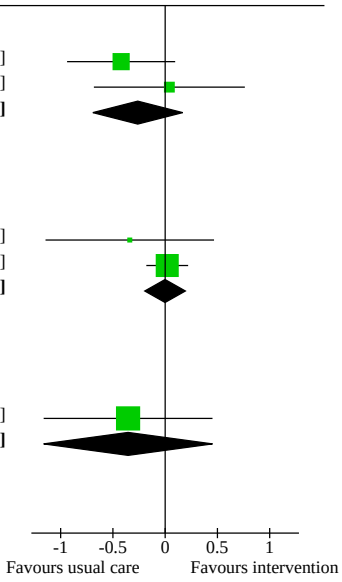


Footnotes

(1) CFQ-R

Analysis 1.36. Comparison 1: Psychological interventions versus usual care, Outcome 36: QoL: Health perceptions (endpoint data)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.36.1 Over 3 months and up to 6 months								
Hind 2017 (1)	45.5	25.4	31	56.8	27.6	28	65.5%	-0.42 [-0.94 , 0.10]
Knudsen 2016 (1)	57.9	29	13	56.9	20	17	34.5%	0.04 [-0.68 , 0.76]
Subtotal (95% CI)			**44**			**45**	**100.0%**	**-0.26 [-0.69 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%								
Test for overall effect: Z = 1.20 (P = 0.23)								
1.36.2 Over 6 months and up to 12 months								
Knudsen 2016 (2)	51.9	26.1	9	60.5	23.9	18	5.8%	-0.34 [-1.14 , 0.47]
Quittner 2019 (1)	72.8	19.7	180	72.4	20.7	206	94.2%	0.02 [-0.18 , 0.22]
Subtotal (95% CI)			**189**			**224**	**100.0%**	**-0.00 [-0.20 , 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%								
Test for overall effect: Z = 0.01 (P = 0.99)								
1.36.3 Over 12 months								
Knudsen 2016 (3)	48.1	26.1	12	58.3	29.3	12	100.0%	-0.35 [-1.16 , 0.45]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**-0.35 [-1.16 , 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								

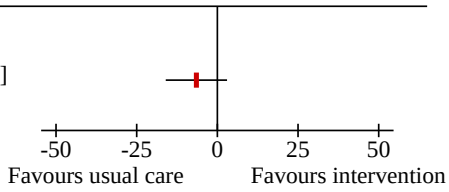


Footnotes

(1) CFQ-R Endpoint data (Teen/ Adult version)
(2) CFQ-R Post-intervention (11 months) - Teen/Adult version
(3) CFQ-R Follow-up (one year post-intervention) - Teen/ Adult version

Analysis 1.37. Comparison 1: Psychological interventions versus usual care, Outcome 37: QoL: Health perceptions (adjusted data)

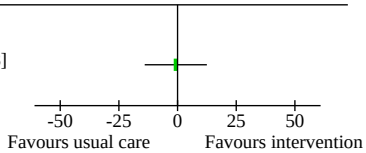
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.37.1 Over 3 months and up to 6 months			
Hind 2017 (1)	-6.5	4.847	-6.50 [-16.00 , 3.00]



Footnotes
(1) CFQ-R

Analysis 1.38. Comparison 1: Psychological interventions versus usual care, Outcome 38: QoL: Treatment issues (endpoint data)

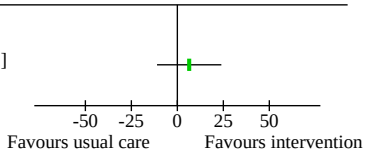
Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.38.1 Up to 3 months							
Quinn 2004 (1)	76.08	21.99	16	76.84	17.12	19	-0.76 [-14.00 , 12.48]



Footnotes
(1) CFQoL

Analysis 1.39. Comparison 1: Psychological interventions versus usual care, Outcome 39: QoL: Career concerns (endpoint data)

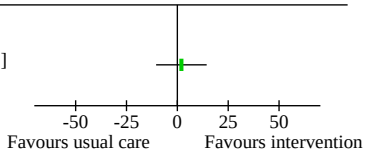
Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.39.1 Up to 3 months							
Quinn 2004 (1)	71.18	28.26	16	64.74	23.72	19	6.44 [-11.04 , 23.92]



Footnotes
(1) CFQoL

Analysis 1.40. Comparison 1: Psychological interventions versus usual care, Outcome 40: QoL: Interpersonal relationships (endpoint data)

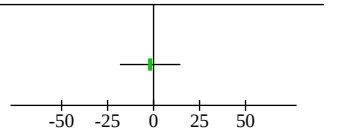
Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.40.1 Up to 3 months							
Quinn 2004 (1)	64.94	20.39	16	62.95	16.42	19	1.99 [-10.43 , 14.41]



Footnotes
(1) CFQoL

Analysis 1.41. Comparison 1: Psychological interventions versus usual care, Outcome 41: QoL: Concerns for the future (endpoint data)

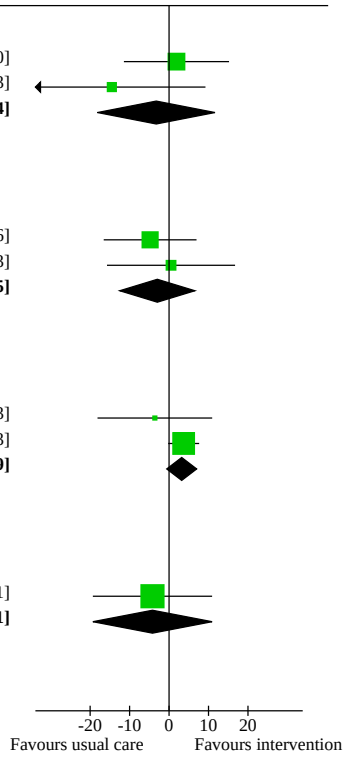
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.41.1 Up to 3 months							
Quinn 2004 (1)	49.02	26.69	16	50.88	22.22	19	-1.86 [-18.32 , 14.60]



Footnotes
(1) CFQoL

Analysis 1.42. Comparison 1: Psychological interventions versus usual care, Outcome 42: FEV1 % predicted (endpoint data)

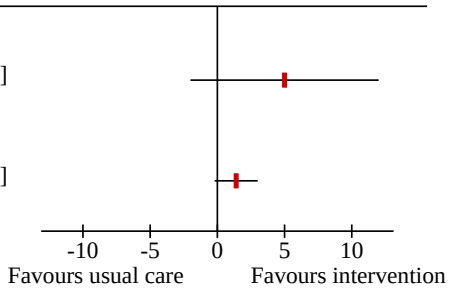
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.42.1 Up to 3 months								
Quinn 2004 (1)	56.25	21.11	16	54.37	18.67	19	68.7%	1.88 [-11.44 , 15.20]
Shakkottai 2017 (2)	77	6.56	3	91.5	16.26	2	31.3%	-14.50 [-38.23 , 9.23]
Subtotal (95% CI)			**19**			**21**	**100.0%**	**-3.25 [-18.13 , 11.64]**
Heterogeneity: Tau² = 37.78; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.42.2 Over 3 months and up to 6 months								
Hind 2017 (2)	54.2	21.1	30	59	23.9	27	65.6%	-4.80 [-16.56 , 6.96]
Knudsen 2016 (2)	74.4	27.9	18	73.9	22.5	20	34.4%	0.50 [-15.73 , 16.73]
Subtotal (95% CI)			**48**			**47**	**100.0%**	**-2.98 [-12.50 , 6.55]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.42.3 Over 6 months and up to 12 months								
Knudsen 2016 (3)	69.9	25.3	18	73.5	19.2	19	6.8%	-3.60 [-18.13 , 10.93]
Wildman 2022 (2)	60.6	24.2	274	56.9	23	282	93.2%	3.70 [-0.23 , 7.63]
Subtotal (95% CI)			**292**			**301**	**100.0%**	**3.20 [-0.59 , 6.99]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 1.66 (P = 0.10)								
1.42.4 Over 12 months								
Knudsen 2016 (4)	71	23	17	75.2	23.2	19	100.0%	-4.20 [-19.31 , 10.91]
Subtotal (95% CI)			**17**			**19**	**100.0%**	**-4.20 [-19.31 , 10.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.54 (P = 0.59)								



Footnotes
(1) FEV1% Predicted - endpoint data (ITT)
(2) FEV1% Predicted - endpoint data
(3) FEV1% Predicted (Post-intervention: 11 months)
(4) FEV1% Predicted (Follow-on: one-year post intervention)

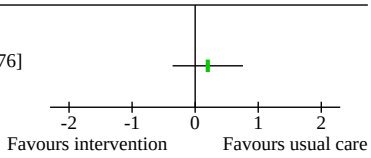
Analysis 1.43. Comparison 1: Psychological interventions versus usual care, Outcome 43: FEV1 % predicted (adjusted mean difference)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Random, 95% CI
1.43.1 Over 3 months and up to 6 months			
Hind 2017	5	3.5715	5.00 [-2.00 , 12.00]
1.43.2 Over 6 months and up to 12 months			
Wildman 2022	1.4	0.8163	1.40 [-0.20 , 3.00]



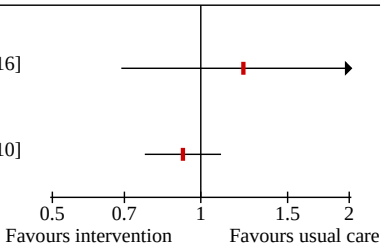
Analysis 1.44. Comparison 1: Psychological interventions versus usual care, Outcome 44: Number of pulmonary exacerbations

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.44.1 Over 3 months and up to 6 months							
Hind 2017	1.1	1.1	32	0.9	1.1	28	0.20 [-0.36 , 0.76]

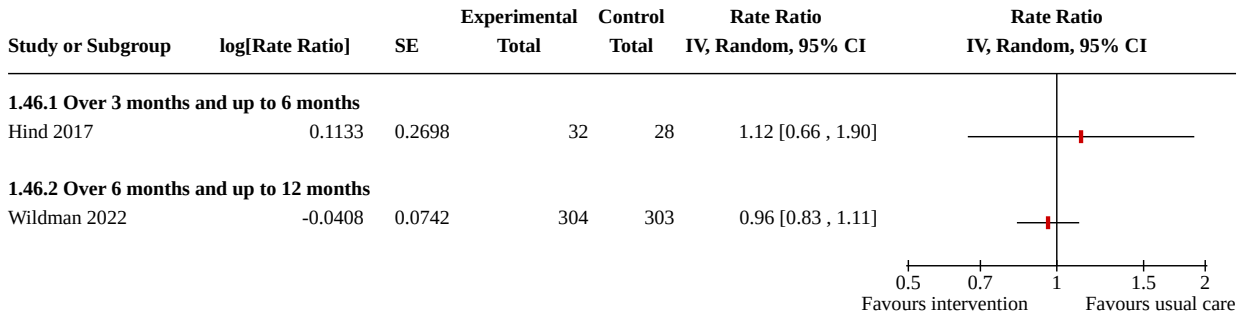


Analysis 1.45. Comparison 1: Psychological interventions versus usual care, Outcome 45: Pulmonary exacerbations incidence rate (unadjusted data)

Study or Subgroup	log[Rate Ratio]	SE	Experimental Total	Control Total	Rate Ratio IV, Random, 95% CI
1.45.1 Over 3 months and up to 6 months					
Hind 2017	0.1989	0.2908	32	28	1.22 [0.69 , 2.16]
1.45.2 Over 6 months and up to 12 months					
Wildman 2022	-0.0834	0.0908	304	303	0.92 [0.77 , 1.10]



Analysis 1.46. Comparison 1: Psychological interventions versus usual care, Outcome 46: Pulmonary exacerbations incidence rate (adjusted data)



ADDITIONAL TABLES

Table 1. Behaviour change techniques present in included studies

Study	Intervention arm	Control arm
Cottrell 1996	• 1.2 Problem solving • 4.1 Instruction on how to perform the behaviour • 9.1 Credible source	None (usual care)
Downs 2006	• 1.1 Goal setting (behaviour) • 1.2 Problem solving • 1.3 Goal setting (outcome) • 1.4 Action planning • 1.6 Discrepancy between current behaviour and goal • 1.9 Commitment • 2.3 Self-monitoring of behaviour • 3.1 Social support (unspecified) • 3.2 Social support (practical) • 3.3 Social support (emotional) • 4.1 Instruction on how to perform the behaviour • 5.1 Information about health consequences • 5.2 Salience of consequences • 6.1 Demonstration of the behaviour • 6.3 Information about others' approval • 7.1 Prompts/cues • 8.1 Behavioural practice/rehearsal • 8.3 Habit formation • 9.1 Credible source • 9.2 Pros and cons • 10.3 Non-specific reward • 10.4 Social reward • 10.7 Self-incentive • 10.9 Self-reward • 11.2 Reduce negative emotions • 12.5 Adding objects to the environment • 13.2 Framing/ reframing • 15.1 Verbal persuasion about capability	None (usual care)

Table 1. Behaviour change techniques present in included studies *(Continued)*

Gur 2016	• 1.2 Problem-solving • 2.1 Monitoring of behaviour by others without feedback	None (usual care)
Hind 2017	• 1.1 Goal setting (behaviour) • 1.2 Problem solving • 1.4 Action planning • 1.5 Review behavioural goal(s) • 1.6 Discrepancy between current behaviour and goal • 2.2 Feedback on behaviour • 2.3 Self-monitoring of behaviour • 3.2 Social support (practical) • 4.1 Instruction on how to perform the behaviour • 5.1 Information about health consequences • 5.2 Salience of consequences • 6.1 Demonstration of the behaviour • 7.1 Prompts/cues • 8.1 Behavioural practice/rehearsal • 8.3 Habit formation • 8.7 Graded tasks • 9.1 Credible source • 10.4 Social reward • 12.1 Restructure the physical environment • 12.5 Adding objects to the environment • 15.3 Focus on past success • 15.4 Self-talk • 16.3 Vicarious consequences	None (usual care)
Knudsen 2016	• 3.1 Social support (unspecified)	None (usual care)
Quinn 2004	• 1.2 Problem solving • 3.1 Social support (unspecified) • 9.2 Pros and cons • 13.3 Incompatible beliefs • 12.1 Restructuring the physical environment • 12.2 Restructuring the social environment	None (usual care)
Quittner 2019	• 1.2 Problem solving; • 4.1 Instruction on how to perform the behaviour	None (usual care)
Riekert 2013	• 2.2 Feedback on behaviour • 2.7 Feedback on outcome(s) of behaviour • 3.1 Social support (unspecified) • 5.1 Information about health consequences	• 1.2 Problem solving • 4.1 Instruction on how to perform the behaviour • 10.4 Social reward
Shakkottai 2017	• 2.4 Self-monitoring of outcome(s) of behaviour • 2.6 Biofeedback • 7.1 Prompts/cues • 12.5 Adding objects to the environment	None (usual care)
Wildman 2022	• 1.1 Goal setting (behaviour) • 1.2 Problem solving • 1.4 Action planning	None (usual care)

Table 1. Behaviour change techniques present in included studies *(Continued)*

- 1.5 Review behavioural goal(s)
- 1.6 Discrepancy between current behaviour and goal
- 2.2 Feedback on behaviour
- 2.3 Self-monitoring of behaviour
- 3.2 Social support (practical)
- 4.1 Instruction on how to perform the behaviour
- 5.1 Information about health consequences
- 5.2 Salience of consequences
- 6.1 Demonstration of the behaviour
- 7.1 Prompts/cues
- 8.1 Behavioural practice/rehearsal
- 8.3 Habit formation
- 8.7 Graded tasks
- 9.1 Credible source
- 10.4 Social reward
- 12.1 Restructure the physical environment
- 12.5 Adding objects to the environment
- 15.3 Focus on past success
- 15.4 Self-talk
- 16.3 Vicarious consequences

[a]Used TIDiER description supplied by authors in study protocol - note these behaviour change techniques were assigned by the authors and we have made no amendments.

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies

BCT present	BCT category	BCT definition	Number of studies present in	Illustrative quotations
1.1. Goal setting (behavior)	1. Goals and planning	Set or agree on a goal defined in terms of the behavior to be achieved *Note: only code goal-setting if there is sufficient evidence that goal set as part of intervention; if goal unspecified or a behavioral outcome, code 1.3, Goal setting (outcome); if the goal defines a specific context, frequency, duration or intensity for the behavior, also code 1.4, Action planning*	3	"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." (Hind 2017; Wildman 2022[a])
1.2. Problem solving	1. Goals and planning	Analyse, or prompt the person to analyse, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators (includes Relapse Prevention and Coping Planning)	6	"This intervention involves a member of the multidisciplinary team working with the adolescent to identify barriers to daily treatments and brainstorm solutions to

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

		Note: barrier identification without solutions is not sufficient. If the BCT does not include analysing the behavioral problem, consider 12.3, Avoidance/changing exposure to cues for the behavior, 12.1, Restructuring the physical environment, 12.2, Restructuring the social environment, or 11.2, Reduce negative emotions		those barriers with their parent." (Quittner 2019)
1.3. Goal setting (outcome)	1. Goals and planning	Set or agree on a goal defined in terms of a positive outcome of wanted behavior *Note: only code guidelines if set as a goal in an intervention context; if goal is a behavior, code 1.1, Goal setting (behavior); if goal unspecified code 1.3, Goal setting (outcome)*	1	"Plan What you want to get out of something is called a goal. What would you like to get out of doing this program? Set goals about doing chest treatments and doing this program. Some goals are already written into the boxes below. Highlight the goals you would like and write any others you'd like in the empty boxes." (Downs 2006)
1.4. Action planning	1. Goals and planning	Prompt detailed planning of performance of the behavior (must include at least one of context, frequency, duration and intensity). Context may be environmental (physical or social) or internal (physical, emotional or cognitive) (includes Implementation Intentions) *Note: evidence of action planning does not necessarily imply goal setting, only code latter if sufficient evidence*	3	"CFHealthHub: • Action planning tool and storage within CFHealthHub." (Hind 2017; Wildman 2022[a])
1.5. Review behavior goal(s)	1. Goals and planning	Review behavior goal(s) jointly with the person and consider modifying goal(s) or behavior change strategy in light of achievement. This may lead to re-setting the same goal, a small change in that goal or setting a new goal instead of (or in addition to) the first, or no change *Note: if goal specified in terms of behavior, code 1.5, Review behavior goal(s), if goal unspecified, code 1.7, Review outcome goal(s); if discrepancy created consider also 1.6, Discrepancy between current behavior and goal*	2	"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." (Hind 2017; Wildman 2022[a])
1.6. Discrepancy between cur-	1. Goals and planning	Draw attention to discrepancies between a person's current behavior (in	3	"CFHealthHub:

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

rent behavior and goal		terms of the form, frequency, duration, or intensity of that behavior) and the person's previously set outcome goals, behavioral goals or action plans (goes beyond self-monitoring of behavior) *Note: if discomfort is created, only code: 13.3, Incompatible beliefs and not 1.6, Discrepancy between current behavior and goal; if goals are modified, also code 1.5, Review behavior goal(s) and/or 1.7, Review outcome goal(s); if feedback is provided, also code 2.2, Feedback on behaviour*		• 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." (Hind 2017; Wildman 2022[a])
1.9. Commitment	1. Goals and planning	Ask the person to affirm or reaffirm statements indicating commitment to change the behavior *Note: if defined in terms of the behavior to be achieved also code 1.1, Goal setting (behavior)*	1	"Practise remembering, fitting in and doing your puffer, nebuliser and ACT treatments. The chest treatments that I need to remember, fit in and do are: _____, ____times/day." (Downs 2006)
2.1 Monitoring of behaviour by others without feedback	2. Feedback and monitoring	Observe or record behaviour with the person's knowledge as part of a behaviour change strategy. *Note: if monitoring is part of a data collection procedure rather than a strategy aimed at changing behaviour, do not code; if feedback given, code only 2.2, Feedback on behaviour, and not 2.1, Monitoring of behaviour by others without feedback; if monitoring outcome(s) code 2.5, Monitoring outcome(s) of behaviour by others without feedback; if self-monitoring behaviour, code 2.3, Self-monitoring of behaviour.*	1	"The interviewer will assess adherence over the week prior to the chat..." (Gur 2016)
2.2. Feedback on behaviour	2. Feedback and monitoring	Monitor and provide informative or evaluative feedback on performance of the behavior *(e.g. form, frequency, duration, intensity)* *Note: if Biofeedback, code only 2.6, Biofeedback and not 2.2, Feedback on behavior; if feedback is on outcome(s) of behavior, code 2.7, Feedback on outcome(s) of behavior; if there is no clear*	3	"The intervention will begin by providing the patient personal feedback on their adherence (using pharmacy refill data) and health outcomes (e.g., trajectory of lung function values, frequency of exacerbations) as well as clinic-level figures showing the association be-

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

		evidence that feedback was given, code 2.1, Monitoring of behavior by others without feedback; if feedback on behaviour is evaluative e.g. praise, also code 10.4, Social reward		tween adherence and health outcomes." (Riekert 2013)
2.3. Self-monitoring of behaviour	2. Feedback and monitoring	Establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy *Note: if monitoring is part of a data collection procedure rather than a strategy aimed at changing behavior, do not code; if monitoring of outcome of behavior, code 2.4, Self-monitoring of outcome(s) of behavior; if monitoring is by someone else (without feedback), code 2.1, Monitoring of behavior by others without feedback*	3	"CFHealthHub: • Charts and tables of objective adherence data presented within CFHealthHub Interventionist: • Introducing and explaining charts and tables to participants." (Hind 2017; Wildman 2022[a])
2.4. Self-monitoring of outcome(s) of behaviour	2. Feedback and monitoring	Establish a method for the person to monitor and record the outcome(s) of their behavior as part of a behavior change strategy *Note: if monitoring is part of a data collection procedure rather than a strategy aimed at changing behavior, do not code ; if monitoring behavior, code 2.3, Self-monitoring of behavior; if monitoring is by someone else (without feedback), code 2.5, Monitoring outcome(s) of behavior by others without feedback*	1	"Subjects in this group were asked to use the Spiro PD personal spirometer to check their lung function once a week for 3 months." (Shakkottai 2017)
2.6. Biofeedback	2. Feedback and monitoring	Provide feedback about the body (e.g. physiological or biochemical state) using an external monitoring device as part of a behavior change strategy *Note: if Biofeedback, code only 2.6, Biofeedback and not 2.2, Feedback on behavior or 2.7, Feedback on outcome(s) of behaviour*	1	"Participants were trained on the appropriate use of their device at the time of enrollment. They also **r**eceived weekly telephone calls from a respiratory therapist to review that week's lung function results." (Shakkottai 2017)
2.7. Feedback on outcome(s) of behavior	2. Feedback and monitoring	Monitor and provide feedback on the outcome of performance of the behavior *Note: if Biofeedback, code only 2.6, Biofeedback and not 2.7, Feedback on outcome(s) of behavior; if feedback is on behavior code 2.2, Feedback on behavior; if there is no clear evidence that feedback was given code 2.5, Monitoring outcome(s) of behavior by others without feedback; if feedback on behaviour is evaluative e.g. praise, also code 10.4, Social reward*	1	"The intervention will begin by providing the patient personal feedback on their adherence (using pharmacy refill data) and health outcomes (e.g. trajectory of lung function values, frequency of exacerbations) as well as clinic-level figures showing the association between adherence and health outcomes." (Riekert 2013)

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

3.1. Social support (unspecified)	3. Social support	Advise on, arrange or provide social support (e.g. from friends, relatives, colleagues, 'buddies' or staff) or non-contingent praise or reward for performance of the behavior. It includes encouragement and counselling, but only when it is directed at the behavior *Note: attending a group class and/or mention of 'follow-up' does not necessarily apply this BCT, support must be explicitly mentioned; if practical, code 3.2, Social support (practical); if emotional, code 3.3, Social support (emotional) (includes 'Motivational interviewing' and 'Cognitive Behavioral Therapy')*	4	"The coaching intervention included the following elements: client-centeredness, empathy and collaboration, focus on preferences, reflective dialogue, use of positive language, and promotion of capacity and self-determination. Sessions included different tools; for example, “the wheel of life” on which coachees could rate their level of satisfaction in different life areas." (Knudsen 2016)
3.2. Social support (practical)	3. Social support	Advise on, arrange, or provide practical help (e.g. from friends, relatives, colleagues, 'buddies' or staff) for performance of the behavior *Note: if emotional, code 3.3, Social support (emotional); if general or unspecified, code 3.1, Social support (unspecified) If only restructuring the physical environment or adding objects to the environment, code 12.1, Restructuring the physical environment or 12.5, Adding objects to the environment; attending a group or class and/or mention of 'follow-up' does not necessarily apply this BCT, support must be explicitly mentioned.*	3	"Find Solutions Remembering: Tick the boxes for the different ways that you could use to remember to do your treatment. Write down more ways that you think of. Put a timetable on fridge; Ask a family member to remind me; Put a sign up in my parent’s bedroom; Put a sign up in my bedroom; I just remember; Other _____." (Downs 2006)
3.3. Social support (emotional)	3. Social support	Advise on, arrange, or provide emotional social support (e.g. from friends, relatives, colleagues, 'buddies' or staff) for performance of the behavior *Note: if practical, code 3.2, Social support (practical); if unspecified, code 3.1, Social support (unspecified)*	1	"Team partners have a big responsibility for chest treatments. Your role includes: doing and helping your child to do regular chest assessment and treatment; teaching your child about treatment and encouraging them to stick with it; being an important role model of a healthy lifestyle; being able to talk and deal with problems when they arise. It is a big job and not always easy." (Downs 2006)

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

4.1. Instruction on how to perform the behavior	4. Shaping knowledge	Advise or agree on how to perform the behavior (includes 'Skills training') *Note: when the person attends classes such as exercise or cookery, code 4.1, Instruction on how to perform the behavior, 8.1, Behavioral practice/rehearsal and 6.1, Demonstration of the behavior*	5	"The intervention also includes provision of a written, Prescribed Treatment Plan, assessment and remediation of gaps in Knowledge of Disease Management, and evaluation and re-instruction/ re-training of skills needed to perform daily treatments." (Quittner 2019)
5.1. Information about health consequences	5. Natural consequences	Provide information (e.g. written, verbal, visual) about health consequences of performing the behavior *Note: consequences can be for any target, not just the recipient(s) of the intervention; emphasising importance of consequences is not sufficient; if information about emotional consequences, code 5.6, Information about emotional consequences; if about social, environmental or unspecified consequences code 5.3, Information about social and environmental consequences*	4	"The intervention will begin by providing the patient personal feedback on their adherence (using pharmacy refill data) and health outcomes (e.g., trajectory of lung function values, frequency of exacerbations) as well as clinic-level figures showing the association between adherence and health outcomes." (Riekert 2013)
5.2. Salience of consequences	5. Natural consequences	Use methods specifically designed to emphasise the consequences of performing the behaviour with the aim of making them more memorable (goes beyond informing about consequences) *Note: if information about consequences, also code 5.1, Information about health consequences, 5.6, Information about emotional consequences or 5.3, Information about social and environmental consequences*	3	"Some children also need to use nebulisers and puffers. Don't wait until you get sick before you do your treatments. BE A GERM BUSTER and BUST GERMS TODAY! Draw some more germs in the box below." (Downs 2006)
6.1. Demonstration of the behavior	6. Comparison of behaviour	Provide an observable sample of the performance of the behaviour, directly in person or indirectly e.g. via film, pictures, for the person to aspire to or imitate (includes 'Modelling'. *Note: if advised to practice, also code, 8.1, Behavioural practice and rehearsal; If provided with instructions on how to perform, also code 4.1, Instruction on how to perform the behaviour*	3	"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." (Hind 2017; Wildman 2022[a])

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

6.3. Information about others' approval	6. Comparison of behaviour	Provide information about what other people think about the behavior. The information clarifies whether others will like, approve or disapprove of what the person is doing or will do	1	"This is what one child said. “Don’t say “It will be OK, I’ll sort it out tomorrow”, because infections can happen slowly. Once I feel tired and have less energy, then I don’t want to do my chest treatments at all.” (Downs 2006)
7.1. Prompts/ cues	7. Associations	Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behavior. The prompt or cue would normally occur at the time or place of performance *Note: when a stimulus is linked to a specific action in an if-then plan including one or more of frequency, duration or intensity also code 1.4, Action planning.*	4	"Devices were programmed to provide daily medication reminders for inhaled hypertonic saline, dornase alfa, and CF multivitamins." (Shakkottai 2017)
8.1. Behavioral practice/rehearsal	8. Repetition and substitution	Prompt practice or rehearsal of the performance of the behavior one or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill *Note: if aiming to associate performance with the context, also code 8.3, Habit formation*	3	"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." (Hind 2017; Wildman 2022[a])
8.3. Habit formation	8. Repetition and substitution	Prompt rehearsal and repetition of the behavior in the same context repeatedly so that the context elicits the behavior *Note: also code 8.1, Behavioral practice/rehearsal*	3	"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 nec-

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

				essary)." (Hind 2017; Wildman 2022[a])
8.7. Graded tasks	8. Repetition and substitution	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	2	"Interventionist: • Discussion and agreement of goals with interventionist • Review of goals • Suggested steady increase in goal as improvements are made." (Hind 2017; Wildman 2022[a])
9.1. Credible source	9. Comparison of outcomes	Present verbal or visual communication from a credible source in favour of or against the behavior *Note: code this BCT if source generally agreed on as credible e.g., health professionals, celebrities or words used to indicate expertise or leader in field and if the communication has the aim of persuading; if information about health consequences, also code 5.1, Information about health consequences, if about emotional consequences, also code 5.6, Information about emotional consequences; if about social, environmental or unspecified consequences also code 5.3, Information about social and environmental consequences*	4	"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." (Hind 2017; Wildman 2022[a])
9.2. Pros and cons	9. Comparison of outcomes	Advise the person to identify and compare reasons for wanting (pros) and not wanting to (cons) change the behavior (includes 'Decisional balance') *Note: if providing information about health consequences, also code 5.1, Information about health consequences; if providing information about emotional consequences, also code 5.6, Information about emotional consequences; if providing information about social, environmental or unspecified consequences also code 5.3, Information about social and environmental consequences*	2	"An important aspect of this work is the weighing up of the pros and cons of the problem and the solution, for example, helping them to make positive evaluations of increasing their nebuliser use (looking for the benefits) and weighing them as more important than the 'costs' of increasing their nebuliser use (time consumption, inconvenience etc.)." (Quinn 2004)
10.3. Non-specific reward	10. Reward and threat	Arrange delivery of a reward if and only if there has been effort and/or progress in performing the behavior (includes 'Positive reinforcement')	1	"This week's activity is to fill the waves with sea creatures for doing all your chest treatments... Did you complete 5 or more waves last week? If you didn't, do the activity

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

		Note: if reward is material, code 10.2, Material reward (behavior), if social, code 10.4, Social reward, and not 10.3, Nonspecific reward; if reward is for outcome code 10.10, Reward (outcome). If informed of reward in advance of rewarded behaviour, also code one of: 10.1, Material incentive (behaviour); 10.5, Social incentive; 10.6, Non-specific incentive; 10.7, Self-incentive; 10.8, Incentive (outcome)		again this week. If you did, enjoy your reward for learning about chest treatments. My reward for learning more about chest treatments is ____". (Downs 2006)
10.4. Social reward	10. Reward and threat	Arrange verbal or non-verbal reward if and only if there has been effort and/or progress in performing the behavior (includes 'Positive reinforcement') *Note: if reward is material, code 10.2, Material reward (behavior), if unspecified code 10.3, Non-specific reward, and not 10.4, Social reward; if reward is for outcome code 10.10, Reward (outcome). If informed of reward in advance of rewarded behaviour, also code one of: 10.1, Material incentive (behaviour); 10.5, Social incentive; 10.6, Non-specific incentive; 10.7, Self-incentive; 10.8, Incentive (outcome)*	3	"This intervention is designed to increase knowledge and enhance the skills needed to optimize CF-management. The strategies used to achieve improved adherence include providing didactic education and skills training, and proscriptively using behavioral modification strategies, such as positive reinforcement for desired behaviors, and problem-solving training to overcome barriers." (Riekert 2013)
10.7. Self-incentive	10. Reward and threat	Plan to reward self in future if and only if there has been effort and/or progress in performing the behavior *Note: if self-reward is material, also code 10.1, Material incentive (behavior), if social, also code 10.5, Social incentive, if unspecified, also code 10.6, Non-specific incentive; if incentive is for outcome code 10.8, Incentive (outcome). If reward is delivered also code one of: 10.2, Material reward (behavior); 10.3, Non-specific reward; 10.4, Social reward, 10.9, Selfreward; 10.10, Reward (outcome)*	1	"This week's activity is to fill the waves with sea creatures for doing all your chest treatments. Find the activity sheet with the picture of the sea. Draw and colour a sea creature in each day's wave when you have remembered, fitted in and done all your treatments. Enjoy watching it fill up." (Downs 2006)
10.9. Self-reward	10. Reward and threat	Prompt self-praise or self-reward if and only if there has been effort and/or progress in performing the behavior *Note: if self-reward is material, also code 10.2, Material reward (behavior), if social, also code 10.4, Social reward, if unspecified, also code 10.3, Non-specific reward; if reward is for outcome code 10.10, Reward (outcome). If informed of reward in advance of rewarded behaviour, also code one of: 10.1, Material incentive (behaviour); 10.5, Social incen-*	1	"This week's activity is to fill the waves with sea creatures for doing all your chest treatments. Find the activity sheet with the picture of the sea. Draw and colour a sea creature in each day's wave when you have remembered, fitted in and done all your treatments. Enjoy watching it fill up." (Downs 2006)

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

		tive; 10.6, Non-specific incentive; 10.7, Selfincentive; 10.8, Incentive (outcome)		
11.2. Reduce negative emotions	11. Regulation	Advise on ways of reducing negative emotions to facilitate performance of the behavior (includes 'Stress management') *Note: if includes analysing the behavioural problem, also code 1.2, Problem solving*	1	"The chapters contain information and exercises to explore the clinical nature of the respiratory aspect of CF; the promotion of co-operative behaviour and teamwork; the use of cognitive theories that promote optimism and help the child cope with negative feelings about long-term treatments; and issues pertaining to recommended aerosol and ACT treatments." (Downs 2006)
12.1. Restructuring the physical environment	12. Antecedents	Change, or advise to change the physical environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments) *Note: this may also involve 12.3, Avoidance/reducing exposure to cues for the behavior; if restructuring of the social environment code 12.2, Restructuring the social environment; if only adding objects to the environment, code 12.5, Adding objects to the environment*	3	"In the Action stage, the person actively modifies their behaviour, experience or environment in order to improve their nebuliser use." (Quinn 2004)
12.2. Restructuring the social environment	12. Antecedents	Change, or advise to change the social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments) *Note: this may also involve 12.3, Avoidance/reducing exposure to cues for the behavior; if also restructuring of the physical environment also code 12.1, Restructuring the physical environment*	1	"In the Action stage, the person actively modifies their behaviour, experience or environment in order to improve their nebuliser use." (Quinn 2004)
12.5. Adding objects to the environment	12. Antecedents	Add objects to the environment in order to facilitate performance of the behavior *Note: Provision of information (e.g. written, verbal, visual) in a booklet or leaflet is insufficient. If this is accompanied by social support, also code 3.2, Social support (practical); if the environment is changed beyond the addition of objects, also code 12.1, Restructuring the physical environment*	4	"...we also conducted a pilot study to assess the feasibility of a portable personal spirometer device that also provided medication reminders among pediatric CF patients." (Shakkottai 2017)

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

13.2. Framing/reframing	13. Identity	Suggest the deliberate adoption of a perspective or new perspective on behavior (e.g. its purpose) in order to change cognitions or emotions about performing the behavior (includes 'Cognitive structuring'); *If information about consequences then code 5.1, Information about health consequences, 5.6, Information about emotional consequences or 5.3, Information about social and environmental consequences instead of 13.2, Framing/reframing*	1	"Write 1 of your negative thoughts about chest treatments in the top thought bubble. Draw a face to show how this makes you feel. Then, think of a positive thought that will help you to feel better about treatment and write this in the bottom thought bubble. Draw a face to show how this might make you feel." (Downs 2006)
13.3. Incompatible beliefs	13. Identity	Draw attention to discrepancies between current or past behavior and self-image, in order to create discomfort (includes 'Cognitive dissonance')	1	"The intervention uses dialogue from the patient to create dissonance when ambivalent about behaviour change by weighing the importance of change against the costs of not changing." (Quinn 2004)
15.1. Verbal persuasion about capability	15. Self-belief	Tell the person that they can successfully perform the wanted behavior, arguing against self-doubts and asserting that they can and will succeed	1	"Getting mucus out of your lungs helps you to stay healthy. You CAN learn how to do your chest treatments well." (Downs 2006)
15.3. Focus on past success	15. Self-belief	Advise to think about or list previous successes in performing the behavior (or parts of it)	2	"Interventionist: • Interventionist encouraging focus on periods of higher adherence on charts." (Hind 2017; Wildman 2022[a])
15.4. Self-talk	15. Self-belief	Prompt positive self-talk (aloud or silently) before and during the behavior	2	"Interventionist: • Interventionist introducing and highlighting relevant content on CFHealthHub • Interventionist eliciting self-talk through discussion of motivation." (Hind 2017; Wildman 2022[a])
16.3. Vicarious consequences	16.3. Vicarious consequences	Prompt observation of the consequences (including rewards and punishments) for others when they perform the behavior *Note: if observation of health consequences, also code 5.1, Information about health consequences; if of emotional consequences, also code 5.6, Information about emotional consequences, if of social, environmental or unspecified consequences, also code*	2	"CFHealthHub: • Demonstration of techniques for nebuliser use, cleaning and treatment mixing • Information about CF, the need for treatment, how each treatment works, and the importance of adherence

Table 2. Definitions and illustrative quotations of behaviour change techniques present in one or more of the included studies *(Continued)*

	5.3, Information about social and environmental consequences	• 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 PWCF, Clinicians, links to scientific papers Interventionist: • **I**nterventionist introducing and highlighting relevant content on CFHealthHub." (Hind 2017; Wildman 2022[a])

BCT: behaviour change technique
BCT definitions taken from the BCT Taxonomy (v1) (Michie 2013).
[a]The same intervention was used in two included studies but with different populations (Hind 2017 was a feasibility trial conducted in two CF centres; Wildman 2022 was a larger RCT conducted in 19 different CF centres).

APPENDICES

Appendix 1. Search Methods – Electronic Searches

Database/Resource	Strategy	Date last searched
PubMed	#1 randomized controlled trial [pt]	11 August 2022
(1946 to present)	#2 controlled clinical trial [pt]	
	#3 randomized [tiab]	
	#4 placebo [tiab]	
	#5 drug therapy [sh]	
	#6 randomly [tiab]	
	#7 trial [tiab]	
	#8 groups [tiab]	
	#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	
	#10 animals [mh] NOT humans [mh]	
	#11 #9 NOT #10	
	#12 "cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR mucoviscidose	

(Continued)

	#13 adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform #14 "psychology"[MeSH Terms] OR "mind-body therapies"[MeSH Terms] OR "psychotherapy"[MeSH Terms] OR "psychology, applied"[MeSH Terms] OR "neuropsychology"[MeSH Terms] OR Psycholog* OR Psychosocial OR psychotherapy OR psychotherapies OR psychotherapist OR psychoanal* OR psychodrama OR behavio* OR attitude* OR communicat* OR reward* OR remind* OR educate OR education OR supervis* OR family* OR families OR train* OR monitor* OR problem* OR team* OR diary OR diaries OR counsel* OR feedback OR reinforc* OR motivat* OR self-regulat* OR cope OR coping OR emotion* OR social* OR sociol* OR cognitive OR cognition OR mental* OR verbal* OR construct OR crisis OR aversion OR assertiv* OR accept* OR mind OR mindful* OR mood* OR support* OR wellness OR habit* OR talk* OR depress* OR goal* OR support* OR hypnosis OR hypnotherap* #15 #11 AND #12 AND #13 AND #14 **NOTE: Lines #1- #11 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format*	
PsychINFO EBSCO (1887 to present)	S1 (TX "cystic fibrosis" OR mucoviscidosis OR mucoviscidose) OR (SU "Cystic Fibrosis") S2 TX adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform S3 SU "Psychology" OR SU "Abnormal Psychology" OR SU "Applied Psychology" OR SU "Clinical Psychology" OR SU "Cognitive Psychology" OR SU "Comparative Psychology" OR SU "Consulting Psychology" OR SU "Correctional Psychology" OR SU "Cross Cultural Psychology" OR SU "Depth Psychology" OR SU "Developmental Psychology" OR SU "Ecological Psychology" OR SU "Evolutionary Psychology" OR SU "Experimental Psychology" OR SU "Feminist Psychology" OR SU "Folk Psychology" OR SU "Forensic Psychology" OR SU "Geropsychology" OR SU "Health Care Psychology" OR SU "Humanistic Psychology" OR SU "International Psychology" OR SU "Mathematical Psychology" OR SU "Metapsychology" OR SU "Neuroeconomics" OR SU "Physiological Psychology" OR SU "Positive Psychology" OR SU "Psychodynamics" OR SU "Psychology of Men" OR SU "Psychology of Women" OR SU "Self Psychology" S4 SU "Mind Body Therapy" S5 SU "Psychotherapy" OR SU "Adlerian Psychotherapy" OR SU "Adolescent Psychotherapy" OR SU "Affirmative Therapy" OR SU "Analytical Psychotherapy" OR SU "Autogenic Training" OR SU "Brief Psychotherapy" OR SU "Brief Relational Therapy" OR SU "Child Psychotherapy" OR SU "Client Centered Therapy" OR SU "Conversion Therapy" OR SU "Couples Therapy" OR SU "Eclectic Psychotherapy" OR SU "Emotion Focused Therapy" OR SU "Existential Therapy" OR SU "Experiential Psychotherapy" OR SU "Expressive Psychotherapy" OR SU "Eye Movement Desensitization Therapy" OR SU "Feminist Therapy" OR SU "Geriatric Psychotherapy" OR SU "Gestalt Therapy" OR SU "Group Psychotherapy" OR SU "Guided Imagery" OR SU "Humanistic Psychotherapy" OR SU "Hypnotherapy" OR SU "Individual Psychotherapy" OR SU "Insight Therapy" OR SU "Integrative Psychotherapy" OR SU "Interpersonal Psychotherapy" OR SU "Logotherapy" OR SU "Narrative Therapy" OR SU "Network Therapy" OR SU "Persuasion Therapy" OR SU "Primal Therapy" OR SU "Psychoanalysis" OR SU "Psychodrama" OR SU "Psychodynamic Psychotherapy" OR SU "Psy-	7 August 2022

(Continued)

	chotherapeutic Counseling" OR SU "Psychotherapeutic Techniques" OR SU "Rational Emotive Behavior Therapy" OR SU "Reality Therapy" OR SU "Relationship Therapy" OR SU "Solution Focused Therapy" OR SU "Strategic Therapy" OR SU "Supportive Psychotherapy" OR SU "Transactional Analysis" S6 SU "Applied Psychology" OR SU "Clinical Psychology" OR SU "Coaching Psychology" OR SU "Community Psychology" OR SU "Consumer Psychology" OR SU "Counseling Psychology" OR SU "Educational Psychology" OR SU "Engineering Psychology" OR SU "Environmental Psychology" OR SU "Industrial and Organizational Psychology" OR SU "Military Psychology" OR SU "Occupational Health Psychology" OR SU "Political Psychology" OR SU "Social Psychology" OR SU "Sport Psychology" OR SU "Suicidology" S7 SU "Neuropsychology" S8 TX Psycholog* OR Psychosocial OR psychotherapy OR psychotherapies OR psychotherapist OR psychoanal* OR psychodrama OR behavio* OR attitude* OR communicat* OR reward* OR remind* OR educate OR education OR supervis* OR family* OR families OR train* OR monitor* OR problem* OR team* OR diary OR diaries OR counsel* OR feedback OR reinforc* OR motivat* OR self-regulat* OR cope OR coping OR emotion* OR social* OR sociol* OR cognitive OR cognition OR mental* OR verbal* OR construct OR crisis OR aversion OR assertiv* OR accept* OR mind OR mindful* OR mood* OR support* OR wellness OR habit* OR talk* OR depress* OR goal* OR support* OR hypnois OR hypnothesrap* S9 (S1 AND S2) AND (S3 OR S4 OR S5 OR S6 OR S7 OR S8)	
Scopus (1823 to present)	1 cystic fibrosis OR mucoviscidosis OR mucoviscidose *[Article title, Abstract, Keywords]* 2 adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform 3 Psycho* OR behavio* OR attitude* OR communicat* OR reward* OR remind* OR educat* OR supervis* OR famil* OR train* OR monitor* OR problem* OR team* OR diar* OR counsel* OR feedback OR reinforc* OR motivat* OR self-regulat* OR cope OR coping OR emotion* 4 social* OR socio* OR cognitive OR mental* OR verbal* OR condition* OR knowledge OR personal OR construct OR crisis OR aversion OR assertiv* OR Accept* OR commit* OR mind* OR mood* OR support* OR well* OR habit* OR talk* OR depress* 5 #3 OR #4 6 #1 AND #2 AND #5 **NOTE: maximum number of characters exceeded in Line #3, so psychological search terms divided into two search lines and combined using OR operator (Line #5)*	7 August 2022
OpenGrey	(cystic fibrosis OR mucoviscidosis OR mucoviscidose) AND (adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform)	14 November 2020
Clinicaltrials.gov	[Advanced Search] CONDITION/ DISEASE: cystic fibrosis OR mucoviscidosis OR mucoviscidose	7 August 2022

(Continued)

	OTHER TERMS: adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform STUDY TYPE: Interventional Studies (Clinical Trials)	
WHO ICTRP	[Basic Search] (cystic fibrosis OR mucoviscidosis OR mucoviscidose) AND (adhere OR adherence OR adhered OR nonadherence OR persist OR persistance OR persisted OR compliance OR comply OR complied OR noncompliance OR concordance OR non concordance OR cooperative OR cooperation OR cooperate OR cooperated OR uncooperative OR conform)	14 August 2022

HISTORY

Protocol first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

Task	Author(s) responsible
Protocol stage: draft the protocol	SD
Protocol stage: review/editing	SD; LC; DCC; CG
Review stage: select which trials to include (2 + 1 arbiter)	SD and LC/CG
Review stage: extract data from trials (2 people)	SD; CG (2 trials: LC; DCC)
Review stage: code BCTs in included trials (2 people)	SD; CG
Review stage: enter data into RevMan	SD
Review stage: carry out the analysis	SD
Review stage: interpret the analysis	SD; LC; DCC
Review stage: draft the final review	SD
Review stage: review/editing	SD; LC; CG; DCC
Update stage: update the review	SD

DECLARATIONS OF INTEREST

SD is employed by Nottingham University Hospitals NHS Trust to work on the CFHealthHub Data Observatory, which aims to embed objective adherence data into routine CF care using quality improvement cycles. She did not have any involvement in either the CFHealthHub feasibility study or RCT included in this review.

CG is employed by the University of Sheffield, Clinical Trials Research Unit, and previously managed a clinical trial related to supporting people with CF with adherence behaviours "CFHealthHub Data Observatory" (IRAS 216782 portfolio 33331); the funding was from NHS England.

LC declares no potential conflict of interest.

DCC declares no potential conflict of interest.

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Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we specified how we would deal with studies reporting multiple measures of adherence (i.e. the most reliable measure would be reported, with objective measures preferentially reported over subjective measures, using the hierarchy of validity detailed in the protocol). However, we did not specify what we would do if trials reported multiple measurements or observations from each participant for other outcomes (e.g. if depression was assessed for each participant using multiple measures). In the review, we decided to present the data for each measure and not present the totals or summary statistics for each of these outcomes which avoids a unit of analysis issue by double-counting participants; we did not select one measure over another because the reported measures were validated, standardised questionnaires (e.g. Major Depression Inventory (MDI) (Bech 2001) and Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977)) and we were not aware that one measure was more valid or reliable than the other. If we had to selectively choose an outcome to include in the data analyses, this could have biased the results. We clarified this in the methods and specified that this was added post hoc (Unit of analysis issues).

We used software for screening which was not stated in the protocol (Covidence).

We have clarified how we interpreted the standardised mean difference (SMD) (Measures of treatment effect).

In the summary of findings tables, we planned to report adherence to inhaled therapies (% completed treatments) using the SMD for all results combined from six to 12 months, but since only one trial was included for this outcome in 'Summary of findings 1', we instead reported using the MD.

In addition, one trial assessed a quality of life (QoL) outcome using a measure that was completed independently by both children or adolescents with cystic fibrosis (CF) and parents or caregivers of people with CF (i.e. both child and parent scores were reported on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009)). As we had not specified how we would deal with this issue in the protocol, we decided to include only data from the children or adolescents with CF in the data analyses, to avoid double-counting of participants. We then narratively described parent or caregiver scores in the results section.

In the review, we included trials that did not just measure adherence to inhaled therapies but used a composite medication possession ratio (cMPR) measure (which included at least one non-inhaled therapy as well as inhaled therapies). We did not specify a method for dealing with this particular issue in the protocol. Where MPR for individual drugs was not available, we decided to contact the investigators to request the subset results for participants on inhaled therapies only. If this was not available or if there was no response from the investigators, we decided to include the cMPR results and to highlight in the methods and results that this outcome included a combination of inhaled and non-inhaled therapies. We also added a proposed subgroup analysis to the methods to look at the effects of these studies where adherence to multiple therapies was being studied compared to inhaled therapies only.

In the protocol, we did not specify which QoL domains we would report in the summary of findings tables (Dawson 2020). As there are many QoL domains, we decided to present data for two domains which were deemed to be most relevant to the review (treatment burden and respiratory symptoms) (Summary of findings 1; Summary of findings 2). We reported the results for all QoL domains in the 'Effects of interventions' and 'Data and analyses' sections.

INDEX TERMS

Medical Subject Headings (MeSH)

Anxiety [therapy]; Anxiety Disorders; *Cognitive Behavioral Therapy; *Cystic Fibrosis [complications] [drug therapy]; Psychosocial Intervention; Quality of Life

MeSH check words

Adolescent; Adult; Child; Humans