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[Intervention Review]

Digital technology for monitoring adherence to inhaled therapies in people with cystic fibrosis

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ABSTRACT

Background

Improved understanding and treatment of cystic fibrosis (CF) has led to longer life expectancy, which is accompanied by an increasingly complex regimen of treatments. Suboptimal adherence to the treatment plan, in the context of respiratory disease, has been found to be associated with poorer health outcomes. With digital technology being more accessible, it can be used to monitor adherence to inhaled therapies via chipped nebulisers, mobile phone apps and web-based platforms. This technology can allow monitoring of adherence as well as clinical outcomes, and allow feedback to both the person with CF and their healthcare team.

Objectives

To assess the effects of using digital technology to monitor adherence to inhaled therapies and health status in adults and children with CF.

Search methods

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

Date of last search: 28 October 2021.

We also searched Embase and three clinical trial registries and checked references of included studies.

Date of last search: 9 November 2021.

Selection criteria

We searched for randomised controlled trials (RCTs) looking at the effects of a digital technology for monitoring adherence of children and adults with CF to inhaled therapies.

Data collection and analysis

Two review authors screened the search results for studies eligible for inclusion in the review and extracted their data. We used Risk of Bias 2 for assessing study quality. We assessed the overall certainty of the evidence using GRADE.

Main results

We included two studies in our review, with 628 participants aged five to 41 years. There was one study each for two different comparisons.

Nebuliser target inhalation mode versus standard inhalation mode

The included parallel study was carried out over 10 weeks after a run-in period of four to six weeks. The study compared the effects of a digitally enhanced inhalation mode (target inhalation mode) for nebulised antibiotics compared to standard mode in children attending a regional CF clinic in the United Kingdom. The study's primary outcome was the time taken to complete the inhaled treatment, but investigators also reported on adherence to therapy. The results showed that there may be an improvement in adherence with the target inhalation mode when this intervention is used (mean difference (MD) 24.0%, 95% confidence interval (CI) 2.95 to 45.05; low-certainty evidence). The target inhalation mode may make little or no difference to forced expiratory volume in one second (FEV_1) % predicted (MD 1.00 % predicted, 95% CI -9.37 to 11.37; low-certainty evidence). The study did not report on treatment burden, quality of life (QoL) or pulmonary exacerbations.

eNebuliser with digital support versus eNebuliser without support

One large multicentre RCT monitored adherence via data-tracking nebulisers. The intervention group also receiving access to an online web-based platform, CFHealthHub, which offered tailored, flexible support from the study interventionist as well as access to their adherence data, educational and problem-solving information throughout the 12-month trial period. We graded all evidence as moderate certainty. Compared to usual care, the digital intervention probably improves adherence to inhaled therapy (MD 18%, 95% CI 12.90 to 23.10); probably leads to slightly reduced treatment burden (MD 5.1, 95% CI 1.79 to 8.41); and may lead to slightly improved FEV_1 % predicted (MD 3.70, 95% CI -0.23 to 7.63). There is probably little or no difference in the incidence of pulmonary exacerbations or QoL between the two groups.

Authors' conclusions

Digital monitoring plus tailored support via an online platform probably improves adherence to inhaled therapies and reduces treatment burden (but without a corresponding change in QoL) in the medium term (low- and moderate-certainty evidence). In a shorter time frame, technological enhancement of inhaling antibiotics may improve adherence to treatment (low-certainty evidence). There may be little or no effect on lung function with either intervention, and online monitoring probably makes no difference to pulmonary exacerbations.

Future research should assess the effect of digital technology on adherence in both children and adults. Consideration of adherence to the total treatment regimen is also important, as an improvement in adherence to inhaled therapies could come at the cost of adherence to other parts of the treatment regimen.

PLAIN LANGUAGE SUMMARY

Do digital technologies help people with cystic fibrosis stick to their inhaled treatments?

Key messages

In the short term, technology may help people with cystic fibrosis (CF) adhere (or 'stick to') their inhaled treatments, but have little or no effect on lung function or pulmonary exacerbations (flare-ups of disease).

In the medium term, combining digital monitoring with tailored support via an online platform probably encourages people to adhere to inhaled treatment and reduces treatment burden (demands on people with CF made by their healthcare needs and the impact this has on their well-being) but without improving quality of life.

Future research should look at using digital technology to help children and adults with CF adhere to their inhaled treatments and consider how this affects other areas of their treatment plan.

What is CF?

CF is a life-threatening, inherited condition where sticky, thick mucus builds up in the lungs and digestive system. Over time, the lungs become damaged and may eventually stop working properly.

How is CF treated?

There is currently no cure for CF, but treatment helps control symptoms and reduce complications. Treatments include antibiotics to prevent and treat chest infections, and medicines to thin the mucus in the lungs, making it easier to cough up. People with CF use inhalers and nebulisers to deliver medicines quickly to the lungs. Nebulisers are small machines that change liquid medicine into a mist which is then inhaled through a mouthpiece or mask.

Treating CF is complicated and time-consuming; people with CF typically spend 2 to 2.5 hours daily on treatment.

Generally, digital technologies are increasingly used to help people monitor their health and fitness via activity trackers and mobile phone apps. For people with CF, digital technologies are used for tracking and improving how they manage their treatment. Some technologies allow information to be uploaded to the Internet, so individuals and their healthcare teams can immediately use this information to monitor and improve treatment.

What did we want to find out?

Can digital technology help people with CF adhere to their inhaled treatments?

Do digital technologies for monitoring adherence have any unwanted or harmful effects?

What did we do?

We searched for studies examining any kind of digital technology for monitoring adherence to inhaled treatments for CF. We summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found two studies using different digital technologies. We could not combine their results and analysed them separately. Both studies put the people taking part into one of two groups at random, with equal chances of being in either group.

One small study compared two breathing modes of a digital nebuliser in 20 children aged 5 to 16 years (the nebuliser delivered an antibiotic as an inhaled mist). One mode encouraged children to take longer, deeper breaths via an adapted mouthpiece; the other mode consisted of the usual breathing pattern. The study lasted for 10 weeks.

The larger study involved 608 people aged 16 years and older. It compared a data-tracking nebuliser paired with a web-based platform called CFHealthHub to the same nebuliser used without the web-based platform. CFHealthHub gave participants access to their adherence data and individual support from study investigators, who collected data for 12 months.

Key results

The study comparing inhalation modes found that the children using the digitally enhanced breathing mode recorded higher adherence to nebuliser treatment than the children using the usual breathing mode. However, this may make little difference to lung function. There were no adverse (harmful or unwanted) effects from using the different inhalation modes.

The second study showed that combining an online programme with a data-tracking nebuliser probably improves adherence compared to just using the nebuliser. The combination of nebuliser plus online support also probably lowers the 'burden of treatment'. However, it probably makes little or no difference to quality of life or the number of flare-ups of disease. The group using the online platform reported slightly more adverse events, but we found no difference between groups in adverse effects we considered directly related to treatment (measured using anxiety and depression scores).

What are the limitations of the evidence?

Our confidence in the evidence from the smaller study is limited because it was very small and focused on children, whereas our question was broader. It also only reported on two of our planned outcomes.

Our confidence in the evidence from the larger study ranged from low to moderate. This study was larger and looked at more of our outcomes. However, this study only included people aged 16 and older, so we do not know whether its findings apply to younger children.

Current evidence for how digital technology can improve adherence to inhaled treatments is limited. Future research should assess how technology can improve adherence to inhaled treatments in children and adults and consider how this affects the total treatment plan (adhering to inhaled treatments may decrease time spent on other treatments).

How up to date is the evidence?

The evidence is current to 28 October 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Digital technology (TIM) compared with standard treatment (TBM) for monitoring adherence to inhaled therapies in people with cystic fibrosis

Digital technology compared with standard treatment for monitoring adherence to inhaled therapies in people with cystic fibrosis						
Patient or population: children aged 5 to 16 years **Settings**: home or outpatient **Intervention**: adaptive aerosol delivery of inhaled therapy with a digitally set TIM **Comparison**: adaptive aerosol delivery of inhaled therapy set in TBM (standard technique)						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	TBM	**TIM**				
Adherence to the inhaled treatment: Follow-up: up to 6 months	The mean (SD) adherence in the TBM group was 65% (33).	The mean adherence in the TIM group was 24% higher (2.95% higher to 45.05% higher).	MD 24.00 (2.95 to 45.05)	20 (1)	⊕⊕⊖⊖**Low**[a,b]	
Treatment burden Follow-up: up to 6 months	This outcome was not measured.					
QoL Follow-up: up to 6 months	This outcome was not measured.					

FEV_1 (mean change from baseline, % predicted) Follow-up: up to 6 months	Mean (SD) FEV_1 (% predicted) improved by 1.2% (12.77).	Mean change in FEV_1 % predicted in the TIM group was 1.00% higher (9.37% lower to 11.37% higher).	MD 1.00 (-9.37 to 11.37)	20 (1)	⊕⊕⊖⊖**Low**[a,b]
Number of pulmonary exacerbations Follow-up: end of study	This outcome was not measured.				

*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).

CI: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **QoL**: quality of life; **TBM**: tidal breathing mode; **TIM**: target inhalation mode

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 one level due to imprecision as the CI around the mean is large.
[b]Downgraded one level due to indirectness as the study was carried out in children aged 5 to 16 years of age. The results may not be applicable to adults.

Summary of findings 2. Digital technology (web-based platform CFHealthHub) compared with usual care for monitoring adherence to inhaled therapies in people with cystic fibrosis

Digital technology (CFHealthHub) compared to usual care for monitoring adherence to inhaled therapies
Patient or population: people with CF aged 16 years and over
Settings: outpatients
Intervention: CFHealthHub - electronic data-logging nebulisers plus a digital web-based platform with feedback to support participants

Comparison: usual care - electronic data-logging nebulisers but no access to digital platform or feedback

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	CFHealthHub				
Adherence to the inhaled treatment: percentage adherence Follow-up: 12 months	The mean (SD) adherence in the usual care group was 34.9% (31.7).	The mean adherence in the CFHealthHub group was 18% higher (2.95% higher to 45.05% higher).	MD 18.00 (12.90 to 23.10)	588 (1)	⊕⊕⊕⊖ **Moderate**[a]	The study authors also present data adjusted for baseline differences MD 9.5 (95% CI 8.6 to 10.4), and once these are allowed for, adherence is still 10% higher in the intervention group (CFHealthHub 2017)
Treatment burden: CFQ-R treatment burden domain score (higher score is better) Follow-up: 12 months	The mean (SD) treatment burden domain score in the usual care group was 51.5 (19.7)	The mean treatment burden score in the CFHealthHub group was 5.10 points higher (1.79 points higher to 8.41 points higher).	MD 5.10 (1.79 to 8.41)	539 (1)	⊕⊕⊕⊖ **Moderate**[a]	P = 0.003 There was an improvement in treatment burden domain score in the intervention group compared to the usual care group which remains the same when the analysis was adjusted for baseline differences MD 3.9 (95% CI 1.2 to 6.7) (CFHealthHub 2017).
QoL: CFQ-R domain scores at end of study Follow-up: 12 months	There was no difference in any quality of life domain score between groups. Physical domain MD 3.20 (95% CI -1.94 to 8.34; P = 0.22); emotional domain MD 0.10 (95% CI -3.92 to 4.12; P = 0.96); social domain MD 0.90 (95% CI -2.48 to 4.28; P = 0.60); eating domain MD 3.00 (95% CI-0.78 to 6.78; P = 0.12); body image domain 2.10 (95% CI-2.68 to 6.88; P = 0.39); respiratory domain MD 1.40 (95% CI -2.37 to 5.17; P = 0.47); digestion domain MD 0.20 (95% CI -3.28 to 3.68; P = 0.91).			538 (1)	⊕⊕⊕⊖ **Moderate**[a]	The results remained the same when the analysis was adjusted for baseline differences. Physical domain MD 2.3 (95% CI -1.0 to 5.6); emotional domain MD 0.2 (95% CI -2.9 to 3.2); social domain MD 0.3 (95% CI -2.2 to 2.7); eating domain MD 1.9 (95% CI -1.3 to 5.2); body image domain MD 1.7 (95% CI -1.4 to 4.8); respiratory domain MD 0.7 (95% CI -2.4 to 3.8); digestion domain MD 1.1 (95% CI -1.7 to 3.9) (CFHealthHub 2017).
FEV_1: mean FEV_1 % predicted at end of study	Mean (SD) FEV_1 % predicted in the usual care group was 56.9% (23)	Mean FEV_1 % predicted in the CFHealthHub group was 3.7% higher (0.23% lower to 7.63% higher).	MD 3.70 (-0.23 to 7.63)	556 (1)	⊕⊕⊖⊖ **Low**[a,b]	When the results were adjusted for baseline differences, the effect was reduced but remained in the same direction (CFHealthHub 2017).

Follow-up: 12 months				
Number of pulmonary exacerbations Follow-up: 12 months	There was no difference between groups in the incidence of pulmonary exacerbations. Incidence rate ratio 0.92 (95% CI 0.77 to 1.11; P = 0.39).	607 (1)	⊕⊕⊕⊖ **Moderate**[a]	Adjusted incidence rate ratio was 0.96 (95% CI 0.83 to 1.12; P = 0.64) (CFHealthHub 2017).

*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).

CFQ-R: Cystic Fibrosis Questionnaire - Revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **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 one level due to indirectness as the study only included people with CF over the age of 16. It is unclear whether the results would be applicable to a paediatric population.
[b]Downgraded one level due to imprecision caused by wide confidence intervals which overlap between benefit and harm.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common autosomal recessive inherited disease amongst people of North European descent (Farrell 2018). It affects over 10,800 people in the United Kingdom (UK) (CF Trust 2020), and over 70,000 people worldwide (CF Foundation 2019). It is caused by a faulty gene which codes for a protein, the cystic fibrosis transmembrane conductance regulator (CFTR), which is responsible for the movement of chloride and water across epithelial surfaces. This in turn leads to a buildup of thickened, dehydrated mucus, which accounts primarily for the multisystem manifestations of CF affecting respiratory, gastrointestinal, reproductive and endocrine systems. Thickened mucus in the lungs results in chronic airway infection, which can progress to bronchiectasis (dilatation and thickening of the airways). Respiratory disease remains the major cause of morbidity and mortality in CF (CF Trust 2020).

Whilst CF was once thought of as a disease of childhood, improved understanding and treatment of the condition has meant that people with CF (pwCF) can live well into adulthood: the median predicted survival age for a child born today is 50.6 years (CF Trust 2020). Longer survival comes at a cost, however, as health needs to be maintained through a complex treatment regimen including: oral, intravenous (IV) and inhaled antibiotics; physiotherapy; mucolytics; nutritional support; and more recently, CFTR modulators. PwCF typically spend two to two and a half hours a day on their treatments (CF Trust 2018). Inhaled medication is generally given via metered dose aerosol, dry powder inhalers or by nebuliser therapy. Nebuliser therapy is used in CF to deliver bronchodilators, antibiotics and mucolytics. As new treatments are added in to the regimen, the burden of treatment to pwCF increases. A James Lind Alliance (JLA) Priority Setting Partnership (PSP) recently found the number one priority for research amongst the CF community was how to simplify their treatment burden (Rowbotham 2018a). In particular, long-term inhaled antibiotics were found to be one of the most burdensome treatments by both the lay community and healthcare professionals (Rowbotham 2018b).

Although adherence can be influenced by a number of factors, when treatment burden is high, it is likely that adherence to the regimen is reduced. Adherence is the extent to which an individual follows a reasonable treatment plan prescribed for them by a qualified caregiver. It is not limited to medication; it also applies to other treatments (such as physiotherapy) and to the correct technique and treatment duration when using inhalation devices (Bender 1997). Suboptimal adherence to the treatment plan, in the context of respiratory disease, has been found to be associated with poorer health outcomes (Blakey 2018; Williams 2004). In CF, a relationship has also been found between medication adherence and lung health, with poor adherence being linked to increased use of IV antibiotics and hospital admissions (Eakin 2013).

Adherence can be monitored using a variety of different measures, including self-reporting, pharmacy refill records and electronic monitoring - all of which have their advantages and disadvantages. Self-reporting is notoriously inaccurate, with individuals tending to overestimate their level of adherence (Daniels 2011); however, it is inexpensive and quick to complete. Collection of prescription refill data is a valid method for monitoring adherence through the calculation of the medication possession ratio (MPR). However, this is still prone to inaccuracies as it is based on the assumption that all the medications refilled are always taken. Digital technologies can objectively record the date, time and duration of treatment for inhalers, nebulised therapies and some oral medications. Additionally, some digital technologies are also capable of assessing the individual's technique for using the prescribed medication, but these are not available for all treatments (Quittner 2008).

The complexity of CF treatment regimens makes measuring adherence difficult, as adherence to individual therapies within a treatment regimen varies. Although the composite MPR in one study was reported as 63%, the median MPR for nebulised hypertonic saline was reported as 49% compared to 76% for oral azithromycin (Eakin 2011). Population demographics may influence adherence in CF. Whilst some studies showed no statistical difference in adherence, assessed by composite MPR, when considering the participants' age (Eakin 2011), others found that greater age, along with maternal parental supervision, were predictors of better adherence to nebulised therapies (Modi 2008). Females have been reported to have worse adherence overall - including to coughing (airway clearance), to consuming high-fat foods and being more likely to miss medications - with a progressive decline in pulmonary function occurring earlier in females than males (Patterson 2008). Higher socioeconomic status was associated with increased adherence to the high-frequency chest wall oscillation (HFCWO) vest for airway clearance in children (Oates 2015). Adherence to an adaptive aerosol delivery system, the I-neb, was found to be significantly better in the evenings compared to mornings, and also better in children compared to teenagers (McNamara 2009). We are not aware of any studies specifically relating to adherence to inhaled nebulisers and socioeconomic status, or the impact on ethnicity and adherence in CF in general.

Description of the intervention

Digital technology is a growing industry and is more accessible than ever before. In the general population, digital technology is being used to track health and fitness via activity trackers and mobile apps. In health care, the current UK National Health Service (NHS) plan specifically targets digital technology as a method for improving prevention, care and treatment via point-of-care testing, websites and mobile phone apps. The aim is that digitally-enabled care will become mainstream across the NHS (NHS 2019). In 2019, the World Health Organization (WHO) published its first global strategy for digital health (WHO 2019). Over the last 10 years, there has been an increase in the emergence of digital technologies to support the delivery and monitoring of inhaled medications, both in CF and other conditions.

Digital technologies for monitoring and improving adherence in CF include data-tracking nebulisers (nebulisers containing a microchip to record adherence data), which capture adherence to inhaled therapies as well as monitoring physiological parameters, technique and respiratory symptoms. Data can be wirelessly transmitted to a remote platform, such as a web platform, accessible by both the pwCF and the healthcare team (Blakey 2018). There is an array of other technologies available, in a variety of formats, designed to capture and monitor physical and psychological data, to provide home-monitoring and to increase accessibility to health care. People with CF are using mobile phone

apps, smartwatches and activity trackers, as well as interactive web-based games and activities, to monitor their health and plan their treatment. These technologies may include measures of adherence to the regimen as a whole or to particular aspects of it.

How the intervention might work

Monitoring adherence to inhaled therapies can be useful in treatment planning as it allows both the pwCF and the healthcare team to understand whether a decline in lung function is related to disease progression, poor adherence to treatment or a combination of the two. The use of feedback via web platforms allows the pwCF and healthcare professionals to monitor their treatment and to see how well they are adhering and how that adherence affects other parameters, such as lung function and respiratory symptoms. There is, however, the danger that any technology might increase the burden to pwCF, as it is an additional task on top of an already burdensome treatment schedule.

Why it is important to do this review

A review of digital technologies and adherence in general respiratory disease found that the majority of published studies in this area are of short duration and do not describe in sufficient detail the technologies used or how they were evaluated (Blakey 2018). The authors also stated that a more complete and detailed understanding of the use of digital technologies and the impact they have on pwCF and healthcare practitioners is needed (Blakey 2018).

It is important that we undertake this Cochrane Review to determine whether using digital technologies to monitor adherence to inhaled therapies for pwCF can subsequently improve overall health without introducing any adverse effects.

OBJECTIVES

To assess the effects of using digital technology to monitor adherence to inhaled therapies and health status in adults and children with CF.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) or quasi-RCTs. We did not find any quasi-RCTs; if we find any in future updates of this review, we will assess these on individual merit and only include those where the method of sequence generation and allocation are described (e.g. alternate allocation, date of birth or record number). We did not find any cross-over trials, but if we find cross-over trials in future updates, we will include these if they have been appropriately analysed by the trial investigators or if the first-arm data are available. Similarly, if we find cluster-randomised trials, we will assess them to determine whether the clusters have been appropriately defined and randomised.

Types of participants

Adults and children with CF diagnosed via sweat testing, genetic testing, or both, and of any disease severity.

Types of interventions

We considered any form of digital technology for monitoring adherence to inhaled therapies (including antibiotics, bronchodilators, mucolytics, and deoxyribonuclease (DNase) delivered via any device). Eligible technologies included: web applications, mobile phones, chipped or data-tracking nebulisers, text messaging and email reminders, calendar reminders, and self-management applications.

Digital technology which provides a feedback loop to the user, either from the technology itself (e.g. providing real-time feedback on inhaled therapy use or technique), or delayed feedback (such as providing a prompt to the study participant if their engagement with their inhaled therapy drops) was eligible for inclusion in the review. We also considered including interactive platforms which allow feedback from the CF team or trial investigators. We acknowledge that it is possible that any digital technology which allows feedback from clinicians may introduce an element of bias, since it may be the clinician feedback which affects adherence rather than the technology per se. We included trials which provided feedback either to the user directly or via the CF team or clinicians.

Not all applications provide feedback, acting more as a reminder or prompt but without consequent action if the inhaled therapy is not taken. We also included these studies, but did not have enough studies to perform subgroup analyses to look at the effects of the type and frequency of feedback (see Subgroup analysis and investigation of heterogeneity).

We compared these interventions to no intervention, usual treatment (which may include monitoring adherence such as paper-based monitoring, participant self-reporting, prescription fulfilment ratio or other, e.g. counting remaining boxes of medications before issuing another prescription) or another digital technology.

Types of outcome measures

The interventions we investigated are intended to monitor adherence to inhaled therapies, which means that these interventions measure our primary outcomes.

Primary outcomes

1. Adherence to inhaled therapy treatment as measured by one or more of the following:
   a. percentage of the inhaled medication taken as prescribed;
   b. full adherence to the inhaled therapy as defined in the study protocol expressed as a binary outcome (yes or no). Where investigators have allowed a lower threshold than 100% for binary adherence (e.g. 80% or 90%), we will report this and combine data where possible;
   c. adherence measured using specific adherence instruments; MPR; medication adherence reporting scale (MARS) (Chan 2020);
   d. adherence rate as given by the technology itself (e.g. chipped or data-tracking nebulisers);
   e. self-reported adherence to inhaled therapies via a diary or a questionnaire.

2. Treatment burden (mean change from baseline) using validated measures, such as the Cystic Fibrosis Questionnaire - Revised (CFQ-R) treatment burden domain score (Quittner 2009)
3. Quality of life (QoL) using validated scales (e.g. CFQ-R (Quittner 2009) or Cystic Fibrosis Quality of Life (CFQoL) (Gee 2000))

Secondary outcomes

1. Adverse effects:
   a. treatment-related adverse effects of using the technology (which may include psychological effects including stress, boredom or frustration; an increase in treatment burden; technical problems with the technology; physical effects of using the technology such as headache, dizziness, fatigue)
   b. any adverse effect experienced during the study
2. Forced expiratory volume in one second (FEV_1) (change from baseline values or absolute post-treatment values):
   a. measured in L
   b. measured in % predicted or expressed as a z score
3. Pulmonary exacerbations (meeting protocol-defined criteria or based on symptoms (Goss 2007) or using validated criteria, e.g. Fuchs criteria (Fuchs 1994)):
   a. number of exacerbations defined by symptoms, signs and X-rays
   b. hospital admissions for pulmonary exacerbation
   c. time to next exacerbation
4. Adherence to complete therapy regimen (all treatment prescribed including, but not limited to: physiotherapy and airway clearance; oral medications; dietary supplements; exercise)
   a. percentage of treatment regimen completed as prescribed (mean change from baseline)
   b. full adherence to treatment regimen as defined in the study protocol (yes or no)
   c. adherence to specific components of the treatment regimen (where this information is provided)
5. Frequency of scheduled healthcare appointments including outpatient clinic visits and teleconsultations

Main outcomes for the summary of findings tables

We reported the following outcomes in our summary of findings tables:

1. adherence to treatment (at up to six months);
2. treatment burden (at up to six months);
3. QoL (at up to six months);
4. FEV_1 % predicted (change from baseline to up to six months); and
5. number of pulmonary exacerbations by the end of the trial.

Timing of outcome assessment

We planned to report outcomes at one month, three months, six months, 12 months and annually thereafter. The studies we included in this review only reported data at up to three months and at 12 months. We will report the other specified time points if they are reported in studies included in a future review update.

Search methods for identification of studies

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

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a systematic search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: (treatment adherence OR telehealth OR monitor*):kw.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated 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 cystic fibrosis 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 the latest search: 28 October 2021.

We also searched the following databases and trial registries:

1. Embase Ovid (1995 to 09 November 2021);
2. US National Institutes of Health Ongoing Trials Register, Clinicaltrials.gov (www.clinicaltrials.gov; searched 9 November 2021);
3. Australia New Zealand Clinical Trials Registry (ANZCTR; http://www.anzctr.org.au/TrialSearch.aspx; searched 9 November 2021);
4. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/; unavailable at time of searching due to Covid-19).

Date of last search: 09 November 2021

For details of our search strategies, please see Appendix 1.

Searching other resources

Reference lists

We checked the bibliographies of included studies for further references to relevant studies or systematic reviews. We also checked the included studies of any systematic reviews that we identified from our electronic searches and bibliography checking. Two review authors scanned the bibliographies independently.

Correspondence

We contacted authors of studies where we had queries about inclusion criteria or applicability of results. Where a study was only reported as a conference abstract or poster, we contacted the author to request a copy of the full paper or any unpublished data relating to the study.

Data collection and analysis

Selection of studies

We uploaded all identified references to Covidence for screening of titles and abstracts, and then for full-text article screening (Covidence).

Two review authors (SS, RC or SH) independently reviewed all titles and abstracts identified by the searches, and discarded any that clearly did not meet the inclusion criteria. We retrieved the full texts of each of the remaining references. Two authors (SS, RC or SH) independently assessed each against the review's inclusion criteria. At this point, we added any articles that we discarded to the list of excluded studies, and gave a reason for exclusion. We referred any disagreements to a third review author (RC, SH or AS, depending on who undertook the original screening) to arbitrate.

For studies including participants with CF and participants with other respiratory conditions, we excluded the study if it did not present data for the people with CF separately.

Data extraction and management

Two review authors (SS, RC or SH) independently extracted data from the included studies using a specially designed data extraction form developed by the Cochrane Cystic Fibrosis and Genetic Disorders Review Group and adapted for this review. We set up the form in Covidence to allow independent data extraction by two authors and inbuilt comparison of responses (Covidence).

Where available in the reports, we collected data on:

1. participant characteristics;
2. study characteristics and design;
3. intervention and comparator;
4. outcome data - we report each outcome separately;
5. risk of bias.

We resolved data extraction discrepancies by discussion between the two data extractors and if we were unable to reach an agreement, a third author (AS) arbitrated.

We exported the extracted data from Covidence into Review Manager Web (RevMan Web) software for analysis (Covidence; RevMan Web 2019). We identified too few studies to be able to present data for different interventions separately (e.g. chipped nebulisers, mobile phone apps and web platforms). We plan to report results in this way if we include more studies in future updates. We compared the interventions to no intervention, usual treatment or another digital technology.

We planned to present the data at up to one month, up to three months, up to six months, up to one year and annually thereafter. Currently, data are only available at two time points: eight to 10 weeks, which we present as 'up to three months' and at 12 months.

Assessment of risk of bias in included studies

We used the Cochrane Risk of Bias 2 (RoB2) tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a) and by Sterne and colleagues (Sterne 2019).

We were interested in two effects for this review: the effect of assignment to the intervention rather than adherence to the assigned treatment, obtained through an intention-to-treat (ITT) analysis; and the effect of adhering to the intervention, obtained through a per-protocol (PP) analysis.

For each of our specified outcomes, we assessed risk of bias within each of the trials contributing data to that outcome across the following domains.

1. Domain 1 - randomisation process
2. Domain 2 - deviations from intended interventions
3. Domain 3 - missing outcome data
4. Domain 4 - measurement of the outcome
5. Domain 5 - selection of the reported result

Using a series of signalling questions within the RoB2 Excel tool, two authors (SS and RC or SH) independently assessed risk of bias in the studies reporting the outcome of interest for each domain (RoB2 Tool 2019). We answered the signalling questions with 'Yes', 'Probably Yes', 'No', 'Probably No' or 'No Information'. We discussed discrepancies in grading and resolved these by discussion, deferring the grading to a third author (AS) to arbitrate where necessary. Using the results of the signalling questions, the RoB2 tool calculated an overall risk of bias for each domain (low risk of bias, some concerns, or high risk of bias) and also an overall risk of bias for the outcome result in question. We used the criteria detailed below to assess the risk of bias for a specific outcome.

We judged an outcome in the study to be at a low risk of bias overall if there was a low risk across all domains for that result. We judged a study as having 'some concerns' about a particular result where there were some concerns in at least one of the domains, but no judgement of high risk for any domain. We judged a study to be at high risk of bias for a particular result if there was high risk of bias in at least one domain or if there were some concerns across multiple domains. We used 'No information' when there were insufficient details to allow any of the other responses in the context of the study.

If we had included cross-over studies, we would have only included first-arm data and therefore employed the same RoB2 tool. Additionally, we would have paid specific attention to Domain 2 and the effect of any carry-over effect. We would have assessed the time period in between interventions as low risk if it was unlikely that there would be a carry-over effect.

If we include cluster-RCTs in a future update, we will assess risk of bias using a variant of the RoB2 tool, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 23.1.2 (Higgins 2022c)

We have shared the data in an Excel spreadsheet on Figshare (Smith 2022).

Measures of treatment effect

We measured the effect of interventions according to the type of data presented in the included studies, following methods detailed in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

Continuous data

For continuous data (adherence to treatment given as a percentage; treatment burden score; QoL scores; FEV_1; number of

exacerbations; number of hospital admissions), we recorded the mean change from baseline for each group or absolute mean post-treatment values with a standard deviation (SD). The authors of one included study provided us with unpublished data to enable us to include data for FEV_1 (McCormack 2011). We used the statistical program SPSS (version 25) to calculate mean change (SD) in FEV_1 for each treatment group (SPSS 2017). If papers included in future updates report standard errors (SE) and it is possible to do so, we will convert these to SDs. We will then present a pooled estimate of treatment effect for outcomes that are reported by more than one paper by calculating the mean difference (MD) and 95% confidence intervals (CIs). If studies included in future updates use different units of measurement, we will use standardised mean difference (SMD) to report the results, as this measure expresses the size of the intervention effect in each study relative to the between-participant variability for the specified outcome (Higgins 2022b).

Dichotomous data

We reported dichotomous data (full adherence; adverse effects) as a pooled estimate of treatment effect using risk ratio (RR) and 95% CIs.

Time-to-event data

We expressed time-to-event data as a hazard ratio (HR) with 95% CIs using the generic inverse variance method.

Unit of analysis issues

We have not included any cross-over studies, but will exercise caution when analysing the results of this type of study if we include them in future updates. CF is a progressive disease, which means that it is unlikely that participants randomised to receive the treatment in the second phase will be the same in terms of baseline demographics as those who received it in the first phase. If we find studies that have appropriately analysed their cross-over data, we will be able to include both treatment phases (Elbourne 2002). However, where investigators have made no allowance for the cross-over design, we will analyse first-phase data only; that is, as if it were a parallel trial. If the authors have not analysed their cross-over data appropriately and no first-phase data are available, we will exclude the study.

We have not included any cluster-randomised studies, but if we include them in a future update, we will assess them to determine how the clusters have been defined and randomised. If it is unclear whether a cluster-randomised controlled study has appropriately accounted for clustering, we will contact the study investigators for further information. Where no appropriate adjustments for clustering exist, we will request individual patient data (IPD) and will calculate an estimate of the intraclass correlation co-efficient. As the inhaled therapy is only one part of an overall treatment regimen, a cluster-randomised design may not be appropriate, as there is the possibility that participants may be on more than one intervention. We will only include such studies if we are certain that baseline characteristics are the same in the intervention clusters and control clusters, and we will be vigilant to contamination or double-counting of participants (or both).

Similarly, we have not included any multi-arm trials in the review to this point. If we include such trials in a future update, we will assess each arm against the control arm separately and include them under the appropriate comparison. A single trial may appear in multiple comparisons.

Dealing with missing data

We reported the number of dropouts and reasons for withdrawal for each included study where these data were presented. We also reported whether the study investigators analysed data using an ITT analysis and so presented the results of each intervention regardless of the original treatment allocation. If this needs clarification in future updates, we will attempt to contact the study authors. For the RoB2 analysis, we looked at the effect of assignment (ITT analysis) as well as effect of adherence (per-protocol analysis).

We contacted the authors of one included study and received additional results within an SPSS file, which allowed us to calculate the mean change in FEV_1 and SD for each of the treatment groups (McCormack 2011). For future updates, we will also attempt to contact the primary investigators where there are insufficient data in the published paper or uncertainty about the data presented (Higgins 2022b).

We do not plan to impute missing data.

Assessment of heterogeneity

Due to the different interventions and time frames, we have been unable to combine results in a meta-analysis and, therefore, could not assess heterogeneity. If we are able to perform a meta-analysis in a future update, we will assess the level of heterogeneity in two ways. We will visually examine the forest plots with specific regard to CIs. In particular, we will look for similar point estimates and overlapping CIs as an indication of low heterogeneity; where the point estimates vary and the CIs do not overlap, we will report high levels of heterogeneity. In conjunction with the visual appearance of the forest plots, we will use the I^2 statistic (Deeks 2022), together with the Chi^2 value, to measure the level of heterogeneity between trial results. The *Cochrane Handbook for Systematic Reviews of Interventions* provides a rough guide to interpretation of the I^2 statistic as follows:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: considerable heterogeneity.

When we interpret the I^2 measure of heterogeneity, we will also take into consideration the magnitude and direction of the effect (Deeks 2022).

To assess clinical heterogeneity, we will inspect the trial characteristics.

Assessment of reporting biases

We attempted to reduce the risk of reporting bias by searching our sources systematically for unpublished as well as published studies. We compared the results of both included studies with their protocols (where a protocol was available) and the methods section of the final publication to assess the risk of selective reporting. We assessed all outcomes included in the RoB2 analysis for reporting bias.

We did not find sufficient studies to assess publication bias, but if we include more studies (at least 10) in a future update, we will try to identify any publication bias by generating a funnel plot. If the funnel plot is asymmetrical, we will explore reasons for this, including reasons other than publication bias (Page 2022).

Data synthesis

We have entered outcome data into forest plots but were unable to carry out a meta-analysis. If we are able to carry out a meta-analysis in future updates, we will only combine studies using similar technologies and measuring the same outcome, in the same way and for the same time period. It is possible, however, that the intervention effects across studies will be different yet related, and so we will use a random-effects model to give a more conservative estimate of statistical significance (Deeks 2022). We will include all trials regardless of whether they are at high or low risk of bias.

Subgroup analysis and investigation of heterogeneity

We planned to investigate any heterogeneity by carrying out subgroup analyses of potential confounding factors. We anticipated the following confounding factors.

1. Age - there is likely to be a difference in use of inhaled therapies and adherence monitoring between children and adults given parental input will have an effect on how well medication is administered. We will compare children (younger than 18 years) with adults and, if possible, we will also compare younger children (up to 12 years) with older children (over 12 years and less than 18 years).
2. Technologies allowing clinician feedback - some digital technologies that promote adherence may have direct feedback of adherence data, results or both, to clinicians. This may prompt greater input from the clinician which in turn may affect adherence. We plan to carry out a subgroup analysis to compare technologies that include clinician feedback with those that do not.
3. Type of technology - where there are enough studies, we plan to carry out a subgroup analysis by the type of technology; for example, web-based applications, electronic trackers and reminders, smart nebulisers.

We did not include enough studies to be able to carry out a subgroup analysis in this version of the review.

Sensitivity analysis

We were unable to carry out sensitivity analysis, but in future updates, we plan to carry out sensitivity analyses to look at the effect of the risk of bias findings on the results. We will look at the effect of adding in and removing studies that are at a high risk of bias across all domains, as identified by our RoB2 assessments and, more specifically, if studies are at a high risk of bias due to selection bias. If we include any quasi-randomised studies, we will carry out a sensitivity analysis to look at the effect of removing them.

Similarly, if we include cluster-RCTs or cross-over trials in a future update, we will look at the effect of adding them in and taking them out of the analyses.

Summary of findings and assessment of the certainty of the evidence

We have generated a summary of findings table for each comparison in the review. In each table, we present the following outcomes.

1. Adherence to the inhaled treatment (at up to six months)
2. Treatment burden (at up to six months)
3. QoL (at up to six months)
4. Change from baseline in FEV_1 (at up to six months)
5. Number of pulmonary exacerbations by the end of the study

For each outcome, we reported the illustrative risk with and without the intervention and the magnitude and direction of effect. For dichotomous outcomes, we reported absolute and corresponding risk as a RR (with 95% CI). For continuous data, we reported the absolute and corresponding risk as MD (with 95% CI). We also presented the number of trials contributing to the outcome and the number of participants (Schünemann 2022a).

We used the GRADE approach to assess the certainty of the body of evidence for each outcome in the summary of findings tables (Schünemann 2022b). We assessed the certainty of evidence based on: the risk of bias within the studies contributing to the outcome (using our RoB2 assessments); the relevance to our population of interest (indirectness); unexplained heterogeneity or inconsistency; imprecision of the results; and high risk of publication bias. In GRADE, a body of evidence from randomised trials begins with a high-certainty rating. We then downgraded the evidence by one level if we deemed the risk of bias to be serious and by two levels if we deemed the risk to be very serious. We assessed each outcome individually and gave it a high, moderate, low or very low rating for the certainty of evidence, using the following definitions.

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.

Where we downgraded the certainty of the evidence, we described our reasons and the supporting information for our decisions in the footnotes of the summary of findings tables.

RESULTS

Description of studies

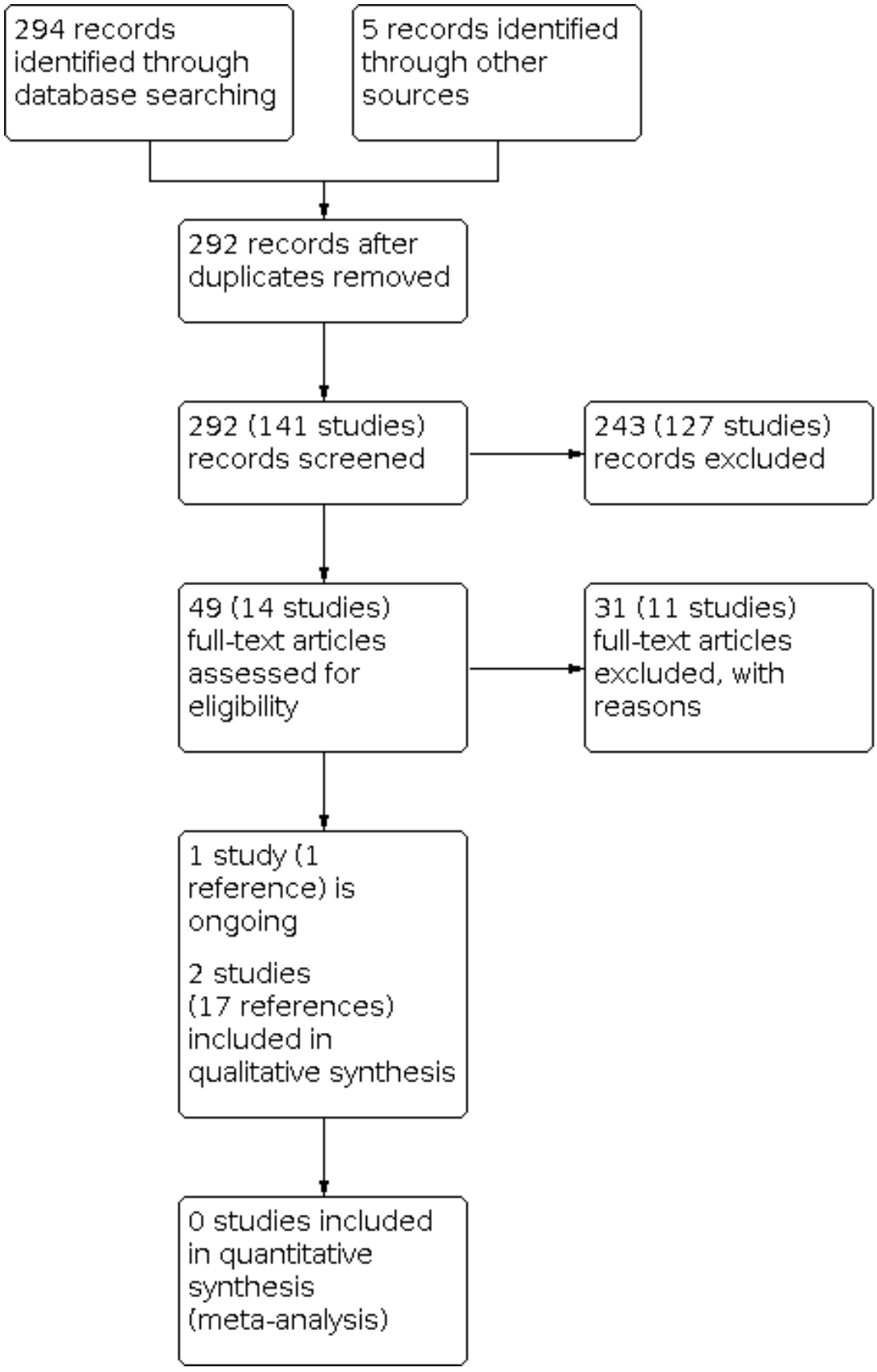
Please see the tables for additional information (Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies).

Results of the search

Our searches identified 292 individual references relating to 141 studies, of which we excluded 243 references to 127 studies

based on title and abstract scanning. We screened the remaining 49 references relating to 14 studies in full text, and we excluded - with reasons - 31 references to 11 studies (Characteristics of excluded studies). We identified three studies which fulfilled all the inclusion criteria for this review: we included two of these (see Characteristics of included studies); the third is still ongoing (Characteristics of ongoing studies). We present the process of study screening and selection in a PRISMA diagram (Figure 1).

Figure 1.



Included studies

We included two RCTs of parallel design (628 participants) in the review (CFHealthHub 2017; McCormack 2011). The study characteristics are described in the Characteristics of included studies tables. One study looked at a web-based application to support the use of eFlow controllers for eFlow technology nebulisers in 608 participants (CFHealthHub 2017). The second study looked at the effects of a digitally enhanced inhalation mode for nebulised antibiotics compared to standard mode in 20 children attending a UK regional CF clinic (McCormack 2011).

Design

The CFHealthHub study had an open-label, multicentre, parallel design, carried out over a period of 12 months in the UK. Data were captured electronically throughout the study period (CFHealthHub 2017).

The McCormack study was partially blinded (outcome assessment) and also had a parallel group design. There was a run-in period of four to six weeks followed by an intervention period of eight to 10 weeks. The sample size was calculated using the SD of treatment time in a previous study (McNamara 2009). Participants were recruited from the CF clinic, but the interventions were carried out in the children's home setting (McCormack 2011).

Participants

One study enroled participants over the age of 16 (CFHealthHub 2017), whilst the second study included children between the ages of five and 16 (McCormack 2011).

The CFHealthHub study randomised 608 participants: 304 participants in each arm, with 607 participants included in primary ITT analysis. The mean age (SD) in the intervention group was 31.1 (10.6) years, and in the usual care group it was 30.3 (10.8) years. There were 156 (51.3%) females in the intervention arm and 154 (50.8%) females in the usual care group. The mean (SD) FEV_1 % predicted was slightly higher in the intervention group at baseline, 60.7 (23.5) % predicted, compared to the usual care group, 58.3 (22.6) % predicted (CFHealthHub 2017).

In the McCormack study, the median age in the intervention group was 11.7 years (range 8.7 to 15.9), and in the control group it was 10.6 years (range 5.2 to 16.9). There were seven boys and three girls in each group. All participants had *Pseudomonas aeruginosa* infection, but were clinically stable on entry to the study and on long-term inhaled antibiotic therapy via an I-neb. At baseline, two out of the 10 participants in the control group had mean adherence of less than 40% compared to the intervention group, where all participants had a mean adherence of over 60% at baseline (McCormack 2011).

Interventions

The CFHealthHub study used a digital web platform to support the use of eNebulisers. All participants were given eTrack data-logging controllers for their eFlow Technology nebulisers (a digital nebuliser system which enhances the flow of medication to the lungs and tracks results); these sent time-stamped and date-stamped data to a 2net Hub (virtual platform for collecting data) for recording of adherence and inhalation calculations. Participants in the intervention group had access to the CFHealthHub digital platform (website and smartphone application) and received tailored, flexible support from the trialist throughout the 12-month study period. The participants in the usual care group used the eTrack data-logging controllers for adherence data collection only and there was no access to CFHealthHub, behavioural change tools or content. The adherence results from the usual care participants were invisible to participants and care teams (CFHealthHub 2017).

In the McCormack study, participants were all given a commercial preparation of colistin (Promixin, Profile Pharma Ltd., Chichester, UK) with a standard treatment dose being 1 MU (mega unit) diluted in 2 mL normal saline (1 mL being used for each of two daily treatments). This was given via an I-neb (a small battery operated, virtually silent drug delivery device). The children were randomised to either the standard adaptive aerosol delivery (AAD) inhalation mode – that is, tidal breathing mode (TBM) – or to the target inhalation mode (TIM). The standard TBM mode monitors the person's first three breaths and then delivers a timed pulse of aerosol during the mid-phase of the next inspiration. Each pulsed delivery is based on the preceding three breaths with audiovisual feedback when the treatment is complete. In the TIM mode, a high-resistance mouthpiece is used to guide the person to take slower and deeper inhalations. A vibratory signal on the lips signals the individual to exhale. This mode encourages the individual to take the longest inhalation they can manage by gradually increasing the time from the beginning of each breath to the vibration. When they can no longer reach the vibration, the time is then shortened to a comfortable level and continues at this level until the treatment is complete. The aim is to shorten the time taken for treatment (McCormack 2011).

Outcomes

Both studies reported on adherence to the inhaled therapy as a percentage of the expected treatments prescribed; both studies also reported on FEV_1 % predicted at the end of treatment (CFHealthHub 2017; McCormack 2011).

The primary outcome for the CFHealthHub study was the pulmonary exacerbation incidence rate over the 12 months. The trialists also measured treatment burden (CFQ-R treatment burden domain); QoL (CFQ-R physical, emotional, social, eating, body image, treatment burden, respiratory, digestion domains); and adverse effects (including anxiety and depression score) (CFHealthHub 2017).

The primary outcome of the McCormack study was the time to complete treatment, but the outcomes relevant to this review were adherence to treatment (measured as % of expected treatments), FEV_1 % predicted at the end of the study period and adverse effects (McCormack 2011).

Excluded studies

We excluded a total of 11 studies (Aitken 2011; Bodnar 2016; Daniels 2013; Elkins 2006; ISRCTN37959826; NCT00185549; NCT01183286; NCT02122289; NCT03052231; Quittner 2001; Sands 2013). One study was not an RCT (Quittner 2001). Two studies used digital technology; however, the objective was to detect exacerbations at an early stage rather than to monitor adherence to inhaled therapies (Aitken 2011; NCT02122289). Two studies were systematic reviews rather than primary research; we scanned the included studies within the reviews for potential inclusion in this review (Bodnar 2016; Daniels 2013). Three studies

looked at the effects of digital technology on adherence to the total prescription regimen rather than inhaled therapies alone (ISRCTN37959826; NCT00185549; NCT03052231). We excluded the remaining three studies because they featured ineligible interventions: all compared different medications and used the same digital technology in all participants for monitoring adherence to the two different pharmacological interventions (Elkins 2006; NCT01183286; Sands 2013).

Ongoing studies

We identified one ongoing study (Thee 2021), for which no results are yet available. It is a multicentre, open-label RCT looking at the effect of digital monitoring of adherence to inhaled therapy plus feedback of adherence and lung function compared to a control group who also have adherence monitored but without feedback to the participant or the CF physician. The intervention phase will run for 18 months after an initial assessment and preparation phase. The primary outcome is the time to the first protocol-defined pulmonary exacerbation after initiation of the intervention phase. Secondary outcomes include the number of pulmonary exacerbations, time between exacerbations, adherence to inhaled therapy, change in FEV_1 and forced vital capacity (FVC) from baseline, hospital admissions, change in health-related QoL (CFQ-R and EQ-5D-5L, a self-assessed quality of life questionnaire), sociodemographic and anthropometric data, days absent from work or school and CF-associated medical treatment and healthcare-related costs (Thee 2021).

Risk of bias in included studies

We assessed risk of bias for each outcome separately and overall for both included studies. The results of the signalling questions across the five risk of bias domains are available as a supplementary document (https://doi.org/10.6084/m9.figshare.19077011.v1). Where we have been able to add outcome data into forest plots, we have displayed the risk of bias decisions within the data tables and graphs for each analysis.

Across the five domains and where outcomes were reported, we deemed both studies to be at low risk of bias for most domains and outcomes. Overall risk of bias across all domains was low for treatment adherence at both three and 12 months; and for treatment burden, QoL, and adverse effects at 12 months. We had 'some concerns' about risk of bias for both change from baseline in FEV_1 % predicted at three months (McCormack 2011), and FEV_1 % predicted as an endpoint measure at 12 months (CFHealthHub 2017).

Bias arising from the randomisation process

Both studies described robust methods of randomisation, but we had some concerns over the CFHealthHub study as their participants were allocated 1:1 to the intervention or usual care using a computer-generated pseudo-random list with random-permuted blocks of randomly varying sizes (CFHealthHub 2017). There were some baseline differences (described in an appendix to the paper) and it is possible that the two levels of stratification (centre and prior days on IV antibiotics) affected baseline data. The intervention group had slightly better lung health at baseline, were older and had better adherence. The study authors state that the play of chance is affected by the block size. We did not feel that all outcomes were affected by this and so gave an overall rating of low risk except for FEV_1 at 12 months, where the better FEV_1 values in the intervention group at baseline may have been a source of bias in the results (CFHealthHub 2017).

Bias due to deviations from intended interventions

Both of the studies were at low risk of bias due to deviations from the intended interventions across all outcomes (CFHealthHub 2017; McCormack 2011). There were no deviations from the intended allocation in the CFHealthHub study (CFHealthHub 2017). The McCormack study used an intention-to-treat analysis and all participants remained in the group to which they were allocated for the duration of the study (McCormack 2011).

Bias due to missing outcome data

The number of participants completing the studies varied for different outcomes, but there were never data missing from more than 15% of the total number of participants. We therefore deemed both studies to be at low risk of bias for this domain across all outcomes (CFHealthHub 2017; McCormack 2011).

Bias in measurement of the outcome

Both studies were open-label in design, where the participants knew if they had been allocated to the intervention or control arm of the study. We did not feel that this was a cause for concern except for QoL outcomes. Only the CFHealthHub study measured QoL and investigators used a validated tool (CFQ-R) which was completed by the participants. It is possible that knowledge of the intervention may bias respondents, although it is unclear in which direction (CFHealthHub 2017).

Bias in selection of the reported result

Both studies were at low risk of bias for this domain across all outcomes (CFHealthHub 2017; McCormack 2011).

Effects of interventions

See: **Summary of findings 1** Digital technology (TIM) compared with standard treatment (TBM) for monitoring adherence to inhaled therapies in people with cystic fibrosis; **Summary of findings 2** Digital technology (web-based platform CFHealthHub) compared with usual care for monitoring adherence to inhaled therapies in people with cystic fibrosis

We have graded the certainty of the evidence for those outcomes included in the summary of findings tables. For the definitions of these gradings, please refer to the tables (Summary of findings 1; Summary of findings 2).

We have only reported on the outcomes from our review that were included in the trials.

Digital technology (TIM) versus standard treatment (TBM)

One study (20 participants) is included in this comparison (McCormack 2011). Results are summarised in Summary of findings 1.

Primary outcomes

1. Adherence to inhaled therapy treatment

a. % of the inhaled medication taken as prescribed

The study reported this outcome for all 20 participants and showed that, after eight to 10 weeks, the mean (SD) adherence of expected treatments was 89% (8) in the TIM group compared to 65% (33) in the TBM group (McCormack 2011). Our analysis shows higher adherence in the TIM group (MD 24%, 95 % CI 2.9 to 45; P = 0.03; Analysis 1.1). We are unclear whether differences at baseline may have affected the result. In the TBM group, two participants had mean adherence of less than 40% and one of less than 60% compared to the TIM group, where mean adherence at baseline was above 60% in all participants. The authors state that the difference between the groups at baseline was not significantly different and also note that all participants in the TBM group showed a decline in adherence from baseline to the end of the study compared to the TIM group, where only two out of the 10 participants showed a decline in adherence (McCormack 2011). We deemed the GRADE certainty of evidence for this outcome to be low.

Secondary outcomes

1. Adverse effects

b. Any adverse effect experienced during the study

There were no reported adverse events or participant withdrawals in either group (20 participants) (McCormack 2011).

2. FEV_1

McCormack measured % predicted change from baseline at the end of the study (McCormack 2011). Investigators reported narratively that there were no changes in lung function in either group. We contacted the authors, and they provided us with data for this outcome. Our analysis confirmed that there was no difference between groups with regard to mean change in FEV_1 % predicted (MD 1.00, 95 % CI -9.37 to 11.37; Analysis 1.2). We deemed the certainty of evidence for this outcome to be low.

Digital technology versus standard treatment

One study (608 participants) is included in this comparison (CFHealthHub 2017). Results are summarised in Summary of findings 2.

Primary outcomes

1. Adherence to inhaled therapy treatment

a. % of the inhaled medication taken as prescribed

CFHealthHub 2017 reported objective treatment adherence at 12 months for 588 out of 608 participants and showed that adherence was markedly better in the intervention group than the usual care group (MD 18%, 95% CI 12.90 to 23.10; P < 0.001; moderate-certainty evidence; Analysis 2.1). The study authors also reported their data adjusted for baseline differences (MD 9.50%, 95% CI 8.60 to 10.40), which showed that adherence was also higher in the CFHealthHub group than the control group, even when baseline differences were accounted for (Table 1).

2. Treatment burden

The study (539 participants) measured treatment burden using the CFQ-R treatment burden domain score at 12 months (CFHealthHub 2017). The CFHealthHub group showed significantly better domain scores and therefore reported a lower treatment burden than the usual care group (MD 5.1, 95% CI 1.79 to 8.41; P = 0.003; moderate-certainty evidence; Analysis 2.2).

3. QoL

The study (538 participants) reported on QoL outcomes using all domains of the CFQ-R domain score (CFHealthHub 2017). No difference was seen between the CFHealthHub group or the usual care group for any of the domains, and we deemed the certainty of evidence to be moderate for each domain: physical domain, MD 3.20 (95% CI -1.94 to 8.34; P = 0.22); emotional domain, MD 0.10 (95% CI -3.92 to 4.12; P = 0.96); social domain, MD 0.90 (95% CI -2.48 to 4.28; P = 0.60); eating domain, MD 3.00 (95% CI-0.78 to 6.78; P = 0.12); body image domain, MD 2.10 (95% CI-2.68 to 6.88; P = 0.39); respiratory domain, MD 1.40 (95% CI -2.37 to 5.17; P = 0.47); digestion domain, MD 0.20 (95% CI -3.28 to 3.68; P = 0.91).

Secondary outcomes

1. Adverse effects

a. Treatment-related adverse effects

The study reported on anxiety (Generalised Anxiety Disorder (GAD-7) anxiety score) and depression scores (Patient Health Questionnaire (PHQ-8) depression score) as markers of negative effects of the intervention (CFHealthHub 2017). No differences in anxiety or depression scores were seen at the end of the study (anxiety: MD 0.40, 95% CI -0.46 to 1.26; P = 0.36; depression: MD -0.10, 95% CI -1.00 to 0.80; P = 0.83; moderate-certainty evidence; Analysis 2.4).

b. Any adverse effect experienced during the study

The CFHealthHub study reported on all adverse events occurring during the study period and serious adverse events. There was no difference between the groups in participants experiencing adverse events (MD 1.19, 95% CI 0.86 to 1.64; P = 0.28) and serious adverse events (MD 1.36, 95% CI 0.88 to 2.10; P = 0.16) (moderate-certainty evidence; Analysis 2.5). None of the serious adverse events were related to the intervention (CFHealthHub 2017).

2. FEV_1

The study reported endpoint values for FEV_1 % predicted (556 participants) (CFHealthHub 2017). There was no difference in FEV_1 % predicted between the CFHealthHub group and the usual care group at 12 months (MD 3.70, 95% CI -0.23 to 7.63; P = 0.06; low-certainty evidence; Analysis 2.6). The study authors noted that FEV_1 values were better in the intervention group at baseline than in the usual care group and carried out adjusted analyses to account for these baseline differences. The adjusted mean difference was 1.4 (95% CI -0.2 to 3.0) which is a lesser effect than the unadjusted value and again did not reach statistical significance (Table 1).

3. Pulmonary exacerbations

The study reported on pulmonary exacerbations both as an adjusted and unadjusted incidence rate ratio (CFHealthHub 2017). In the intervention group (n = 304), there were 482 exacerbations in 294.9 person years, while in the usual care group (n = 303), there were 526 exacerbations in 297.2 person years, giving an unadjusted incidence rate ratio of 0.92 (95% CI 0.77 to 1.11; P = 0.39). The adjusted incidence rate ratio was 0.96 (95% CI 0.83 to 1.12; P =

0.64) (Table 1). Both analyses suggest that there was no difference between groups in pulmonary exacerbation rate (CFHealthHub 2017). We deemed the certainty of evidence for this outcome to be moderate.

DISCUSSION

Summary of main results

Our searches identified two studies which fulfilled our inclusion criteria: McCormack 2011, a small study with 20 participants, and CFHealthHub 2017, a larger multicentre RCT with 608 participants. The studies compared different digital technologies to usual care.

Digital technology (TIM) versus standard treatment (TBM)

McCormack 2011 compared the effect of using a digital nebuliser (iNeb) with an adapted mouthpiece which used feedback to encourage deeper inhalations during treatment (TIM) to using a standard breathing mode which used tidal breathing to set delivery of the treatment (TBM) (McCormack 2011). The main aim of the study was to reduce treatment time and improve adherence. Investigators only reported three of our outcomes: adherence to inhaled therapy treatment; adverse events; and FEV_1. The results showed that TIM may improve adherence compared to TBM (MD 24.0%, 95 % CI 2.95 to 45.05; low-certainty evidence). The digitally enhanced breathing mode may make little or no difference to FEV_1 (low-certainty evidence). No adverse events were reported in either group. See Summary of findings 1.

Digital technology (eNebuliser with digital support) versus standard treatment (eNebuliser without support)

The CFHealthHub 2017 study looked at the use of a web-based platform (CFHealthHub), in conjunction with a data-tracking nebuliser to give participants tailored, flexible support and feedback by a trialist throughout the 12-month study, compared to usual care, where adherence and lung function were monitored electronically but this information was not fed back to participants (CFHealthHub 2017). The CFHealthHub intervention probably improves adherence to inhaled therapy (moderate-certainty evidence), probably leads to slightly reduced treatment burden (moderate-certainty evidence) and may have little effect on FEV_1 (low-certainty evidence) compared to usual care. There is probably little or no difference in the incidence of pulmonary exacerbations or QoL between the two groups. There were slightly more adverse events in the CFHealthHub group, but none of the serious adverse events were related to the intervention. There was no difference between groups in treatment-related adverse effects (anxiety and depression scores) (CFHealthHub 2017). See Summary of findings 2.

Overall completeness and applicability of evidence

We are confident that our searches have identified all the relevant studies at the current time. The two included studies looked at very different interventions; consequently, we separated them into two distinct comparisons.

The older TIM versus TBM study in this review looked at the effect of an AAD method for inhaled medication via a chipped nebuliser, whereby the technology guides the participant into taking deeper breaths (McCormack 2011). This trial was a small RCT consisting of 20 children aged five to 16 years (median age under 12 years). Thus, it is unclear how generalisable the results would be to an adult population where treatment regimens are generally longer, treatment burden is often higher and therapies are managed more independently, without parent or carer supervision.

Additionally, the trial only reported on three of our outcome measures (adherence, adverse events and lung function). It did not assess our pre-defined primary outcomes of treatment burden and QoL, or several of our secondary outcomes. It is typical for pwCF to spend two to three hours per day on therapies, with treatment burden given as a reason for non-adherence to treatment in CF (Calthorpe 2020). The included study did not assess whether reducing the length of treatment time improved adherence through a reduction of treatment burden (McCormack 2011).

The CFHealthHub study was a large RCT which directly sought to answer our review question (CFHealthHub 2017). The study was well-powered, used rigorous methodology and reported on six of our eight pre-specified outcomes. The study only recruited participants aged 16 or over; therefore, we cannot assess if the intervention would be suitable for use in children younger than 16 years of age.

Certainty of the evidence

We have reported low-certainty evidence that the use of digital technology (TIM) may lead to an improvement in adherence to inhaled therapy compared to standard care (TBM) (McCormack 2011). The study was carried out in children with CF and compared specific techniques for administration of inhaled medication. The study itself was well-conducted and well-reported, and we deemed it to be at low risk of bias across all domains. However, it only fully addressed three of our outcomes (adherence, adverse events and lung function). We downgraded the certainty of the evidence due to imprecision from a very small sample size (n = 20) and for indirectness, as the study was carried out in children and therefore may not be generalisable to an adult population. A description of reporting of the certainty of evidence is given in Summary of findings 1.

We have reported moderate-certainty evidence across all outcomes in the CFHealthHub 2017 study, except for FEV_1. We have reported low-certainty evidence for FEV_1 due to wide CIs causing imprecision. There was a low risk of bias across most of the domains for each outcome. There were some concerns around the randomisation process leading to baseline differences, but this was well described in the paper and in supplementary documentation. Participants were stratified based on centre and prior days of antibiotics. Baseline differences described suggest that the intervention group had slightly better lung health (FEV_1), were slightly older, had slightly fewer days of intravenous antibiotics in recent years and slightly higher objectively measured adherence. However, results were adjusted for this and reported as adjusted MDs. The only reason we downgraded the certainty of the evidence was due to indirectness since the study only included participants aged 16 years or older. It is not clear whether the results would be replicated in younger children (Summary of findings 2).

Potential biases in the review process

A strength of this review is that we are confident that we have identified all the studies that fit our inclusion criteria as we

carried out a thorough search of the literature, including scanning reference lists of included studies, of excluded systematic reviews and of clinical trials databases. Two review authors independently screened the articles' titles, abstracts and full texts, as well as extracted data and assessed risk of bias. At all points in the process, we discussed discrepancies and referred these to a third author if we were unable to come to a final agreement.

A limitation of this review was that there were only two studies meeting our inclusion criteria. The studies looked at different technologies, and we were unable to include any of the results in a meta-analysis. We aim to address this in future versions of this review as more studies become available for inclusion.

Agreements and disagreements with other studies or reviews

The role of digital technologies within CF is an emerging field. As a result, at present, there are only a few relevant RCTs using digital technologies in CF, with the majority of studies being small interventional and before-after studies not eligible for inclusion in this review (Calthorpe 2019). For example, there was a small study in children aged two to 15 years (48 participants) with *Pseudomonas aeruginosa* which used an adaptive aerosol delivery device (I-neb) for the delivery of colistin (Promixin) with a data-logging facility within the device to capture adherence data for the participants (McNamara 2009). Although the study demonstrated the use of digital technology to monitor adherence to nebuliser therapy, this was an observational study and the lack of a comparator group prevented its inclusion within this review. It is perhaps not surprising that this review contained only two RCTs to monitor adherence to inhaled therapies (CFHealthHub 2017; McCormack 2011).

The McCormack study showed improved adherence to inhaled therapy with the use of a digitally enhanced breathing mode (TIM) to encourage longer and deeper breaths. The adherence data in this study for TBM mode were similar to the above-mentioned retrospective observational study of the use of the I-neb in children with CF for delivering nebulised medication over a 12-month period (McNamara 2009). The McNamara study demonstrated an overall treatment adherence through the I-neb of 67% over six months, compared to the included McCormack 2011 study with adherence of 65% at the end of the eight- to 10-week study period. McCormack and colleagues postulated that better adherence in the intervention group was due to the novelty of a new breathing mode, and therefore also explained why a decline was seen in the TBM mode. However, this decline may also reflect the true overall adherence of this population group, given its similarity with the results of the McNamara 2009 study, and may have been artificially elevated at study entry. This phenomenon was also seen as part of the CFHealthHub 2017 study, in which a rapid initial decline in adherence was seen in both groups at the start of the study period, which the authors felt likely reflected a higher level of adherence at study entry due to a short-term manifestation of device novelty and white coat adherence.

The primary outcome of the included McCormack 2011 study was treatment time, but the study did not discuss any possible relationship between shorter treatment times with improved adherence and did not assess treatment burden and QoL. However, treatment times in CF are long and associated with a high treatment burden. Not having enough time was the most common theme identified impacting on adherence in an international survey of the CF community (Davies 2020). The Davies study, which described the views of pwCF on treatment burden, found that the most burdensome treatments were the most likely to be omitted. Nebulised therapies, along with airway clearance techniques, were described as one of the more difficult and most burdensome treatments to complete by pwCF and healthcare professionals, and were most commonly omitted when busy or tired (Davies 2020). The reduced time taken with the TIM group in the McCormack study may also therefore account for the improved adherence in this group.

The CFHealthHub 2017 study was the first large RCT looking at adherence to inhaled therapy using digital technology which automatically captured date and time-stamped data to a 2net Hub for accurate recording of adherence data. The intervention group also had access to the CFHealthHub digital platform and tailored support throughout the 12-month study period. The intervention group showed improved adherence to inhaled therapy with significantly reduced treatment burden scores at 12 months with the concurrent use of CFHealthHub. This is similar to other studies within CF; for example, the Early Intervention in Cystic Fibrosis Exacerbation (eICE) trial, which used digital technology via home spirometry monitoring for the early detection of pulmonary exacerbations (Lechtzin 2017). This study demonstrated a poor adherence to the digital technology, possibly as a result of the increased treatment demand in the intervention group, with participants failing to upload their data regularly (Lechtzin 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Both of our included studies report improvement in adherence to inhaled therapies with digital technology (CFHealthHub 2017; McCormack 2011). One study in children with cystic fibrosis (CF) used a digitally enhanced inhalation mode via an adapted mouthpiece, whilst the second study monitored adherence in participants aged 16 years and over via a data-tracking nebuliser in conjunction with an online, multicomponent, self-management intervention hosted on an online platform with tailored support from a trialist.

The body of evidence we present here does not allow us to come to a firm conclusion with regard to using digital technology for monitoring adherence to inhaled therapy in both adults and children with CF. One of our included studies provides low-certainty evidence that an adaptive aerosol delivery system can be used to monitor adherence in children with CF, and that a target inhalation mode may lead to better adherence to nebuliser therapy than standard tidal breathing mode without any adverse effects. The second study was larger and more robust. It showed that the CFHealthHub online platform probably improves adherence to inhaled therapies without an increase in treatment burden in people with CF aged 16 and over, although there was little or no difference to quality of life or pulmonary exacerbations (moderate-certainty evidence).

Implications for research

Whilst there is much research into digital technologies for people with CF to manage their treatments and lifestyle with the development of apps and web-based platforms, there are

few studies addressing the issue of adherence, specifically to inhaled therapy. Many of the published studies are observational in nature and without a comparator group, but some provide comparisons with other methods of data capture such as self-report (McNamara 2009; Thorton 2013). Whilst these studies provide useful information on the feasibility of using digital technology to monitor adherence to therapy, randomised controlled trials (RCTs) provide more information on the effectiveness of this strategy. We were able to include only two RCTs in this review (CFHealthHub 2017; McCormack 2011), and whilst the results are promising in terms of adherence, it is also important to measure outcomes not reported in our included studies. Neither study reported on the effect of the digital technology on adherence to the total treatment regimen. It is possible that an improvement in adherence to inhaled therapies could be at the detriment of adherence to other parts of the treatment regimen. Similarly, it would be important to look at the effect of digital adherence monitoring on frequency of healthcare appointments in both children and adults.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

CFHealthHub 2017

Study characteristics	
Methods	RCT open-label parallel design Multicentre trial carried out in 19 UK centres Participants were allocated 1:1 to the intervention or usual care using a computer-generated pseudo-random list with random-permuted blocks of randomly varying sizes, via a central, web-based randomisation system. The allocation sequence was hosted by the Sheffield Clinical Trials Research Unit, with the sequence created by a statistician (not otherwise involved with the trial) and held on a secure server. After recruiting each participant, the trialist logged into the server and entered basic demographic information, then the allocation was revealed to the participants. The paper states that "the trial statistician remained blind to treatment allocation until database freeze", which we understand means that the trial statistician was blinded to treatment allocation until after all data had been collected and entered into the database. Duration: 12 months
Participants	608 participants from 19 centres. Diagnosed with CF and within UK CF Registry. Aged 16 years and over. Participants had to be willing to take all inhaled mucoactive agents and antibiotics via eFlow Technology nebulisers with eTrack data-logging Controllers (PARI Pharma GmbH, Starnberg, Germany). **Age- mean age (SD)** CFHealthHub (CFHH) – 31.1 (10.6) N = 304 Usual care – 30.3 (10.8) N = 303 **Gender - n (%) female, N** CFHH – 156 (51.3) N = 304 Usual care – 154 (50.8) N = 303 **Adherence:objectively measured effective adherence (weekly) mean % (SD), N** CFHH: 54.1 (33.0) N = 293 Usual care: 45.5 (34.1) N = 295 **CFQ-Rmean score (SD), N** Physical domain – CFHH: 54.3 (30.6) N = 304 Usual care: 53.0 (30.2) N = 302 Emotional domain – CFHH: 66.5 (21.6) N = 304 Usual care: 66.2 (24.1) N = 302 **FEV1 % predicted, mean (SD), N** CFHH: 60.7 (23.5) N = 304 Usual care: 58.3 (22.6) N = 302 Baseline differences described suggest that the intervention group had slightly better lung health (FEV1), were slightly older, had slightly fewer days of IVs over the past year and slightly higher objectively measured adherence. **Exclusion criteria:** on active lung transplant list; post lung transplant; receiving palliative care; using inhaled dry powder devices.

CFHealthHub 2017 *(Continued)*

Interventions	All participants were given eTrack data-logging controllers for their eFlow Technology nebulisers which sent time-stamped and date-stamped data to a 2net Hub for recording of adherence and inhalation calculation. **Intervention** Intervention participants had access to the CFHealthHub digital platform (website and smartphone application) and received tailored, flexible support from the interventionist throughout the 12-month trial period. **Control (usual care)** Usual care participants used the eTrack data-logging controllers for adherence data collection. There was no access to CFHealthHub, behavioural change tools or content. Adherence results were invisible to participants and care teams.
Outcomes	Objectively measured effective adherence (%) Treatment burden (CFQ-R treatment burden domain) Quality of life (CFQ-R physical, emotional, social, eating, body image, treatment burden, respiratory, digestion domains) Adverse effects (including anxiety and depression score) FEV_1 % predicted Pulmonary exacerbation (exacerbation rate and number of exacerbations and person years)
Notes	The RCT was one part of a larger cohort study which measured adherence to inhaled medication and provided data for further work on improving adherence and behaviour change. Funding source: NIHR Grants for Applied Research programme (RP-PG-1212-20015) and NHS England Commissioning for Quality and Innovation (IM2 Cystic Fibrosis Patient Adherence).

McCormack 2011

Study characteristics	
Methods	RCT Parallel group design Location: UK Duration: 4- to 6-week run-in period followed by an 8- to 10-week intervention period
Participants	Clinically stable children with CF (5 to 16 years). Participants with *Pseudomonas aeruginosa* infection who were on long-term (> 3 months) antibiotic therapy through the I-neb using standard TBM of inhalation. 20 children randomised in total, 10 children to TIM and 10 to TBM. No dropouts or loss to follow-up. Exclusion criteria: pulmonary exacerbation in the previous 4 weeks (defined as: increase in cough, increased sputum production, reduction in FEV1 > 10%). Baseline characteristics between the 2 groups were similar. One child in the TIM group had a fault with the base unit which was replaced during the course of the study. **Age, median (range)** TIM group: 11.7 years (8.7 to 15.9) TBM group: 10.6 years (5.2 to 16.9) **Sex** TIM group: 7 males, 3 females TBM group: 7 males, 3 females **FEV1 % predicted, median (range)** TIM group: 74% (60 to 105)

McCormack 2011 *(Continued)*

	TBM group: 80% (53 to 100) **Schwachman score, median (range)** TIM group: 85/100 (65 to 95) TBM group: 88/100 (60 to 100) **AAD TBM therapy, mean (SD) duration prior to study** TIM group: 42.2 months (10.4) TBM group: 34.7 months (12.5)
Interventions	Both groups used AAD via an I-neb to deliver a commercial preparation of colistin (Promixin, Profile Pharma Ltd., Chichester, UK) with a standard treatment dose being 1 MU diluted in 2 mL normal saline (1 mL being used for each of 2 daily treatments). Some participants were prescribed a once-daily dose of 1 MU colistin in 1 mL normal saline. Once-daily dornase alfa (Pulmozyme) was also prescribed in several particpants. **Schedule** Both groups were given a run-in period of 4 to 6 weeks on TBM, followed by 8 to 10 weeks of either TIM or TBM. **Intervention group (AAD TIM)** A high-resistance mouthpiece guides the participant to use slower and deeper inhalations. The participant is encouraged to lengthen each inhalation by a vibratory feedback on the lip, which is the signal to exhale. TIM guides the participant into taking the longest inhalation they can manage by gradually increasing the time from the beginning of each breath to the vibration. Once the maximum length of inhalation has been found (i.e. when the patient is unable to reach the vibration), the time is then shortened to a comfortable level for the patient and remains at this level until the preset dose is achieved. **Comparator (AAD TBM)** Delivers aerosol particles of medication during tidal breathing. The I-neb monitors the first 3 breaths and delivers a timed pulse of aerosol during the mid-phase of the next inspiration. Each pulsed delivery is based on the previous 3 breaths. Audio and visual feedback is given when the treatment is complete.
Outcomes	Treatment adherence (% of expected treatments) FEV_1 Adverse effects
Notes	Funding source: not stated

AAD: adaptive aerosol delivery
FEV_1: forced expiratory volume in 1 second
MU: mega unit
RCT: randomised controlled trial
TIM: target inhalation mode
TBM: tidal breathing mode

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

Study	Reason for exclusion
Aitken 2011	Digital technology used for early identification of pulmonary exacerbations and not adherence monitoring.
Bodnar 2016	Systematic literature review not primary research
Daniels 2013	Cochrane Review not primary research

Study	Reason for exclusion
Elkins 2006	Ineligible intervention: this RCT compared 2 different strengths of saline (0.9% saline or 7% hypertonic saline) with adherence measured in all participants via diary and nebuliser refill data. Investigators took a random sample of 145 participants and measured adherence in 3 ways, including via a device that logged nebuliser use. Participants were not randomised to a digital intervention or to a control.
ISRCTN37959826	Not specifically adherence to inhaled medication. The study used a programme of online information describing how medications work and how they should be taken. The outcomes are measures of total prescription adherence and not specifically inhaled therapies.
NCT00185549	Not specifically adherence to inhaled therapies. The study used an internet-based programme to encourage self-care behaviour leading to improved nutritional status.
NCT01183286	Ineligible intervention. Digital technology was not used for monitoring adherence to inhaled therapy. The intervention was a smartphone app which contained medical and behavioural information, disease management tools and social networking features with the aim of increasing CF knowledge, improving adherence to the treatment regimen, improving quality of life and enhancing social support. Adherence was measured using Pharmacy Refill Data.
NCT02122289	Study did not monitor adherence to inhaled therapy. It was a digital intervention to detect and identify exacerbations at an earlier stage.
NCT03052231	Ineligible participant group. The study aimed to provide interactive mobile health information to support health professionals by supporting patient empowerment. The programme encompassed information, appointment reminders, medication adherence reminders and general health education. It was not specifically looking at adherence to inhaled therapies.
Quittner 2001	Not an RCT
Sands 2013	Ineligible intervention. No comparison of digital technology. Participants were randomised to 1 of 2 tobramycin solutions and digital technology was used to monitor adherence of all participants.

RCT: randomised controlled trial

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

Thee 2021

Study name	ConneCT CF
Methods	Multicentre, randomised, controlled, non-blinded trial 1:1 randomisation performed by an electronic data capture system
Participants	Aiming to recruit 402 participants aged 12 years or over with CF Participants must have had at least one pulmonary exacerbation (Bilton criteria) in the year before enrolment, FEV_1 < 90%, and if on CFTR modulator therapy, participants must be stable for the last three months.
Interventions	There is a six-week preparation phase where participants are trained to use the study devices. **Intervention group:** participants are given a telemedicine-capable nebuliser (eFlow rapid+ nebuliser system consisting of an eTrack Controller with eFlow rapid nebuliser handset, PARI Pharma GmbH, Germany), home spirometry (mySpiroSense, PARI GmbH, Germany) and a CF therapy management app (PARI Connect App, PARI Pharma GmbH, Germany) to support self-management, provide adherence monitoring and transfer lung function values. Data on date, duration and inhaled

Thee 2021 *(Continued)*

	agent will be collected and automatically transferred to a web cloud-based telemedicine data server. **Control group:** also receives a telemedicine-capable nebuliser (eTrack Controller with eFlow rapid nebuliser, PARI Pharma Ltd, Germany, and 2net Hub, Philips, North America). Data on adherence will be automatically tracked for final evaluation without any data access for participants or caring CF physicians in this group. After the preparation phase, there is a four-week assessment phase where adherence to inhaled therapy will be tracked in both groups to provide a baseline. In the intervention phase (18 months), continuous digital monitoring of adherence and lung function is performed in the intervention group. Adherence is calculated and displayed to the participant and the CF physician. Lung function measurements are performed once a week and a graph is generated which is displayed to the participant and the CF physician. Intervention group participants can also make use of video conferencing with their CF physician up to three times a quarter. The CF physician will also request a videoconferencing session if FEV_1 drops by 5% compared to the mean of the two previous values. There will also be psychological support. In the control group, there will also be continuous monitoring of adherence to inhaled therapies but this is not displayed to the participant or the CF physician.
Outcomes	Primary outcome is time to first protocol-defined pulmonary exacerbation after initiation of the intervention phase. Secondary outcomes include: the number of pulmonary exacerbations; time between exacerbations; adherence to inhaled therapy; change in FEV_1 and FVC from baseline; hospital admissions; change in health-related quality of life (Cystic Fibrosis Questionnaire - Revised (CFQ-R) and EuroQoL 5-dimension (EQ-5D-5L)); sociodemographic and anthropometric data; days absent from work or school and CF-associated medical treatment and healthcare-related costs.
Starting date	March 2021
Contact information	Marcus Mall Address: Augustenburger Platz 1 13353 Berlin Germany Telephone:030 450 566 128 Email:marcus.mall@charite.de Stephanie Thee Address: Augustenburger Platz 1 13353 Berlin Germany Telephone: 030 450 566 128 Email: Stephanie.thee@charite.de
Notes	

CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
RCT: randomised controlled trial

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 Treatment adherence

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Up to 3 months						
McCormack 2011	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 Mean change from baseline in FEV_1 % predicted

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Up to 3 months						
McCormack 2011	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.1 Treatment adherence

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 At 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 Quality of Life CFQ-R score: treatment burden

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.2.1 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 Quality of Life CFQ-R score: other domains

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 CFQ-R: physical domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.2 CFQ-R: emotional domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.3 CFQ-R: social domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.4 CFQ-R: eating domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.5 CFQ-R: body image domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.6 CFQ-R: respiratory domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓
Subgroup 2.3.7 CFQ-R: digestion domain score at 12 months						
CFHealthHub 2017	~	✓	✓	✗	✓	✓

Risk of bias for analysis 2.4 Adverse effects - anxiety and depression score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.4.1 GAD-7 anxiety score at 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.4.2 PHQ-8 depression score at 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓

Risk of bias for analysis 2.5 Adverse effects

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.5.1 All adverse events at 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓
Subgroup 2.5.2 Serious adverse events at 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	✓

Risk of bias for analysis 2.6 FEV_1 % predicted

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.6.1 At 12 months						
CFHealthHub 2017	~	✓	✓	✓	✓	~

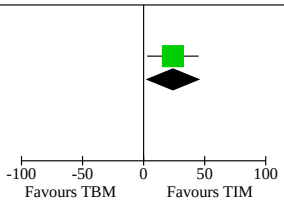
DATA AND ANALYSES

Comparison 1. Digital technology (TIM) versus standard treatment (TBM)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment adherence	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Up to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	24.00 [2.95, 45.05]
1.2 Mean change from baseline in FEV_1 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Up to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	1.00 [-9.37, 11.37]

Analysis 1.1. Comparison 1: Digital technology (TIM) versus standard treatment (TBM), Outcome 1: Treatment adherence

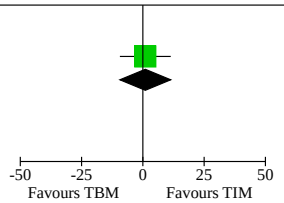
Study or Subgroup	TIM Mean	TIM SD	TIM Total	TBM Mean	TBM SD	TBM Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Up to 3 months								
McCormack 2011	89	8	10	65	33	10	100.0%	24.00 [2.95 , 45.05]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**24.00 [2.95 , 45.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Digital technology (TIM) versus standard treatment (TBM), Outcome 2: Mean change from baseline in FEV_1 % predicted

Study or Subgroup	TIM Mean	TIM SD	TIM Total	TBM Mean	TBM SD	TBM Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Up to 3 months								
McCormack 2011	2.2	10.81	10	1.2	12.77	10	100.0%	1.00 [-9.37 , 11.37]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**1.00 [-9.37 , 11.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Digital technology (web-based online platform) versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Treatment adherence	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1.1 At 12 months	1	588	Mean Difference (IV, Fixed, 95% CI)	18.00 [12.90, 23.10]
2.2 Quality of Life CFQ-R score: treatment burden	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.2.1 12 months	1	539	Mean Difference (IV, Fixed, 95% CI)	5.10 [1.79, 8.41]
2.3 Quality of Life CFQ-R score: other domains	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 CFQ-R: physical domain score at 12 months	1	538	Mean Difference (IV, Fixed, 95% CI)	3.20 [-1.94, 8.34]
2.3.2 CFQ-R: emotional domain score at 12 months	1	538	Mean Difference (IV, Fixed, 95% CI)	0.10 [-3.92, 4.12]
2.3.3 CFQ-R: social domain score at 12 months	1	538	Mean Difference (IV, Fixed, 95% CI)	0.90 [-2.48, 4.28]
2.3.4 CFQ-R: eating domain score at 12 months	1	538	Mean Difference (IV, Fixed, 95% CI)	3.00 [-0.78, 6.78]
2.3.5 CFQ-R: body image domain score at 12 months	1	538	Mean Difference (IV, Fixed, 95% CI)	2.10 [-2.68, 6.88]
2.3.6 CFQ-R: respiratory domain score at 12 months	1	534	Mean Difference (IV, Fixed, 95% CI)	1.40 [-2.37, 5.17]
2.3.7 CFQ-R: digestion domain score at 12 months	1	535	Mean Difference (IV, Fixed, 95% CI)	0.20 [-3.28, 3.68]
2.4 Adverse effects - anxiety and depression score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 GAD-7 anxiety score at 12 months	1	535	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.46, 1.26]
2.4.2 PHQ-8 depression score at 12 months	1	534	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.00, 0.80]
2.5 Adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 All adverse events at 12 months	1	608	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.86, 1.64]
2.5.2 Serious adverse events at 12 months	1	608	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.88, 2.10]

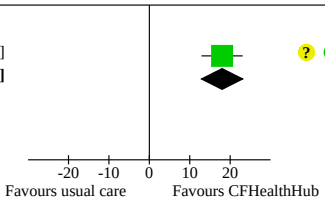
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 FEV_1 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 At 12 months	1	556	Mean Difference (IV, Fixed, 95% CI)	3.70 [-0.23, 7.63]

Analysis 2.1. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 1: Treatment adherence

Study or Subgroup	CFHealthHub Mean	CFHealthHub SD	CFHealthHub Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 At 12 months								
CFHealthHub 2017	52.9	31.4	293	34.9	31.7	295	100.0%	18.00 [12.90 , 23.10]
Subtotal (95% CI)			**293**			**295**	**100.0%**	**18.00 [12.90 , 23.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.92 (P < 0.00001)

Test for subgroup differences: Not applicable



Risk of Bias: A B C D E F — ? + + + + +

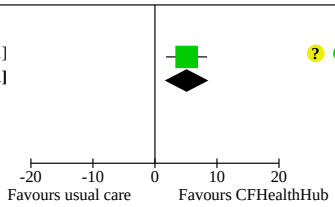
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 2: Quality of Life CFQ-R score: treatment burden

Study or Subgroup	CFHealthHub Mean	CFHealthHub SD	CFHealthHub Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 12 months								
CFHealthHub 2017	56.6	19.5	265	51.5	19.7	274	100.0%	5.10 [1.79 , 8.41]
Subtotal (95% CI)			**265**			**274**	**100.0%**	**5.10 [1.79 , 8.41]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.003)

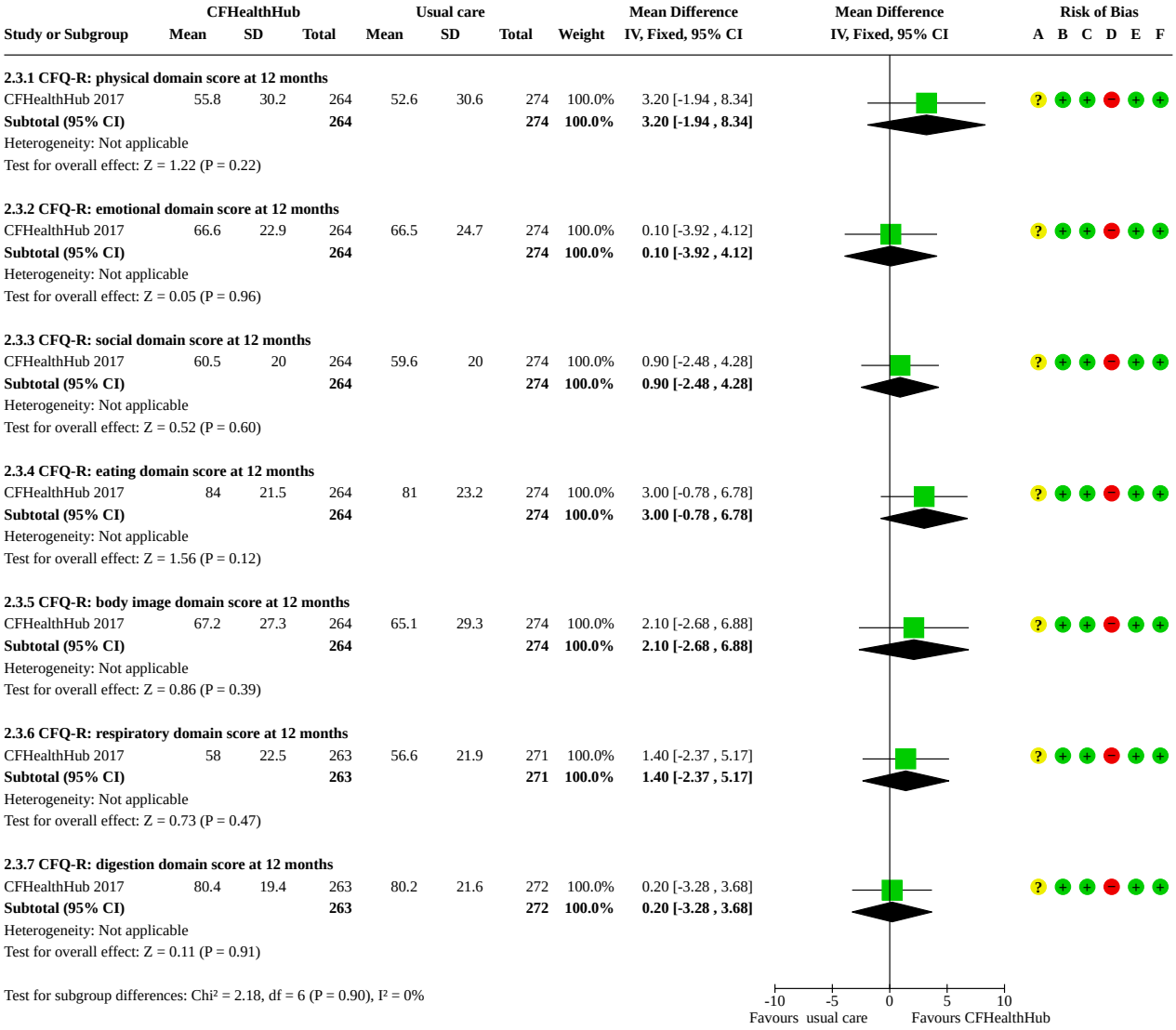
Test for subgroup differences: Not applicable



Risk of Bias: A B C D E F — ? + + + + +

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 3: Quality of Life CFQ-R score: other domains

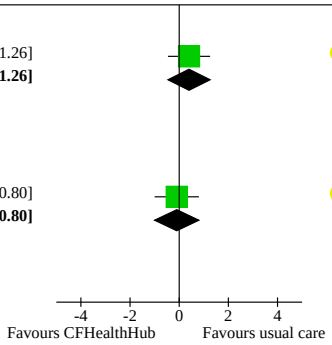


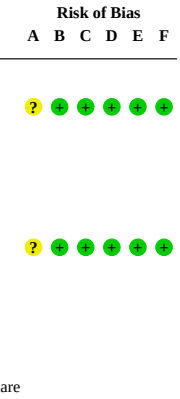
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 4: Adverse effects - anxiety and depression score

Study or Subgroup	CFHealthHub Mean	CFHealthHub SD	CFHealthHub Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
2.4.1 GAD-7 anxiety score at 12 months								
CFHealthHub 2017	4.9	5.3	262	4.5	4.8	273	100.0%	0.40 [-0.46 , 1.26]
Subtotal (95% CI)			**262**			**273**	**100.0%**	**0.40 [-0.46 , 1.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
2.4.2 PHQ-8 depression score at 12 months								
CFHealthHub 2017	6.3	5.6	262	6.4	5	272	100.0%	-0.10 [-1.00 , 0.80]
Subtotal (95% CI)			**262**			**272**	**100.0%**	**-0.10 [-1.00 , 0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.83)								
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%								

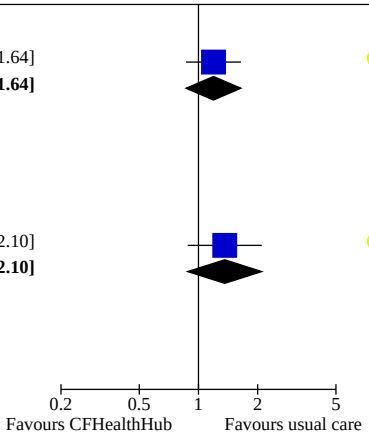




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

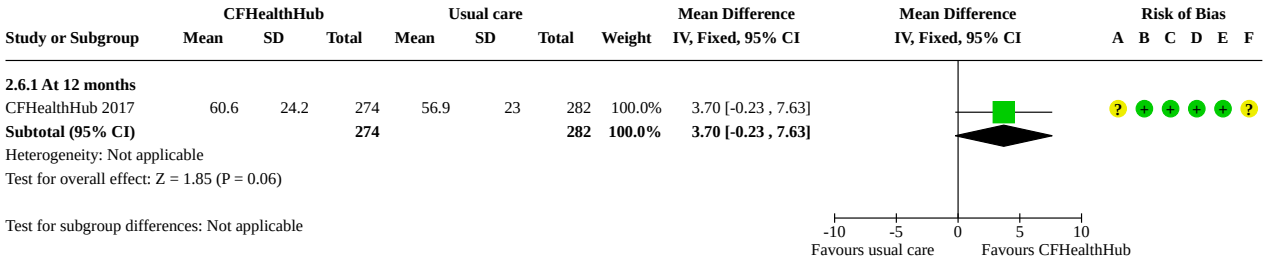
Analysis 2.5. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 5: Adverse effects

Study or Subgroup	CFHealthHub Events	CFHealthHub Total	Usual care Events	Usual care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 All adverse events at 12 months						
CFHealthHub 2017	139	305	125	303	100.0%	1.19 [0.86 , 1.64]
Subtotal (95% CI)		**305**		**303**	**100.0%**	**1.19 [0.86 , 1.64]**
Total events:	139		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
2.5.2 Serious adverse events at 12 months						
CFHealthHub 2017	56	305	43	303	100.0%	1.36 [0.88 , 2.10]
Subtotal (95% CI)		**305**		**303**	**100.0%**	**1.36 [0.88 , 2.10]**
Total events:	56		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.16)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: Digital technology (web-based online platform) versus usual care, Outcome 6: FEV_1 % predicted



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Adjusted mean differences (MD) reported in the CFHealthHub study

Outcomes (measured at 12 months)	Unit of measurement	CFHealthHub		Usual care		Adjusted MD (95% CI) as reported in the original paper
		n	Mean (SD)	n	Mean (SD)	
Objectively measured effective adherence	%	293	52.9 (31.4)	295	34.9 (31.7)	9.5% (95% CI 8.6 to 10.4)
Treatment burden: CFQ-R treatment burden domain score	CFQ-R score (0 to 100); higher is better	265	56.6 (19.5)	274	51.5 (19.7)	3.9 (95% CI 1.2 to 6.7)
QoL: physical domain	CFQ-R score (0 to 100); higher is better	264	55.8 (30.2)	274	52.6 (30.6)	2.3 (95% CI -1.0 to 5.6)
QoL: emotional domain	CFQ-R score (0 to 100); higher is better	264	66.6 (22.9)	274	66.5 (24.7)	0.2 (95% CI -2.9 to 3.2)
QoL: social domain	CFQ-R score (0 to 100); higher is better	264	60.5 (20.0)	274	59.6 (20.0)	0.3 (95% CI -2.2 to 2.7)
QoL: eating domain	CFQ-R score	264	84.0 (21.5)	274	81.0 (23.2)	1.9 (95% CI -1.3 to 5.2)

Table 1. Adjusted mean differences (MD) reported in the CFHealthHub study *(Continued)*

	(0 to 100); higher is better					
QoL: body image domain	CFQ-R score (0 to 100); higher is better	264	67.2 (27.3)	274	65.1 (29.3)	1.7 (95% CI -1.4 to 4.8)
QoL: respiratory domain	CFQ-R score (0 to 100); higher is better	263	58.0 (22.5)	271	56.6 (21.9)	0.7 (95% CI -2.4 to 3.8)
QoL: digestion domain	CFQ-R score (0 to 100); higher is better	263	80.4 (19.4)	272	80.2 (21.6)	1.1 (95% CI -1.7 to 3.9)
Adverse effects: GAD-7 anxiety score	GAD-7 (0 to 21); lower is better	262	4.9 (5.3)	273	4.5 (4.8)	0.3 (95% CI -0.4 to 1.0)
Adverse effects: PHQ-8 depression score	PHQ-8 (0 to 24); lower is better	262	6.3 (5.6)	272	6.4 (5.0)	-0.1 (95% CI -0.8 to 0.7)
FEV_1	% predicted	274	60.6 (24.2)	282	56.9 (23.0)	1.4 % predicted (95% CI -0.2 to 3.0)
Exacerbation rate (number of exacerbations per year)	Adjusted rate	304	1.63 (482 exacerbations, 294.9 person years)	303	1.77 (526 exacerbations, 297.2 person years)	0.96 (95% CI 0.83 to 1.12)

Taken directly from the paper (CFHealthHub 2017).
CFQ-R: Cystic Fibrosis Questionnaire - Revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **GAD-7**: Generalised Anxiety Disorder score; **MD**: mean difference; **PHQ-8**: Patient Health Questionnaire; **QoL**: quality of life

APPENDICES

Appendix 1. Search methods - electronic searches

Database/resource	Strategy	Date last searched
Embase Ovid	1. crossover procedure.de. 2. double-blind procedure.de.	10/11/2020

(Continued)

3. randomized controlled trial.de.

4. single-blind procedure.de

5. 1 or 2 or 3 or 4

6. random*.de,ab,ti.

7. factorial*.de,ab,ti.

8. crossover*.de,ab,ti.

9. (cross adj1 over*).de,ab,ti.

10. placebo*.de,ab,ti.

11. (doubl* adj1 blind*).de,ab,ti.

12. (singl* adj1 blind*).de,ab,ti.

13. assign*.de,ab,ti.

14. allocat*.de,ab,ti.

15. volunteer*.de,ab,ti.

16. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. cystic fibrosis.mp. or cystic fibrosis/

18. CF.mp.

19. (fibrocystic adj disease).tw.

20. mucoviscido$.tw.

21. (cystic$ adj10 fibros$).tw.

22. or/17-21

23. inhaled.mp.

24. nebuliser.mp. or nebulizer/

25. inhal*.mp.

26. 23 or 24 or 25

27. ehealth.mp. or telehealth/

28. telemonitoring.mp. or telemonitoring/

29. internet.mp. or Internet/

30. smartphone.mp. or mobile phone/ or smartphone/ or telemedicine/ or personal digital assistant/

31. electronic monitoring.mp.

32. technology/ or technology.mp.

33. app.mp. or mobile application/

34. email.mp.

35. reminder.mp.

(Continued)

	36. (smart adj3 nebulis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 37. ineb.mp. 38. or/27-37 39. adhere*.mp. 40. 16 and 22 and 26 and 38 and 39 41. limit 40 to human	
ClinicalTrials.gov www.clinicaltrials.gov	[Advanced Search] CONDITION OR DISEASE: cystic fibrosis OTHER TERMS: technology OR telehealth OR telemedicine OR monitoring OR interactive OR mobile OR web OR internet OR online OR app OR text OR messaging OR telemonitoring OR chip OR chipped OR tracking OR tracker OR digital OR bluetooth OR video OR smartphone OR electronic OR computer OR email OR reminder STUDY TYPE: Interventional Studies (Clinical Trials)	10/11/2020
Australia New Zealand Clinical Trials Registry ANZCTR http://www.anzctr.org.au/default.aspx	[Basic Search] SEARCH 1 (cystic fibrosis) AND (technology OR telehealth OR telemedicine OR monitoring OR interactive OR reminder) SEARCH 2 (cystic fibrosis) AND (mobile OR web OR internet OR online OR app OR text) SEARCH 3 (cystic fibrosis) AND (messaging OR telemonitoring OR chip OR chipped OR tracking OR tracker) SEARCH 4 (cystic fibrosis) AND (digital OR bluetooth OR video OR smartphone OR electronic OR computer)	10/11/2020
WHO ICTRP https://www.who.int/ictrp/en/	*Search terms to be based on other register search strategies*	Unavailable at time of searching due to Covid-19

HISTORY

Protocol first published: Issue 9, 2020

CONTRIBUTIONS OF AUTHORS

Task	Author(s) responsible
Protocol stage: draft the protocol	SS (with input from all authors)
Review stage: select which trials to include (2 + 1 arbiter)	SS, RC, SH, AS
Review stage: extract data from trials (2 people)	SS, RC, SH
Review stage: enter data into RevMan	SS
Review stage: carry out the analysis	SS
Review stage: interpret the analysis	SS, RC, SH, AS
Review stage: draft the final review	SS (with input from all authors)
Update stage: update the review	SS, RC, SH, AS

DECLARATIONS OF INTEREST

Sherie Smith: none known.

Dr Rebecca Calthorpe: none known.

Dr Sophie Herbert: none known.

Professor Smyth declares participation in a sponsored symposium (Vertex) and a lecture paid for by TEVA; both of whom are pharmaceutical companies who do not market or manufacture products eligible for inclusion in this review. He has received a research grant from Vertex (outside the submitted work).

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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

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Anti-Bacterial Agents [therapeutic use]; *Cystic Fibrosis [complications]; Digital Technology; Nebulizers and Vaporizers; Quality of Life

MeSH check words

Adult; Child; Humans