Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Oscillating positive expiratory pressure devices for airway clearance in chronic hypersecretory lung conditions

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: are oscillating positive expiratory pressure (OPEP) devices more clinically and cost-effective than other techniques for airway clearance in chronic hypersecretory lung conditions?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Positive expiratory pressure (PEP) devices are often used as a form of chest physiotherapy to clear mucus from the lungs of individuals with hypersecretory conditions. This review focused on use of the oscillatory PEP devices in people with hypersecretory conditions, including cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchiectasis, which are described briefly below. Feedback from clinical experts suggests that they are also used in patients with primary ciliary dyskinesia and that there is potential in the future for their use post-surgery in patients experiencing mucus retention due to the nature of the surgery.

Cystic fibrosis is relatively common and there were around an estimated 10,250 individuals with the condition in the UK in 2018, 38.6% of whom were aged less than 16 years (Cystic Fibrosis Trust 2020). A genetic defect results in abnormal mucus secretion in the airways, which can cause airway obstruction and mucus plugging. This, in turn, predisposes the individual to infection and inflammation of the airways, promoting further mucus secretion. Persistent infection and inflammation can result in airway damage and progressive loss of respiratory function. Most interventions are needed daily and an estimated average of 108 minutes are spent on treatment activities each day by adults with cystic fibrosis, the majority of which is spent on airway clearance and exercise (Dwyer et al. 2017).

Bronchiectasis (previously known as non-cystic fibrosis bronchiectasis) is a chronic and progressive respiratory condition which typically results in irreversible and abnormal dilation of the bronchial lumen (Lee et al. 2015a). As with cystic fibrosis, resulting impairment of mucociliary clearance in turn leads to continued presence of micro-organisms and colonisation, resulting in chronic inflammation and tissue damage. There are multiple possible causes, including immunological disorders and systemic respiratory conditions. Prevalence in the UK was

estimated to be around 566.1 and 485.5 per 100,000 population for females and males, respectively, in 2013 (Lee et al. 2017). The mortality rate is estimated to range from 10% to 16% over a 4-year period and hospitalisation and medical therapy is often required (Lee et al. 2015a). Frequent acute exacerbations and decline in respiratory function have been shown to be predictors of poor prognosis (Lee et al. 2015a).

COPD is defined as airflow obstruction which is not fully reversible (Osadnik et al. 2012). It is a disabling condition which is usually progressive and a major source of mortality and burden on healthcare worldwide. Pathological changes in the small airways with inflammation can cause increased mucus secretions, which further narrow the airway (Gastaldi et al. 2015). However, not all cases are mucus producing. Prevalence is currently increasing in many countries. As with cystic fibrosis and bronchiectasis, symptoms include dyspnoea, cough and sputum production. There is some evidence that airway clearance techniques (ACTs) can benefit patients with COPD in a similar way to patients with these other respiratory diseases (Osadnik et al. 2012).

The three conditions represent three different populations. Over 75% of individuals with cystic fibrosis are diagnosed by the age of two years (Cystic Fibrosis Foundation 2020). However, it is unclear at what age individuals typically start using ACTs or OPEP, in particular. In contrast, almost all (99%) of individuals with bronchiectasis are aged over 40 years when diagnosed, with around 60% aged older than 70 years (British Lung Foundation 2020a). Most individuals living with COPD are also aged older than 40 years (British Lung Foundation 2020b). The prevalence of cystic fibrosis is similar for men and women, but females have been shown to have worse outcomes than males, particularly in the incidence of respiratory tract infections. It is unclear whether this results in a differential uptake of ACTs, or OPEP in particular, but is seems likely. Bronchiectasis is more common in females than males (prevalence of 0.38% and 0.28%, respectively) while COPD is more common in males than females (prevalence of 0.21% and 0.18%, respectively).

3. Health technology

PEP is an ACT that can help clear mucus from the airways and lungs. When exhaling through a PEP mouthpiece, the device gives resistance that makes it more difficult to breathe out. This helps to loosen and move mucus out of the lungs. After using the PEP device, the user 'huff' coughs to help clear the mucus from the body.

Oscillatory airway devices seek to interrupt expiratory airflow (Morrison & Milroy 2017) and can be either intra- or extra-thoracic. Intra-thoracic oscillatory devices are usually placed in the individual's mouth and provide resistance during exhalation. This causes the airways to vibrate and loosen the mucus. They include oscillating PEP (OPEP) devices and intrapulmonary percussive ventilation. Extra-thoracic oscillatory devices are placed outside the body and vibrate at the frequency and intensity as set by the operator. McIlwaine et al. (2017) report that adding oscillations to PEP, either via an OPEP device or an extra-thoracic device, increases mucociliary clearance and reduces the viscoelastic properties of mucus, potentially rehydrating the mucus.

This review focuses on OPEP devices for hypersecretory conditions. Commonly used OPEP devices include Flutter, Cornet, Acapella, Quake, Pari-OPEP and Aerobika. Flutter is a small plastic device which uses a large ball bearing to repeatedly interrupt the outward flow of air. Acapella employs a counter-weighted plug and magnet to create the oscillatory resistance. Cornet is a horn-shaped tube with a rubber inner tube, the rotation of which reflects the resistance generated. In comparison, Quake uses a manually turned cylinder rather than relying on an oscillating valve. Air flow only occurs when the turning cylinder is lined up with the cylinder it sits within so that air flow is regularly interrupted at the frequency that the cylinder is turned. Aerobika devices do not contain any magnetic parts or ball bearings and resistance settings are adjusted to the

patient's capacity. OPEP devices are likely to be used in combination with other interventions such as pharmacological therapies or other physical techniques (McIlwaine et al. 2019).

OPEP devices are already available through NHS prescribing, and several OPEP devices are available in Wales. Feedback from clinical experts suggests that they are used as an option for patients alongside traditional ACTs where the patient is unable to undergo conventional types of physiotherapy. These devices are reported to be considered most useful where the secretions are more tenacious as they enable both the positive pressure to improve alveolar ventilation by increasing functional residual capacity (FRC) and recruiting under-ventilated regions, but also using oscillation to generate variable resistances within the airways. Use does not appear to be limited to specific demographic groups but dependent on factors such as patient preference, ease of use, and familiarity of the Practitioner. Use of Aerobika, Acapella, Flutter and Pari-OPEP is reported and supported by prescribing data (though this does not capture devices obtained without prescription).

4. Current guidance

Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient (Bott et al. 2009) were published by the British Thoracic Society and Association of Chartered Physiotherapists in Respiratory Care. They recommend considering the active cycle of breathing techniques, autogenic drainage and plain or oscillating PEP for patients with stable COPD who need ACT to assist in the removal of secretions. For adults with cystic fibrosis or non-cystic fibrosis bronchiectasis, they recommend considering OPEP devices when recommending an ACT.

4.1 Cystic fibrosis

NICE guidance for cystic fibrosis (NG78) does not mention OPEP specifically but recommends individualised plans to determine an appropriate ACT for cystic fibrosis, including preferences and adherence factors (NICE 2017). The Cystic Fibrosis Foundation Pulmonary Therapies Committee issued guidance on ACTs in 2009 (Flume et al. 2009). They found that, in general, no ACT had demonstrated superiority to others, but recommended that for an individual, one form of ACT may be superior to others and that the prescription should be based on individualised factors such as age, patient preference, and adverse events. In addition, aerobic exercise was recommended for patients as adjunctive therapy.

The Cystic Fibrosis Trust produced Standards of Care and Good Clinical Practice in 2020 (Physiotherapy Working Group 2020). The following good practice points were highlighted for oscillatory devices:

- Oscillating PEP has not been proven to be more or less effective overall than other airway clearance techniques. There is no evidence that one device is superior to another.
- Consider patient preference and their health beliefs when selecting an appropriate airway clearance technique for a patient with cystic fibrosis.
- Consider the age-appropriateness of specific airway clearance devices when recommending them for use as an airway clearance technique.
- Patients must be instructed in appropriate cleaning regimens of oscillatory PEP devices as per manufacturer guidelines.

4.2 Bronchiectasis and COPD

The British Thoracic Society guideline for bronchiectasis in adults (Hill et al. 2019) recommends teaching individuals with bronchiectasis to perform airway clearance. In particular, regular

twice-daily respiratory physiotherapy was found to increase sputum expectoration, improve cough-related health status, quality of life and exercise capacity in individuals with stable bronchiectasis and chronic sputum expectoration. It was considered good practice for ACTs to be taught by a respiratory physiotherapist. In terms of choice of ACT, the following evidence statements are made:

- The active cycle of breathing techniques is as effective as OPEP (Flutter and Acapella) at clearing sputum.
- The active cycle of breathing techniques plus postural drainage enhances the quantity of sputum expectorated compared with the active cycle of breathing techniques in the sitting position or OPEP (Flutter) in the sitting position.
- OPEP (Acapella) is more effective at clearing sputum than a threshold inspiratory muscle trainer.
- OPEP (Acapella) improves quality of life, sputum volume expectorated and exercise capacity compared with no ACT over a 3-month period

For acute exacerbations:

- OPEP (Acapella) (plus postural drainage) is effective and safe to use during an acute exacerbation.

They recommend that individuals with bronchiectasis are offered an active cycle of breathing technique or OPEP.

In addition, the European Respiratory Guidelines (Polverino et al. 2017) recommend that adult bronchiectasis patients with chronic productive cough or difficulty expectorating are taught an ACT by a trained respiratory physiotherapist to be performed once- or twice-daily (this was a weak recommendation based on low-quality evidence).

NICE guidance for COPD (NG115) does not mention OPEP specifically, but recommends PEP and active cycle techniques (NICE 2018).

5. Evidence search methods

We searched for evidence that could be used to answer the review question: are OPEP devices more clinically and cost-effective than other techniques for airway clearance in chronic hypersecretory lung conditions?

A systematic literature search for evidence was undertaken and last updated on 19 October 2020. Databases searched included Medline, Embase and the Cochrane Library; as well as ongoing clinical trials databases and selected websites. The search strategies are available upon request.

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts. Appendix 2 summarises the selection of articles for inclusion in the review.

6. Clinical effectiveness

We identified and included seven systematic reviews and 10 further primary studies which were not covered by the reviews. Three systematic reviews (McIlwaine et al. 2019, Morrison & Milroy 2017, Morrison & Milroy 2020) and three additional primary studies (Dwyer et al. 2017, McCarren & Alison 2006, Radtke et al. 2018) focused on patients with cystic fibrosis. Three systematic reviews (Lee et al. 2015a, Lee et al. 2017, Phillips et al. 2020) and two primary studies (Silva et al.

2017, Valente et al. 2004) looked at patients with bronchiectasis, while one systematic review (Osadnik et al. 2012) and three primary studies (Gastaldi et al. 2015, Milan et al. 2019, Nicolini et al. 2018) looked at patients with COPD. One primary study in patients with chronic bronchitis (Bellone et al. 2000) and one in patients with COPD or chronic bronchitis (Tse et al. 2020) were identified. One study in patients with a lower respiratory tract infection (Ni et al. 2018) and one study in children and adolescents with asthma (Felicio-Junior et al. 2020) were also identified.

Findings by type of OPEP device were available in one of reviews for cystic fibrosis and included results for Flutter and Cornet. The three additional primary studies looked at Flutter and Acapella. Two of the reviews for bronchiectasis (Lee et al. 2017, Phillips et al. 2020) included separate results for Flutter and Acapella, while the two additional primary studies looked at Flutter and Lung Flute. In the review of ACTs in individuals with COPD, emphysema or chronic bronchitis, studies reported findings for Flutter and Cornet. The five additional primary studies looked at Flutter, Acapella, Aerobika and Lung Flute.

A range of lung function measures were reported as an outcome, with forced expiratory volume (FEV1) and forced vital capacity (FVC) being the most commonly reported. Measures of lung clearance and sputum production were also common. Less commonly reported outcomes included exacerbations and hospital admissions, health-related quality of life, other measures of symptoms, and participant satisfaction and acceptability. Adverse events or participant withdrawal were rarely reported. Findings by type of outcome are reported in Appendix 4. The findings did not vary significantly between conditions and were of similar quality.

We identified five ongoing trials (see section 6.4). None focused on patients with cystic fibrosis; one included adult patients with stable bronchiectasis; and three included patients with COPD. The fifth included adults with any airway hypersecretory symptoms.

6.1 Cystic fibrosis

6.1.1 Overview of findings

No significant difference was found between treatment groups in any lung function outcome measure with the exception of a recent small study comparing peak expiratory flow (PEF) following OPEP and control. Findings for respiratory exacerbations and hospitalisation comparing OPEP and other ACTs were mixed. No studies found a significant difference in health-related quality of life between OPEP and other PEPs. Measures of sputum production, lung clearance, and patient satisfaction and acceptability (including self-reported measures) had mixed findings. Few studies reported adverse events in any group (though this may not have been an outcome measure). The few studies comparing types of OPEP device found no difference between Flutter and Cornet.

6.1.2 Systematic reviews

Two systematic reviews of OPEP for cystic fibrosis were identified and included, and an update of one of these was identified in the update search and additional information included. McIlwaine et al. (2019) included randomised controlled trials (RCTs) comparing PEP devices with other forms of physiotherapy and identified seven studies which reported findings specifically for OPEP. Their findings included a comparison of outcomes for PEP versus OPEP. Morrison & Milroy (2017) and Morrison & Milroy (2020) reviewed RCTs to assess the effectiveness of oscillatory devices (both intra- and extra-thoracic). Following the update, they included a total of 21 studies which assessed OPEP, five of which were later included by McIlwaine et al. (2019) (McIlwaine et al. 2001, Newbold et al. 2005, Pryor et al. 2010, van Winden et al. 1998, West et al. 2010). The 19 included studies involved comparisons between OPEP and PEP (seven studies), OPEP and breathing techniques (five studies), OPEP and conventional physiotherapy (five studies), OPEP and IPV (one study), OPEP and thoracic oscillatory devices (three studies), and between

OPEP and OPEP (one study). In the review by Morrison & Milroy (2017), eight out of 35 included studies were conducted in the UK. This information was not reported in the review by McIlwaine et al. (2019).

Flume et al. (2009) undertook a review of clinical trials and systematic reviews of ACTs which they believed to be used regularly in patients. Of the seven systematic reviews and 13 additional studies included, 14 reported findings for OPEP. Eight of these studies are also included in the later reviews by McIlwaine et al. (2019) and Morrison & Milroy (2017), and hence this review was excluded. McKoy et al. (2016) undertook a review of RCTs of active cycle breathing technique (ACBT) compared to other ACTs. Three of the 19 studies included reported findings for OPEP versus ACBT, all of which had been included by either, or both, McIlwaine et al. (2019) and/or Morrison & Milroy (2017). This review was therefore excluded. In addition, a review was identified (Wilson et al. 2019) which sought to summarise the evidence from Cochrane reviews of ACTs in people with cystic fibrosis. Separate results for OPEP devices were only available from one of the included reviews which identified one study looking at OPEP. This study was included in the review by McIlwaine et al. (2019) and hence this review was excluded.

6.1.3 Primary studies

In addition to the included systematic reviews and their studies, three further small primary studies had been published (N < 25), all of which were RCTs. One (Dwyer et al. 2017) compared use of a Flutter device plus forced expiratory technique to treadmill exercise and to 20-minutes of resting breathing. Radtke et al. (2018) compared a combination of the Flutter device and interval cycling exercise to continuous cycling exercise. McCarren & Alison (2006) compared Flutter, Acapella and PEP. None of the primary studies included were conducted in the UK.

6.1.4 Lung function

None of the reviews or studies found a significant difference in lung function measures of FEV1, FVC, or forced expiratory flow (FEF) between 25% and 75% of FVC (FEF [25 to 75]). This included moderate- to low-quality studies comparing OPEP versus PEP, thoracic oscillation, intrapulmonary percussive ventilation (IPV), and OPEP. The exception was one low-quality study, which found that PEF was significantly higher for Flutter compared to control, and a review which found that studies reported mixed findings for FEF(25 to 75) in OPEP versus thoracic oscillation studies.

6.1.5 Exacerbations and hospital admissions

Findings for respiratory exacerbations and hospital admissions were mixed. One review identified moderate-quality evidence from three studies comparing OPEP (Acapella, Flutter and Cornet) versus PEP. One found significantly fewer hospitalisations with PEP compared to OPEP at one year, while the other two studies found no difference between groups. A different review identified a low-quality study comparing OPEP (Flutter) and IPV which found no difference.

6.1.6 Health-related quality of life

No studies found a significant difference in health-related quality of life between interventions. This included moderate- to low-quality evidence comparing OPEP (Acapella, Flutter and Cornet) to PEP using the modified shuttle test for exercise tolerance (two studies), and low-quality evidence for the Chronic Respiratory Disease Questionnaire (CRQ), Quality of Well-being (QWB) scale, and cystic fibrosis Short-Form-36 (SF-36).

6.1.7 Lung clearance and sputum production

No significant difference between interventions was found for sputum water or solids content when comparing Flutter to control or treadmill exercise, or Flutter with cycling exercise to cycling

exercise alone (low-quality evidence). One low-quality study found sputum mechanical impedance to have a significantly greater reduction with Flutter compared to control but not compared to treadmill exercise. One review found low-quality evidence for lean lung clearance index to be lower for OPEP (including Acapella, Flutter and Cornet) than for PEP over one year (mean lung clearance index [LCI] for PEP was 0.80 [95% confidence interval [CI]: -1.36 to 2.96] higher than for OPEP). One study of low-quality reported a significantly greater number of coughs during the intervention with OPEP (Flutter) compared to control and to treadmill exercise (24, two and four coughs, respectively), but not during recovery. A second low-quality study also found no difference in the number of coughs during recovery between OPEP (Flutter and Acapella) and PEP, vibration or percussion.

In two studies of low-quality, no significant difference in patient-reported ease of expectoration was found between OPEP (Flutter) and control or treadmill exercise. However, there was a significantly greater improvement in the absolute change in ease of expectoration from pre-exercise to 45 minutes post-exercise for OPEP (Flutter) plus cycling exercise, compared to cycling exercise alone (median: 0.8 versus -1.1; p=0.016). This difference wasn't seen immediately post-exercise. One study of low-quality found that patient-reported sense of chest congestion was significantly better for OPEP (Flutter) than for control immediately post-intervention and at 20 minutes recovery (mean difference: 0.8 centimetres [cm], 95% CI: 0.1 to 1.4; and 0.9 cm, 95% CI: 0.2 to 1.7, respectively). However, no significant difference was seen when comparing OPEP (Flutter) with treadmill exercise.

6.1.8 Participant satisfaction and acceptability

In terms of participant satisfaction, there was low-quality evidence that when compared to OPEP (Flutter), 67% of children and adults using IPV wanted to continue with it at 24 weeks instead of other ACTs. One review found low-quality evidence comparing OPEP (Flutter) with thoracic oscillation and found OPEP to be significantly better for convenience at 24 weeks. One of the studies identified found thoracic oscillation to score higher for efficacy ($p < 0.02$) but other scores showed no difference.

6.1.9 Adverse events and participant withdrawal

One study of low-quality comparing OPEP (Flutter) to PEP, vibration and percussion reported no adverse events in any group. A review also provided low-quality evidence comparing OPEP (Acapella, Flutter and Cornet) to PEP and reported that five participants experienced dizziness with OPEP, which improved with further instruction on breathing techniques. No adverse events were reported in the PEP group.

6.1.10 Comparisons of OPEP versus OPEP

One study of low-quality was found by Morrison & Milroy (2017), which compared lung function between Flutter and Cornet, and found no significant difference in FEV1 or FVC. The study also found no significant difference in exercise tolerance (modified shuttle test) or well-being (CRQ).

6.2 Bronchiectasis

6.2.1 Overview of findings

The majority of studies found no difference in measures of lung function between OPEP and various comparators. The exception was one low-quality study comparing OPEP to no ACT, which found a difference in some measures but not others. No difference in respiratory exacerbations was found by one study. One study found an improvement in health-related quality of life with OPEP compared to no ACT. None of the studies comparing OPEP to other ACTs found a significant difference in this outcome. Measures of lung clearance and sputum production reported mixed findings. No significant difference was found between interventions for other reported

symptoms such as chest discomfort, dyspnoea, or breathlessness. Findings for participant satisfaction and acceptability were limited and mixed. Adverse events were rarely reported. One comparison between OPEP devices (Flutter versus Lung Flute) was identified and findings were mixed.

6.2.2 Systematic reviews

Three systematic reviews were included which looked at OPEP in individuals with bronchiectasis. Lee et al. (2017) reviewed RCTs comparing PEP with other ACTs for stable or acute exacerbation of bronchiectasis. Of the nine studies included, eight reported findings for OPEP devices. These included comparisons between OPEP versus slow expiration with the glottis open (two studies), OPEP versus ACBT (three studies), OPEP versus breathing control with gravity assisted drainage (GAD) (one study), OPEP versus ACBT with GAD (one study), and OPEP versus autogenic drainage (one study).

Lee et al. (2015a) previously reviewed RCTs of ACTs in patients with acute and stable bronchiectasis. However, only those with no intervention, sham or coughing alone were included. Of the seven studies included, six reported findings for OPEP, only one of which was later included in the review by Lee et al. (2017). No subgroup analysis was undertaken for OPEP devices and limited data on individual studies was reported in the text.

Phillips et al. (2020) reviewed studies of any design which assessed ACT in patient experience of acute exacerbation of bronchiectasis. Of the six studies included, two reported findings for OPEP. Both of these studies were included in the review by Lee et al. (2017); however, the earlier review did not report findings for patients with acute exacerbation separately, and hence both reviews were included.

One relevant review was identified and excluded as the population and comparisons between interventions were covered by the other reviews identified. Lee et al. (2015b) undertook a review of RCTs of OPEP compared to other ACTs or no treatment in adults with stable bronchiectasis. They included seven studies, of which five were also included in either the review by Lee et al. (2015a) or the review by Lee et al. (2017) and one study was included by both.

None of the included reviews reported outcomes by country of trial or how many of the included studies were conducted in the UK. Where primary studies were reported by more than one included systematic review, the results were not reported unless they formed part of a meta-analysis.

6.2.3 Primary studies

In addition to the included systematic reviews and their studies, two further primary studies have been published. Both were RCTs looking at OPEP in outpatients with stable bronchiectasis, one of which was very small (N = 8) (Valente et al. 2004). Silva et al. (2017) compared two types of OPEP (Flutter and Lung Flute) in adults with stable bronchiectasis. While Valente et al. (2004) compared Flutter with a PEP (Flutter with the orifices of the protective cover closed). Neither study was conducted in the UK.

6.2.4 Lung function

None of the reviews reporting FEV1, FVC, FEV1/FVC, EV/FVC, FEF(25 to 75), inspiratory capacity (IC), PEF (absolute or percentage), or residual volume (RV)/total lung capacity (TLC) (Lee et al. 2015a, Lee et al. 2017, Phillips et al. 2020) found a significant difference between interventions, including comparisons of: OPEP with no ACT, GAD, ACBT, ACBT plus GAD, or autogenic drainage in patients with acute or stable disease; and comparisons of OPEP with any ACT or OPEP plus GAD and breathing and coughing cycle with breathing and coughing cycle alone in patients with acute exacerbation. For most outcomes, the evidence was of low to very low quality, with the exception

of comparisons between OPEP with postural drainage versus usual ACT where the evidence was of moderate quality. Where reported, the OPEP used was Flutter or Acapella.

One study was identified by a review, which provided low-quality evidence for FRC, TLC, RV and IC/TLC being significantly lower for OPEP compared to no ACT immediately after the intervention in patients with acute or stable disease. This did not hold true for FEV1, FVC, FEV1/FVC, FEF(25 to 75), IC or RV/TLC.

6.2.5 Exacerbations and hospital admissions

There was low-quality evidence of no significant difference in the frequency of respiratory exacerbations between OPEP and no ACT at 12 weeks.

6.2.6 Health-related quality of life

Low-quality evidence comparing OPEP with no ACT was found by Lee et al. (2015a), showing that at 12 weeks patients receiving OPEP had significantly better scores on both the St. George's Respiratory Questionnaire (median: -7.8 versus -0.7; p = 0.005) and the Leicester Cough Questionnaire (total median difference: 1.3; p = 0.002). The latter included significantly better scores in the physical, psychological and social domains.

Comparisons of OPEP (Flutter) with ACBT plus GAD at four weeks using the CRQ found no significant differences in any domain. One moderate-quality study comparing OPEP (Acapella) with other ACT plus postural drainage found no significant difference in exercise tolerance. Another very low-quality study comparing OPEP (Flutter) with ACBT at 4 weeks found no significant difference in SF-35 general health score.

6.2.7 Lung clearance and sputum production

No significant difference in cough, including frequency or severity, was found for OPEP compared to no ACT, other ACT plus postural drainage, or ACBT, with the exception of cough frequency at 15 days for OPEP compared to no ACT (p = 0.003). In one low-quality comparison of OPEP with no ACT, patient-reported ease of expectoration was significantly improved with OPEP at 15 days (p > 0.001).

There was low-quality evidence of a significant increase in sputum volume at 15 days and 24 hours compared to no ACT. When compared with ACBT plus GAD, one review found a mean difference of 5.1 millilitres (mL) (95% CI: .2 to 8.0) after one treatment session. However, the reviews found no significant difference in sputum volume when comparing OPEP with ACBT alone after one treatment session, with autogenic drainage immediately post-treatment, or with other ACT plus postural drainage. For sputum weight, no significant difference between groups was found for OPEP compared to no ACT, GAD, ACBT or autogenic drainage. One review reported mixed findings from two studies comparing OPEP with ACBT plus GAD after one treatment session, and no significant difference at four weeks. The same review reported mixed findings from two studies for a comparison of OPEP with slow expiration with the glottis open (SEGO) after one treatment session.

One review reported no significant difference in self-reported sputum colour when comparing OPEP (Acapella) to other ACT plus postural drainage. One recent primary study provided very low-quality evidence of a larger sputum displacement with OPEP (Flutter) compared to PEP, but it was unclear whether this was statistically significant.

6.2.8 Other symptoms

No significant difference was found in chest discomfort or dyspnoea (Borg score) for OPEP compared to no ACT, ACBT plus GAD, or ACBT alone, or between OPEP and other ACT plus postural drainage for sinus discharge or appetite. No significant difference was found between OPEP and

ACBT plus GAD or other ACT plus postural drainage for fatigue. There was moderate-quality evidence of a mean difference of 0.7 between OPEP and ACBT alone but it was unclear whether this was statistically significant.

6.2.9 Participant satisfaction and acceptability

There was moderate-quality evidence from one primary study that favoured Flutter over Lung Flute for assisting with secretions, being easy to understand and simple to use. There was no difference between groups in how tiring, time consuming, or uncomfortable to use the OPEP was, how much embarrassment was caused, or interference with daily life.

6.2.10 Adverse events and participant withdrawal

There was low-quality evidence from one review of OPEP versus no ACT of no adverse events in any group.

6.2.11 Comparisons of OPEP versus OPEP

One recent primary study of moderate quality compared Flutter and Lung Flute in adults with stable disease (Silva et al. 2017). Mean wet sputum weight was significantly greater with Flutter (5.10 versus 3.74; p=0.038) during the intervention. However, the opposite was true at 30 minutes from the end of the intervention (0.68 versus 2.02; $p < 0.001$). No significant difference was found in total wet or dry weight. The same study reported that patients with stable disease significantly preferred Flutter to Lung Flute for assisting with secretions ($p = 0.01$), being easy to understand ($p = 0.03$), and being simple to use ($p = 0.01$). There was no significant difference in the following self-reported outcomes: how tiring it was, how uncomfortable to use it was, how time consuming it was, how it interferes with daily life, or whether it causes embarrassment.

6.3 Other respiratory conditions

6.3.1 Overview of findings

The majority of studies and reviews found no difference between OPEP and comparators in lung function measures for COPD or chronic bronchitis. Findings for respiratory exacerbations, hospital admissions, health-related quality of life, lung clearance and sputum production, and other symptoms were mixed. Where reported, no differences in adverse events were found. The evidence ranged from very low to moderate quality.

6.3.2 Systematic reviews

One systematic review was initially included (Osadnik et al. 2012) which included RCTs of ACT in individuals diagnosed with acute or stable COPD, emphysema or chronic bronchitis. However, only RCTs using no intervention, sham or coughing alone were included. In total, 28 studies were included, of which eight reported findings for OPEP. Subgroup analysis was performed for PEP devices but no results were reported separately for OPEP devices. Some data were available from analyses which only found OPEP studies for that outcome. None of the included studies which looked at OPEP devices were conducted in the UK. The update search identified a second systematic review (Sethi et al. 2014) which included one OPEP study in patients with stable COPD not previously identified.

6.3.3 Primary studies

In addition to the above systematic review, seven further primary studies were included, none of which were conducted in the UK. Gastaldi et al. (2015) compared OPEP with sham OPEP and OPEP with bronchodilator in patients with COPD. Milan et al. (2019) specifically looked at patients with acute exacerbation of COPD and compared OPEP plus standard management with sham OPEP and with standard COPD management. Nicolini et al. (2018) specifically looked at patients with

stable COPD (severe to very severe) and compared OPEP to temporary PEP (T-PEP) and to pharmacological therapy alone. Bellone et al. (2000) looked at patients with an acute exacerbation of chronic bronchitis and compared OPEP to SEGO in lateral position and to postural drainage. Tse et al. (2020) compared two OPEP devices in patients with COPD or chronic bronchitis using a large retrospective cohort study. The four other studies were RCTs - two were very small in size (N $\leq$ 15) (Bellone et al. 2000, Gastaldi et al. 2015) and two were moderately sized (N = 90 to 120) (Milan et al. 2019, Nicolini et al. 2018).

One study (Ni et al. 2018) was included, which compared OPEP to mechanical percussion in patients diagnosed with lower respiratory tract infection. This included patients with severe pneumonia (52%), and acute exacerbation of COPD (22%) or bronchiectasis (7%). It was a small (N = 27), retrospective cohort study. Felicio-Junior et al. (2020) compared OPEP plus hypertonic saline to OPEP and hypertonic saline alone in children and adolescents with asthma.

6.3.4 Lung function

No significant difference between groups was found for FEV1 (absolute or percentage change) in a review for OPEP compared to no ACT for stable COPD; in a low-quality study comparing OPEP (Flutter) to sham OPEP and to OPEP plus bronchodilator; in a moderate-quality study comparing OPEP (Lung Flute) to T-PEP and to pharmacological therapy alone for stable, severe or very severe COPD; or in a very low-quality study comparing OPEP (Flutter) to SEGO and to postural drainage for acute exacerbation of chronic bronchitis.

No significant difference between groups was found FVC (absolute or percentage change) in a low-quality study comparing OPEP (Flutter) to sham OPEP and to OPEP plus bronchodilator; or in a moderate-quality study comparing OPEP (Lung Flute) to T-PEP and to pharmacological therapy alone for stable, severe or very severe COPD.

The latter study comparing OPEP (Lung Flute) to T-PEP and to pharmacological therapy alone for stable, severe or very severe COPD also found no significant difference between groups for FVC%, FEV1/FVC, diffusing lung capacity monoxide (DLCO%), maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP). The study comparing OPEP (Flutter) to sham OPEP and to OPEP plus bronchodilator found no significant difference in EV/FVC or MEF(25 to 75). The review comparing OPEP (Flutter) to no ACT found no significant difference in vital capacity .

One moderate-quality study found no difference in TLC, TLC%, RV or RV% between OPEP (Lung Flute) and T-PEP in patients with stable, severe or very severe COPD. However, there was a significant improvement for OPEP when compared to pharmacological therapy alone (p = 0.02, p = 0.024, p = 0.04 and p = 0.02, respectively).

Very low-quality evidence of no significant difference in FEV1, PEF or FEV1/FVC was found for OPEP plus hypertonic saline compared to hypertonic saline or OPEP alone in children and adolescents with asthma.

6.3.5 Exacerbations and hospital admissions

There was low-quality evidence of significantly fewer hospital admissions for OPEP compared to no ACT in patients with stable COPD, but no difference in the number of days hospitalised. There was very low-quality evidence suggesting no difference in hospital or intensive care length of stay between OPEP and mechanical percussions for patients with lower respiratory tract infection. In addition, there was moderate-quality evidence of no difference between OPEP and T-PEP or pharmacological therapy alone in exacerbations of COPD at 1, 2 or 3 months, and low-quality evidence of fewer exacerbations in patients with stable COPD at 26 weeks with OPEP compared to usual care. In addition, there was low-quality evidence of significantly fewer severe exacerbations in COPD or chronic bronchitis patients using Aerobika compared to Acapella OPEP devices.

6.3.6 Health-related quality of life

There was low- to moderate-quality evidence of significantly improved health-related quality of life scores for OPEP compared to usual care, no ACT or pharmacological therapy alone in patients with stable COPD using the SGRQ and 6- or 12-minute walk tests. There was moderate-quality evidence of no significant difference between OPEP and T-PEP using the 6-minute walk test.

6.3.7 Lung clearance and sputum production

One study provided low-quality evidence of a greater number of spontaneous coughs, in patients with COPD, with OPEP (Flutter) than with sham OPEP or OPEP plus bronchodilator, but it was unclear whether this was statistically significantly different. There was moderate-quality evidence of significantly greater sputum production for OPEP plus standard management compared to PEP in patients with acute exacerbation of COPD within five days of hospitalisation. In addition, low-quality evidence was found of significantly greater sputum volume with OPEP (Flutter) compared to sham OPEP in patients with COPD, but moderate-quality evidence of no difference in sputum weight when comparing OPEP (Flutter) with no ACT.

There was very low-quality evidence of significantly less sputum production for OPEP compared to mechanical percussion in patients with lower respiratory tract infection at day 7 after chest physiotherapy. There was also very low-quality evidence of increased sputum weight and induction time for OPEP plus hypertonic saline compared to OPEP or hypertonic saline in patients with asthma.

6.3.8 Other symptoms

Low- to very low-quality evidence was found of no difference in purulence between OPEP and sham OPEP, OPEP plus bronchodilator, or mechanical percussion for patients with COPD or lower respiratory tract infection. There was low-quality evidence of a significantly better breathlessness score (Borg scale) for OPEP compared to no ACT immediately after treatment in patients with stable COPD. Findings for dyspnoea (MMRC scale) were mixed with moderate-quality evidence of no difference between OPEP plus standard management and PEP 1 to 5 days after hospitalisation in patients with acute exacerbation of COPD, and moderate-quality evidence of a significantly improved score with OPEP compared to pharmacological therapy alone for patients with stable COPD. Similarly, there was moderate-quality evidence of an improved score on the COPD Assessment Test scale for OPEP compared to pharmacological therapy alone. However, no difference was found in 'breathlessness cough sputum' score for this comparison. In addition, there was very low-quality evidence of no difference in the duration of chest physiotherapy needed between OPEP and mechanical percussion for patients with lower respiratory tract infection.

6.3.9 Participant satisfaction and acceptability

Moderate-quality evidence of no difference in self-reported compliance between OPEP plus standard management versus PEP for acute exacerbation of COPD was found. Similarly, there was moderate-quality evidence of no difference in patient acceptance between OPEP versus T-PEP for stable COPD.

6.3.10 Adverse events and participant withdrawal

There was low-quality evidence of no difference in withdrawal rates between OPEP and no ACT for patients with acute COPD. In addition, there was very low-quality evidence of no significant difference amongst survivors for in-hospital mortality or intensive care unit mortality between OPEP and mechanical percussion for patients with lower respiratory tract infection.

6.4 Ongoing trials

We identified five ongoing studies, the details of which are outlined in Table 1. Three of the studies are specific to COPD patients, two of which are limited further by age group and gender or smoking status. Two of the studies, comparing OPEP to sham OPEP and extra-thoracic oscillations vests, are based in Egypt and their estimated completion date has passed. We were unable to contact the authors for further details. One study comparing OPEP to usual care is based in the UK and due to complete in January 2022.

One study is in patients with stable bronchiectasis and compares OPEP to autogenic drainage. This study was based in Israel and the findings are due for publication in the near future. The final study is open to adults with any airway hypersecretory condition and compares oxygen jet atomisation with and without OPEP. This is based in China and is estimated to complete in July 2021.

Table 1. Ongoing studies

Study	Country	Comparison	Population	No. of patients	Estimated completion date	Outcomes
ChiCTR1900023495	China	Oxygen jet atomisation vs Oxygen jet atomisation plus OPEP	Adults with airway hypersecretory symptoms	60	July 2021	Sputum volume; cough & sputum score; Borg score; COPD Assessment Test score; days of hospitalisation
ISRCTN44651852	UK	OPEP (Acapella) vs usual care	Adults with chronic COPD	102	January 2022	Quality of life; severity of cough; cough monitor; activity monitor
NCT03299231	Egypt	OPEP (Aerobika) vs sham OPEP	Aged 40+ years; smokers or ex-smokers; COPD	160	July 2020	Lung function, exercise capacity (6 minute walking distance); quality of life; shortness of breath; hospital stay; hospital readmission; severe exacerbation; moderate exacerbation
NCT03013452	Israel	OPEP (Aerobika) vs autogenic drainage	Adults with stable bronchiectasis	50	June 2020	Lung clearance index; quality of life; lung function
NCT03885128	Egypt	OPEP (Quake) vs high frequency extra-thoracic oscillations vest	Male; aged 45-72 years; COPD	60	May 2019	Lung function (spirometry); impulse oscillometry

COPD: chronic obstructive pulmonary disease; OPEP: Oscillating positive expiratory pressure device

7. Economic evaluation

7.1 Evidence review

Four potential papers were identified from the literature search. One paper was excluded as it reported a Corrigendum to one of the papers (change of author affiliation and corresponding author address) and did not affect the assessment (Thanh et al. 2019b). Another paper was excluded as it was available as an abstract only and therefore did not provide sufficient detail for a full assessment (Coppolo et al. 2016). Two papers were included in the review of health economic evidence (Khoudigian-Sinani et al. 2017, Thanh et al. 2019a). Both studies reported the cost-effectiveness of the Aerobika device compared to no OPEP/PEP therapy and both studies were funded by Trudell Medical International (TMI). A summary of the included health economics studies is presented in Appendix 7.

An economic model was constructed by Khoudigian-Sinani et al. (2017) to assess the cost-effectiveness of Aerobika compared to no OPEP/PEP therapy in avoiding exacerbations of COPD. A US-payer perspective was taken over a one-year time horizon. A Markov model was constructed with data inputs obtained from published sources; with key sources of evidence coming from observational studies of the use of Aerobika with other inputs (e.g. resource use, mortality) taken from a Medicare population and general US population data. Published US unit costs were applied and valued in 2016 US $. The study reported that Aerobika cost $553 less per patient per year than no OPEP/PEP therapy and avoided six exacerbations per 100 patients per year, with Aerobika dominating no OPEP/PEP. When a one-way sensitivity analysis was conducted (based on +/- 20% variance in parameters), Aerobika remained the dominant strategy in most cases. However, results were sensitive to the risk of exacerbation and resource use.

Thanh et al. (2019a) used a similar model to Khoudigian-Sinani et al. (2017) to undertake a cost-utility analysis based on a Canadian health care system perspective. This study aimed to address a limitation of the previous model, which did not consider the increase in mortality as a result of severity of exacerbation and there was limited generalisability of findings to a Canadian population. Literature searches were used to derive inputs. Data were obtained from Burudpakdee et al. (2017) and the economic analysis by Khoudigian-Sinani et al. (2017), with resource use and costs estimated from the Alberta Health Care System database. Utilities were derived from published sources and company data. The costs of Aerobika were estimated to be $694.15 less and generated an additional 0.04 Quality Adjusted Life Year (QALY) compared to no OPEP/PEP therapy; i.e. Aerobika was dominant over no OPEP/PEP therapy. One-way sensitivity analyses identified that findings were particularly sensitive to severity of exacerbation. When it was assumed that exacerbations with Aerobika remained the same (risk ratio = 0.72) for one year, Aerobika remained dominant. The probability for the Aerobika device to be cost-effective at a Willingness to Pay (WTP) threshold of Canadian $50,000 per QALY gained was 76.8%.

Whilst the findings from the two economic analyses presented indicate Aerobika is a cost-effective strategy compared to no OPEP/PEP strategy, there are a number of issues, which limit the applicability of these findings to a Welsh Population. Appropriate caution should be given to the conclusion drawn given the quality of evidence available to inform the economic analyses conducted.

7.2 Resource impact analysis

We developed a resource impact analysis to estimate the potential cost associated with introducing OPEP devices for airway clearance in COPD into clinical practice in NHS Wales. This was based on the Aerobika device as all available effectiveness data focused on this device in the management of COPD.

New incidence of COPD in Wales was estimated to be 197 in 100,000 population in 2012 (British Lung Foundation 2020b). Based on the Welsh population of 3,152,879 people (ONS 2020c), this would result in an annual new incidence of 6,211 cases of COPD in Wales. This yearly figure was kept the same over the time horizon of the resource impact analysis of five years. The prevalence of 76,319 people living with COPD in Wales was taken from the Quality and Outcomes Framework disease register for 2018/19 for Wales (StatsWales 2019) and increased every year by the new incidences, resulting in the number of COPD patients in Wales in Year 1 (82,530), increasing to 107,374 in Year 5.

In 2018, 2,047 people died from COPD-related causes in Wales, with a mean increase of deaths of 1.7% between 2001 and 2018 (ONS 2020a). This means that an estimated 2,118 patients are predicted to die from their COPD in 2020, increasing to 2,269 in 2024. This does not include the impact of COVID-19 on this vulnerable population. Taking into account an all-cause mortality of 1.05% (ONS 2020b), the COPD patient population is estimated to be 79,543 in 2020, increasing to 103,975 in 2024. Based on English Hospital Episode Statistics (Merinopoulou et al. 2016), it was assumed that, of these patients, 32.4% would be in Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity category A with 0.83 exacerbations per year, 21.6% in GOLD B with 1.17 annual exacerbations, 19.2% in GOLD C with 1.78 exacerbations, and 26.7% in GOLD D suffering on average 2.51 exacerbations a year, respectively. In the absence of data on severity distributions of COPD exacerbations, the GOLD distributions were taken as proxy. GOLD A and B patients were assumed to experience mild exacerbations, with GOLD C patients having moderate and GOLD D patients having severe exacerbations. While this is a limitation of the analysis, it is thought that it will reasonably reflect exacerbation severity distributions. As a result, 41,273 mild exacerbations were assumed in Year 1, increasing to 53,951 in Year 5. The number of moderate exacerbations increased from 27,220 in Year 1 to 35,581 in Year 5, and severe exacerbations ranged from 53,357 in Year 1 to 69,746 in Year 5. Based on Welsh hospital episode statistics (DHCW 2020), 16.4% of severe exacerbations resulted in hospitalisation. The Aerobika OPEP device was assumed to reduce exacerbations by 2.3% over the course of the year for every patient who received it (Khoudigian-Sinani et al. 2017).

The cost of the Aerobika device was set at £45.50 per patient per year (MIMS 2020), and it was assumed in the base case that 50% of COPD patients with severe disease (GOLD D) would be prescribed the device. Comparator costs were not taken into account as treatment as usual was assumed to be received by all patients.

Mild exacerbations were assumed to incur the cost of a GP appointment (Curtis & Burns 2019), with 77.4% of patients also receiving antibiotics (Butler et al. 2019), costed as amoxicillin 500 milligrams (mg) over 21 days (MIMS 2020). Moderate exacerbations and severe exacerbations that did not require hospitalisation were assumed to accrue the cost of an Emergency Department visit, with a follow-up consultant-led outpatient appointment (NHS Reference Costs 2018) and antibiotics for all patients. Costs of hospitalised patients included an Emergency Department visit and non-elective inpatient stay (weighted across all COPD-related options; NHS Reference Costs, 2018).

Scenario 1 (base case): 50% of patients with GOLD D status assumed to receive Aerobika OPEP device.

Scenario 2: 100% of patients with GOLD D status assumed to receive Aerobika OPEP device.

Scenario 3: 100% of GOLD C and D patients assumed to receive Aerobika OPEP device.

Scenario 4: Average cost of all available OPEP devices used (£38.74).

Scenario 5: No downstream cost savings/no effect of device on frequency of exacerbations.

The results of the analysis for each of the five scenarios are shown in Table 2. Downstream cost savings cannot offset the cost of the device in all scenarios. However, the resource impact highly depends on the effect size of the OPEP device on the reduction of COPD exacerbation frequency, the OPEP device costs and the proportion of patients expected to use the device. Considering the paucity of data, the results of the resource impact analysis are subject to considerable uncertainty.

The net cost of introducing the Aerobika over five years (assuming not already used in Wales) ranged from £1.17 million for prescriptions to 50% of COPD patients with GOLD severity category D, to £5.31 million for prescriptions to 100% of COPD patients with severity category C or D. Where the average cost of all OPEP devices was used instead of Aerobika (and assuming 50% of category D COPD patients are prescribed), the net cost decreased from £2.38 million to £0.76 million. Where it was assumed that OPEP resulted in no reduction in acute exacerbations, the net cost increased from £1.17 million to £2.79 million over five years.

Table 2. Results of resource impact analysis over five years

Cost component	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Cost of introducing Aerobika OPEP device	£2,789,469	£5,578,937	£9,592,223	£2,375,033	£2,789,469
Downstream cost impact of introducing Aerobika OPEP device	-£1,615,740	-£3,231,480	-£4,284,373	-£1,615,740	£0
Net cost of introducing Aerobika OPEP device	£1,173,729	£2,347,457	£5,307,851	£759,293	£2,789,469

OPEP: oscillatory positive expiratory pressure

8. Organisational issues

Evidence is limited, but current use of OPEP devices is likely to vary geographically and by condition. Barker et al. (2017) analysed English prescribing data for patients with COPD from 2013 to 2016 and undertook a survey of physiotherapists in respiratory care. During this period, 4,989 OPEP devices were prescribed. The authors found variation in physiotherapist's thresholds for use of sputum adjuncts, and when asked to choose between Acapella, Flutter or PEP mask, the responses were 69%, 24% and 6%, respectively. Hoo et al. (2014) analysed data from annual reviews of people with cystic fibrosis aged 11 and over in 2011. OPEP devices were the second most commonly recorded form of ACT (22.8%) after forced expiratory techniques (28.1%). Exercise was the third most common (15.9%). McIlwaine et al. (2017) report that, traditionally, the choice of ACT for cystic fibrosis has been based on what is available locally, the training and expertise of the local physiotherapist and the culture. In bronchiectasis, prescription of ACTs is reported to be part of routine management alongside medical treatment such as oral or intravenous antibiotics and steroids. A change in ACT may be needed during an acute exacerbation (Phillips et al. 2020).

Feedback from clinical experts suggests that OPEP is often provided by secondary or tertiary care and used in conjunction with hypertonic saline. Prescribing data suggests that Aerobika, Flutter and Acapella are commonly used in Wales. However, patients may also purchase the device without a prescription. Prescription of OPEP is reported to be at clinic review for cystic fibrosis and bronchiectasis patients following review by a respiratory physiotherapist and is guided by a computed tomography (CT) of the thorax. Other triggers for prescription of OPEP may include

difficulty clearing secretions, tenacious viscid secretions, shortness of breath associated with exacerbation or enhanced cough productive of sputum. Patients need instruction on using and cleaning the device and are seen again at three months to ensure the technique remains good and has been beneficial. It is reported that different approaches are used to access OPEP across Wales, with some health boards purchasing a supply for teams to issue and others relying on prescribing. This again makes estimating the true usage of the OPEP devices in Wales challenging.

Flume et al. (2009) suggest that airway clearance is best taught by an experienced healthcare practitioner and that it is performed in the hospital setting, typically with the assistance of a respiratory or physical therapist; airway clearance is reported to be part of their educational curriculum and the Pulmonary Therapies Committee consider them the most experienced in the practice, but recognise that there may be others in a cystic fibrosis centre who are well-trained, for example, nurses, physicians, nurse practitioners, physician's assistants, or exercise physiologists. Feedback from clinical experts suggests that OPEP is typically prescribed by, and training in their use provided by, respiratory physiotherapists for patients with cystic fibrosis, severe COPD or bronchiectasis in Wales. They may be prescribed by GPs following advice from respiratory physiotherapists; however, this approach can be limited by availability of staff to teach the correct technique. In some cases, clinical nurse specialists are reported to be able to provide the training. Both funding and availability of respiratory physiotherapists in the community setting are cited by clinical experts as challenges to the use of OPEP in Wales, which may lead to regional variation.

9. Patient issues

The effectiveness of OPEP devices can potentially be impacted by a range of factors, including the condition and factors specific to individual patients. McIlwaine et al. (2017) have proposed a framework for selecting the most appropriate ACT for each patient. They recommend that an individualised strategy takes into account the patient's disease status, preference, motivation and maturity. They also recommend that when using an OPEP device, the clinician should consider what method they want to use to first ventilate behind the obstructed units. For example, Flutter is reported to use a 3-second breath hold, while Acapella, like PEP, increases FRC and splints airways open. Increasing FRC during tidal volume breathing is suggested to even out intrapulmonary distribution of ventilation and open up regions that are otherwise closed off, and would therefore be effective in both restricted and obstructed patients. Splinting the airways open during expiration is thought to avoid airway collapse and be a favourable technique for patients with unstable airways. The Pulmonary Therapies Committee of the Cystic Fibrosis Foundation (Flume et al. 2009) recommend that ACT is individualised based on patient age and preference, severity of disease, availability of a partner and observed efficacy based on subjective and objective measures.

Feedback from clinical experts suggest that choice of OPEP over other ACTs may be influenced by frequency of exacerbations, lung function, ease of expectoration, likely adherence, findings of the CT of the thorax, the patient's ability to perform other ACTs, and the impact on the patient's independence. There may also be wider benefits to the patient associated with the simplicity of using a device over a breathing technique. For example, breathing techniques may require subtle adjustments for the patient to gain the greatest benefit and some patients may find it harder to follow the instructions.

HTW received an independent patient submission from the Cystic Fibrosis Trust on the use of OPEP devices for patients with cystic fibrosis. This submission can be read in full in Appendix 8. Some of the main considerations posed in this submission are summarised below;

- The difference OPEP makes to the lives of people with cystic fibrosis varies depending on the person.
- 78% of respondents to a survey on experiences of OPEP stated to have a 70 to 90% adherence rate of all their treatments. When a person with cystic fibrosis reduces their adherence, some have stated not to notice a difference as they will increase other medications, whereas others have said they will experience increased exacerbations and increased mucus build up.
- This variation in response is what makes cystic fibrosis so unique as patients can have a variation of symptoms requiring individualised treatments, including the use of OPEP.
- 72% of respondents are using OPEP as part of their regular treatment regime. The results also showed that all respondents use it because their clinicians have included OPEP in their regime, and 80% of respondents preferred the use of OPEP as an airway clearance technique over others available.
- The importance of shared decision-making between the person with cystic fibrosis, clinicians and specialist physiotherapists, to ensure people with cystic fibrosis have some control on treatment management, particularly given the heavy treatment burden.
- Therefore, it is important that all people with cystic fibrosis continue to have access to an array of treatments, such as OPEP, so that they can choose the best technique for them.

10. Conclusions

OPEP are relatively well-established devices for hypersecretory conditions, though there are variations in the mechanisms used and new versions occasionally enter the market. However, evidence for the clinical effectiveness remains limited despite numerous systematic reviews in this area. This is partly due to a lot of heterogeneity in the patient populations and their place in the care pathways, which is very dependent on the individual patient. The evidence available centres mainly around their use in cystic fibrosis, bronchiectasis and COPD. Change in lung function measures are regularly reported for each condition but rarely identifies a benefit for OPEP over their comparator. The evidence found suggests that there is no benefit to health-related quality of life between interventions in cystic fibrosis patients and only in comparison to no other ACT in bronchiectasis patients. Findings for other outcomes were mixed. There was a lack of studies comparing different OPEP devices but where these existed, they did not find significant differences in outcomes for cystic fibrosis patients, and reported mixed findings for bronchiectasis patients. The majority of the evidence base was of low quality (range: very low to moderate).

A resource impact analysis has been developed but was limited to the use of Aerobika in COPD patients where there was economic evidence available. Assuming 50% of patients with severe COPD are prescribed a device, and using the average cost of all OPEP devices, the net cost of introducing OPEP to the COPD patient population in Wales over five years could be estimated at £0.76 million. Given the limited data available to base the analysis on, these results are subject to considerable uncertainty.

11. Contributors

This topic was proposed by Jayne Price, Deputy Head of Pharmacy, Powys Teaching Health Board.

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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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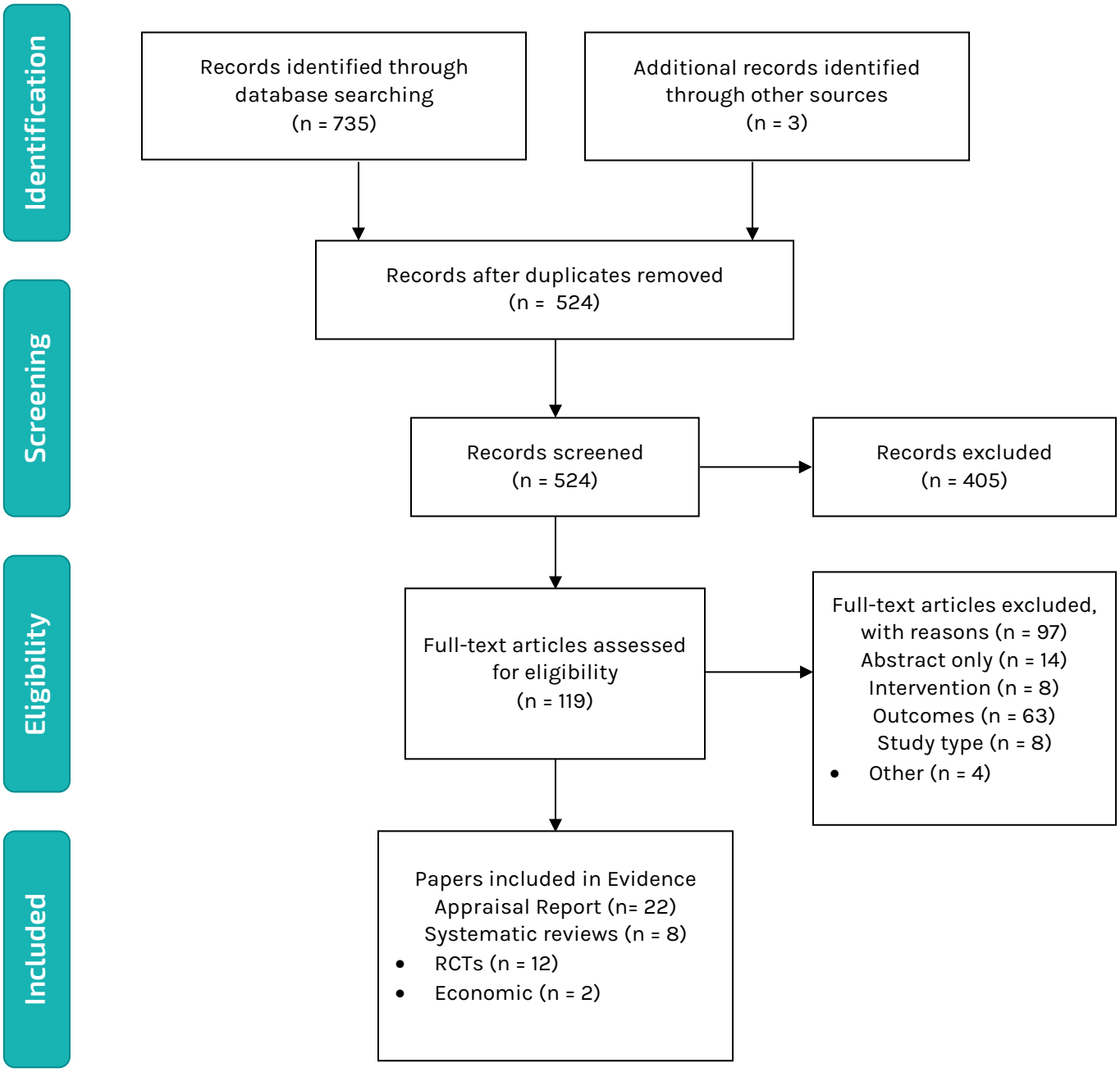
Appendix 1. PICO framework

	Inclusion criteria	Exclusion criteria
Population	People with hypersecretory conditions, including: • cystic fibrosis • COPD • bronchiectasis *Evidence for each condition will be reported and evaluated separately, if possible.*	
Intervention	Oscillating positive expiratory pressure devices	
Comparison/ Comparators	Other airway clearing techniques (ACTs), including: • Non-oscillating positive expiratory pressure techniques • Active cycle of breathing technique • Autogenic drainage Chest wall chest compression (or other external oscillatory/frequency techniques)	
Outcome measures	Pulmonary function (FEV, FVC, FEF) Patient preference/adherence/acceptability Quality of life outcomes Respiratory exacerbations (incidence, rate, duration) Hospital admissions (incidence and duration) Sputum volume (successful treatment indicated by increase in expulsed sputum) Economic/cost-effectiveness outcomes Safety / adverse events	
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised trials. • Non-randomised trials. We will only include evidence for lower priority evidence where outcomes are not reported by a higher priority source. We will also search for economic evaluations or original research that can form the basis of an economic assessment.	
Search limits	We will only include evidence published in English language No date limits will be applied	

Appendix 2. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (up to 19/10/20)



Appendix 3. Definitions

Outcome	Comparison
ACBT	Active cycle of breathing technique
ACTs	Airway clearance techniques
AD	Autogenic drainage
COPD	Chronic obstructive pulmonary disease
FEF(25-875)	Forced expiratory flow between 25% and 75% of FVC
FEV	Forced expiratory volume
FRC	Functional residual capacity
FVC	Forced vital capacity
GAD	Gravity assisted drainage
HTW	Health Technology Wales
IC	Inspiratory capacity
IPV	Intrapulmonary percussive ventilation
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
OPEP	Oscillatory positive expiratory pressure
PEF	Peak expiratory flow
PEP	Positive expiratory pressure
RCT	Randomised controlled trial
RV	Residual volume
SEGO	Slow expiration with the glottis open
TLC	Total lung capacity
T-PEP	Temporary positive expiratory pressure

Appendix 4. Summary of outcomes

Lung function

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
FEV1%	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	Single treatment to 13 months	217 (7)	No significant difference between treatment groups in any study.	GRADE: moderate
	OPEP vs thoracic oscillation	Children & adults	Flutter	NR	48 (1)	No significant difference between groups	GRADE: low
	OPEP vs usual care	Children & adults	Acapella	Up to 1 week	22 (1)	No significant difference between groups	GRADE: low
FEV1 – change from baseline	OPEP vs IPV	Children & adults	Flutter	24 weeks	16 (1)	No significant difference between groups (p=0.208)	GRADE: low
	OPEP vs thoracic oscillation	Children & adults	Flutter	NR	166 (1)	No significant change from baseline for either group	GRADE: low
	OPEP vs OPEP	Children & adults	Flutter & Cornet	NR	75 (1)	No significant difference between groups (p=0.35)	GRADE: low
FVC	OPEP vs IPV	Children & adults	Flutter	24 weeks	16 (1)	No significant difference between groups (p=0.292)	GRADE: low
	OPEP vs OPEP	Children & adults	Flutter & Cornet	NR	75 (1)	No significant difference between groups	GRADE: low
	OPEP vs usual care	Children & adults	Acapella	Up to 1 week	22 (1)	No significant difference between groups (p=0.63)	GRADE: low
FVC%	OPEP vs thoracic oscillation	Children & adults	Flutter	NR	48 (1)	No significant difference between groups	GRADE: low
FEF(25-75)	OPEP vs IPV	Children & adults	Flutter	24 weeks	16 (1)	No significant difference between groups (p=0.126)	GRADE: low
	OPEP vs thoracic oscillation	Children & adults	Flutter	24 weeks	48 (1)	Studies report mixed findings	GRADE: low
	OPEP vs usual care	Children & adults	Acapella	Up to 1 week	22 (1)	No significant difference between groups (p=0.80)	GRADE: low
PEF	OPEP vs control	Adults	Flutter		24 (1)	Significantly higher for OPEP (p<0.01)	GRADE: low
Bronchiectasis							
FEV1	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
				12 weeks	NR (1)	No significant difference between groups	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
				15 days	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs GAD	Acute & stable; children & adults	NR	Day 2 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day 4 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day of discharge	10 (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT	Acute & stable; children & adults	Flutter	4 weeks	10 (1)	No significant difference between groups	GRADE: very low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	Acapella	NR	10 (1)	No significant difference between groups	GRADE: very low
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
FVC	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
				12 weeks	NR (1)	No significant difference between groups	GRADE: low
				15 days	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs GAD	Acute & stable; children & adults	NR	Day 2 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day 4 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day of discharge	10 (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT	Acute & stable; children & adults	Flutter	4 weeks	10 (1)	No significant difference between groups	GRADE: very low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	Acapella	NR	10 (1)	No significant difference between groups	GRADE: very low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
FEV1/FVC	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
FEF(25-75)	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
				12 weeks	NR (1)	No significant difference between groups	GRADE: low
FRC	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	Significantly lower with OPEP: median difference 30.07%; p<0.05	GRADE: low
TLC	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	Significantly lower with OPEP: median difference 22.9%; p<0.05	GRADE: low
				15 days	NR (1)	No significant difference between groups	GRADE: low
IC	OPEP vs no ACT	Acute & stable; children & adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
IC/TLC ratio	OPEP vs no ACT	Acute & stable; children & adults	NR	Immediately after intervention	NR (1)	Significantly lower with OPEP: median difference 16.07%; p<0.05	GRADE: low
RV	OPEP vs no ACT	Acute & stable; children & adults	NR	Immediately after intervention	NR (1)	Significantly lower with OPEP: median difference 26.7%; p<0.05	GRADE: low
RV/TLC ratio	OPEP vs no ACT	Acute & stable; adults	NR	Immediately after intervention	NR (1)	No significant difference between groups	GRADE: low
PEF	OPEP vs ACBT + GAD	Acute & stable; children & adults	Flutter	4 weeks	10 (1)	No significant difference between groups in morning or afternoon sessions	GRADE: low
	OPEP vs autogenic drainage	Acute & stable; children & adults	Acapella	NR	10 (1)	No significant difference between groups	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP vs SEGO	Acute & stable; children & adults	Flutter	4 treatment sessions	10 (1)	No significant difference between groups	GRADE: low
	OPEP vs GAD	Acute & stable; children & adults	NR	Day 2 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day 4 of admission	10 (1)	No significant difference between groups	GRADE: low
				Day of discharge	10 (1)	No significant difference between groups	GRADE: low
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
PEF%	OPEP vs ACBT + GAD	Acute & stable; children & adults	Acapella	NR	10 (1)	No significant difference between groups	GRADE: very low
Other respiratory conditions							
FEV1	OPEP vs no ACT	Stable COPD	Flutter	Immediate	NR (1)	No significant difference between groups	GRADE: low
			Cornet & Flutter	Short-term	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	Immediate	15 (1)	No significant difference between groups	GRADE: low
	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
	OPEP vs SEGO vs postural drainage	Acute exacerbation of chronic bronchitis	Flutter	During intervention	10 (1)	No significant difference between groups	GRADE: very low
				Up to 1 hour after intervention	10 (1)	No significant difference between groups	GRADE: very low
	OPEP + hypertonic saline vs hypertonic saline	Asthma; children and adolescents	NR	NR	33 (1)	No significant difference between groups	GRADE: very low
FEV1%	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
FVC	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	Immediate	15 (1)	No significant difference between groups	GRADE: low
	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
FVC%	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
FEV1/FVC	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
	OPEP + hypertonic saline vs hypertonic saline	Asthma; children and adolescents	NR	NR	33 (1)	No significant difference between groups	GRADE: very low
TLC	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. Significantly improved for OPEP vs pharmacological therapy alone; p=0.02	GRADE: moderate
TLC%	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. Significantly improved for OPEP vs pharmacological therapy alone; p=0.024	GRADE: moderate
EV/FVC	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	Immediate	15 (1)	No significant difference between groups	GRADE: low
VC	OPEP vs no ACT	Stable COPD	Flutter	Immediate	NR (1)	No significant difference between groups	GRADE: low
			Cornet & Flutter	Short-term	90 (1)	No significant difference between groups	GRADE: low
MEF(25-75)	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	Immediate	15 (1)	No significant difference between groups	GRADE: low
RV	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. Significantly improved for OPEP vs pharmacological therapy alone; p=0.04	GRADE: moderate
RV%	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. Significantly improved for OPEP vs pharmacological therapy alone; p=0.02	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
DLCO%	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
MIP	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
MEP	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
PEF	OPEP + hypertonic saline vs hypertonic saline	Asthma; children and adolescents	NR	NR	33 (1)	No significant difference between groups	GRADE: very low

FEV1 = forced expiratory volume during the first second; FVC = forced vital capacity; PEF = peak expiratory flow; FEF(25-75) = forced expiratory flow between 25% and 75% of FVC; FRC = functional residual capacity; RV = residual volume; SEGO = slow expiration with glottis open; MEF(25-75) = medium expiratory flow between 25% and 75% of FVC

Exacerbations and hospital admission

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
Number of respiratory exacerbations	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	1 year to 13 months	112 (3)	One study of 1 year duration found significantly fewer hospitalisations with PEP compared to OPEP. The other two studies found no significant differences in the number of respiratory exacerbations between groups.	GRADE: moderate
	OPEP vs IPV	Children & adults	Flutter	24 weeks	16 (1)	No significant difference between groups	GRADE: low
Bronchiectasis							
Number of respiratory exacerbations	OPEP vs no ACT	Acute & stable; adults	NR	12 weeks	NR (1)	No significant difference in frequency of exacerbations between OPEP and no ACT (5 vs 7 respectively; p=0.48)	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Other respiratory conditions							
Hospital admission	OPEP vs no ACT	Stable COPD	Cornet	Long-term	50 (1)	Significantly lower for OPEP: OR 0.27 95% CI 0.08 to 0.95	GRADE: low
Number of days hospitalised	OPEP vs no ACT	Stable COPD	Cornet	Long-term	50 (1)	No significant difference between groups	GRADE: low
Hospital length of stay	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups for all patients and for survivors	GRADE: very low
Intensive care length of stay	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups for survivors	GRADE: very low
Exacerbations	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	1 month	120 (1)	No significant difference between groups	GRADE: moderate
				2 months	120 (1)	No significant difference between groups	GRADE: moderate
				3 months	120 (1)	No significant difference between groups	GRADE: moderate
	OPEP vs usual care	Stable COPD	Lung Flute	26 weeks	69 (1)	Significantly fewer with OPEP (p=0.03)	GRADE: low
Severe exacerbations	OPEP vs OPEP	COPD or bronchitis	Acapella vs Aerobika	12 months	5,029 (1)	Significantly fewer with Aerobika (p=0.03)	GRADE: low

Health-related quality of life

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
Exercise tolerance	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	10 days to 1 year	68 (2)	No significant difference between treatment groups in either study.	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
(modified shuttle test)	OPEP vs OPEP	Children & adults	Flutter & Cornet	NR	75 (1)	No significant difference between groups	GRADE: low
Well-being (QWB scale, CF SF-36 and CRQ)	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	1 year	75 (2)	No significant change from baseline between groups in QWB scale or any domain.	GRADE: low
Well-being (CRQ)	OPEP vs OPEP	Children & adults	Flutter & Cornet	NR	75 (1)	No significant difference between groups	GRADE: low
Bronchiectasis							
Leicester Cough Questionnaire	OPEP vs no ACT	Acute & stable; adults	NR	12 weeks	NR (1)	Cough-related quality of life was significantly better for OPEP: total median difference 1.3 (p=0.002), including physical domain (p=0.002); psychological (p<0.0001); and social (p=0.02)	GRADE: low
St. George's Respiratory Questionnaire	OPEP vs no ACT	Acute & stable; adults	NR	12 weeks	NR (1)	Median: -7.8 (IQR -14.5 to -0.99) vs -0.7 (IQR -2.3 to 0.05); p=0.005	GRADE: low
SF-36: general health	OPEP vs ACBT	Acute & stable; children & adults	Flutter	4 weeks	NR (1)	Borderline not significantly different: p=0.048	GRADE: very low
CRQ	OPEP vs ACBT + GAD	Acute & stable; children & adults	Flutter	4 weeks	NR (1)	No significant difference in mean total score, dyspnoea, fatigue, emotional function or mastery	GRADE: low
Exercise tolerance	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Other respiratory conditions							
SGRQ	OPEP vs no ACT	Stable COPD	Flutter	Short-term	NR (1)	Significantly better scores for OPEP: mean difference -6.1 (95% CI -8.93 to -3.27)	GRADE: low
	OPEP vs usual care	Stable COPD	Lung Flute	26 weeks	69 (1)	Significantly fewer with OPEP (p=0.03)	GRADE: low
Exercise tolerance (6	OPEP vs no ACT	Stable COPD	Flutter	Short-term	NR (2)	Significantly better scores for OPEP: mean difference 12.93 (95% CI 5.98 to 19.89)	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
minute walk test)	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. OPEP significantly improved vs pharmacological therapy alone: 11.5 vs -4.8; p=0.01	GRADE: moderate
Exercise tolerance (12 minute walk test)	OPEP vs no ACT	Stable COPD	Flutter	Long-term	20 (1)	Significantly better scores for OPEP: mean difference 111 (95% CI 66.46 to 155.54)	GRADE: moderate
QWB = Quality of Well-being scale; CRQ = Chronic Respiratory Disease Questionnaire; GAD = gravity assisted drainage							

Lung clearance and sputum production

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
Lung clearance index (LCI)	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	1 year	30 (1)	Mean (SD) LCI for OPEP was 0.2 (2.47). Mean LCI for PEP was 0.80 higher (1.36 lower to 2.96 higher).	GRADE: low
Sputum water content	OPEP vs control	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
Sputum solids content	OPEP + cycling exercise vs cycling exercise alone	Adults	Flutter	Immediately post-exercise	15 (1)	No significant difference between groups	GRADE: low
				45 minutes post-exercise	15 (1)	No significant difference between groups	GRADE: low
Sputum mechanical impedance	OPEP vs control	Adults	Flutter	NR	24 (1)	Significantly greater reduction with OPEP	GRADE: low
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
Coughs during intervention	OPEP vs control	Adults	Flutter	NR	24 (1)	Significantly greater number of coughs with OPEP (average 24 vs 2)	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	Significantly greater number of coughs with OPEP (average 24 vs 4)	GRADE: low
Coughs during recovery	OPEP vs control	Adults	Flutter	NR	24 (1)	No significant difference between groups (average 2 vs 1)	GRADE: low
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	No significant difference between groups (average 2 vs 2)	GRADE: low
	OPEP vs PEP, vibration & percussion	Children & adults	Flutter & Acapella	NR	18 (1)	No significant difference between interventions	GRADE: low
Patient-reported ease of expectoration	OPEP vs control	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
	OPEP + cycling exercise vs cycling exercise alone	Adults	Flutter	Immediately post-exercise	15 (1)	No significant difference between groups	GRADE: low
				45 minutes post-exercise	15 (1)	Absolute change from pre-exercise (median cm): -1.1 (IQR -1.8 to 0.1) for OPEP + exercise vs 0.80 (IQR -0.1 to 1.2); p=0.016	GRADE: low
Patient-reported sense of chest congestion	OPEP vs control	Adults	Flutter	NR	24 (1)	Flutter versus control: mean difference of 0.8 cm (95% CI 0.1 to 1.4) immediately post intervention and 0.9 cm (95% CI 0.2 to 1.7) after 20 minutes recovery	GRADE: low
	OPEP vs treadmill exercise	Adults	Flutter	NR	24 (1)	No significant difference between groups	GRADE: low
Bronchiectasis							
Patient-reported ease of expectoration	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	Significantly improved with OPEP (p>0.001)	GRADE: low
Cough frequency	OPEP vs no ACT	Acute & stable; children & adults	NR	15 days	NR (1)	Significantly improved with OPEP (p=0.003)	GRADE: low
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Cough severity	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	No significant difference between groups	GRADE: low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Sputum volume	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	Significant increase with OPEP: mean difference 8.40 mL (95% CI 3.40 to 13.40)	GRADE: low
				24 hours	NR (1)	Significant increase with OPEP: mean difference 3 mL; p=0.02	GRADE: low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	NR	1 treatment session	NR (1)	Mean difference: 5.1 mL (95% CI 2.2 to 8.0)	GRADE: moderate
	OPEP vs autogenic drainage	Acute & stable; children & adults	Acapella	Immediately post-treatment	NR (1)	No significant difference between groups	GRADE: low
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Self-reported sputum volume	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Sputum weight	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	No significant difference in dry weight between groups	GRADE: low
	OPEP vs GAD	Acute & stable; children & adults	Flutter	Day 2 of admission	NR (1)	No significant difference between groups	GRADE: low
				Day 4 of admission	NR (1)	No significant difference between groups	GRADE: low
				Day of discharge	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	NR	1 treatment session	NR (2)	No significant difference between groups in one study. Mean difference: 5.6 g (95% CI 2.9 to 8.3) in other study	GRADE: low
				4 weeks	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT	Acute & stable; children & adults	NR	1 treatment session	NR (1)	No significant difference between groups	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP s SEGO	Acute & stable; children & adults	NR	1 treatment session	NR (1)	Median 0.15 g vs 0.38 g; p<0.05	GRADE: low
			Flutter	1 treatment session	NR (1)	No significant difference between groups in dry or wet weight	GRADE: low
	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	During intervention	40 (1)	Mean wet weight was significantly greater with Flutter: 5.10 vs 3.74; p0.038	GRADE: moderate
				30 minutes from end of intervention	40 (1)	Mean wet weight was significantly greater with Lung Flute: 2.02 vs 0.68; p<0.001	GRADE: moderate
				NR	40 (1)	No significant difference in total wet or dry weight	GRADE: moderate
Self-reported sputum colour	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Sputum displacement	OPEP vs PEP	Stable; adults	Flutter	NR	8 (1)	Larger displacement with Flutter: 114 to 146 mm vs 118 to 138 mm. Unclear whether statistically significant	GRADE: very low
Other respiratory conditions							
Spontaneous coughs	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	NR	15 (1)	More with OPEP than sham OPEP or OPEP + bronchodilator: 2.54 vs 0.69 vs 3.63. Unclear if statistically significant	GRADE: low
Sputum production (not specified)	OPEP + standard management vs PEP	Acute exacerbation of COPD; adults	Acapella	1-5 days of hospitalisation	91 (1)	Significantly greater with OPEP than PEP; p<0.05	GRADE: moderate
	OPEP vs SEGO vs postural drainage	Acute exacerbation of chronic bronchitis	Flutter	30 minutes after starting intervention	10 (1)	Increased significantly in all groups. Unclear if any difference between groups.	GRADE: very low
				1 hour after end of the intervention	10 (1)	Increased significantly in all groups. Unclear if any difference between groups.	GRADE: very low
	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	Significantly lower for OPEP; p=0.001	GRADE: very low

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Sputum weight	OPEP vs no ACT	Stable COPD	Flutter	Immediate	NR (1)	No significant difference between groups	GRADE: moderate
	OPEP + hypertonic saline vs hypertonic saline	Asthma; children and adolescents	NR	NR	33 (1)	Significantly more sputum with OPEP + hypertonic saline (p=0.02)	GRADE: very low
Sputum volume	OPEP vs sham OPEP	COPD	Flutter	NR	15 (1)	Significantly greater with OPEP than with sham OPEP: mean 2.54 vs 1.5 g; p<0.05	GRADE: low
Time to sputum induction	OPEP + hypertonic saline vs hypertonic saline	Asthma; children and adolescents	NR	NR	33 (1)	Significantly longer with OPEP + hypertonic saline compared to hypertonic saline or OPEP (p=0.001)	GRADE: very low

Other symptoms

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Bronchiectasis							
Chest discomfort	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	NR	NR	NR (1)	No significant difference between groups	GRADE: moderate
	OPEP vs ACBT	Acute & stable; children & adults	Flutter	NR	NR (1)	No significant difference between groups	GRADE: moderate
Dyspnoea (Borg score)	OPEP vs no ACT	Acute & stable; adults	NR	15 days	NR (1)	No significant difference between groups	GRADE: low
	OPEP vs ACBT + GAD	Acute & stable; children & adults	NR	NR	NR (1)	No significant difference between groups	GRADE: low
Fatigue	OPEP vs ACBT + GAD	Acute & stable; children & adults	NR	NR	NR (1)	No significant difference between groups	GRADE: moderate
	OPEP vs ACBT	Acute & stable; children & adults	NR	NR	NR (1)	Mean difference: 0.7 (95% CI 0.15 to 1.25)	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Sinus discharge	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Appetite	OPEP + postural drainage vs usual ACT	Acute; children & adults	Acapella	10-14 days	20 (1)	No significant difference between groups	GRADE: moderate
Other respiratory conditions							
Breathlessness (Borg scale)	OPEP vs no ACT	Stable COPD	Flutter	Immediate	50 (1)	Significantly better for OPEP: mean difference -0.3 (95% CI -0.53 to -0.07)	GRADE: low
Purulence	OPEP vs sham OPEP vs OPEP + bronchodilator	COPD	Flutter	NR	15 (1)	No significant difference between groups	GRADE: low
	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups	GRADE: very low
Subjective dyspnoea (MMRC scale)	OPEP + standard management vs PEP	Acute exacerbation of COPD; adults	Acapella	1-5 days of hospitalisation	91 (1)	No significant difference between groups	GRADE: moderate
	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. OPEP significantly improved vs pharmacological therapy alone: -0.4 vs 0.1; p=0.012	GRADE: moderate
COPD Assessment Test scale	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP. OPEP significantly improved vs pharmacological therapy alone: -6.4 vs -1.6; p=0.008	GRADE: moderate
Breathlessness cough sputum score	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between groups	GRADE: moderate
Duration of chest physiotherapy	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups	GRADE: very low

Participant satisfaction and acceptability

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
Participant satisfaction (any)	OPEP vs IPV	Children & adults	Flutter	24 weeks	16 (1)	IPV was well tolerated with 67% of participants wanting to continue using it instead of other ACTs	GRADE: low
	OPEP vs thoracic oscillation	Children & adults	Flutter	24 weeks	166 (1)	In both studies, Flutter was significantly better for convenience. In one study, the comparator scored significantly higher for efficacy ($p<0.02$). Other scores showed no difference.	GRADE: low
Bronchiectasis							
Assists with secretions	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	Favours Flutter; p=0.01	GRADE: moderate
Easy to understand	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	Favours Flutter; p=0.03	GRADE: moderate
Simple to use	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	Favours Flutter; p=0.01	GRADE: moderate
Tiring	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	No significant difference between groups	GRADE: moderate
Uncomfortable to use	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	No significant difference between groups	GRADE: moderate
Time consuming	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	No significant difference between groups	GRADE: moderate
Interferes with everyday life	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	No significant difference between groups	GRADE: moderate
Causes embarrassment	OPEP vs OPEP	Stable; adults	Flutter & Lung Flute	NR	40 (1)	No significant difference between groups	GRADE: moderate
Other respiratory conditions							
Self-reported compliance	OPEP + standard management vs PEP	Acute exacerbation of COPD; adults	Acapella	1-5 days of hospitalisation	91 (1)	No significant difference between groups	GRADE: moderate

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Acceptance	OPEP vs T-PEP vs pharmacological therapy alone	Stable, severe or very severe COPD	Lung Flute	NR	120 (1)	No significant difference between OPEP vs T-PEP on Likert scale (1-7)	GRADE: moderate

Adverse events and participant withdrawal

Outcome	Comparison	Population	Type of OPEP (where reported)	Follow up	No. of participants (studies)	Findings	Quality of evidence
Cystic fibrosis							
Any adverse event	OPEP vs PEP	Adults	Acapella, Flutter & Cornet	2 weeks	22 (1)	Five participants experienced dizziness with OPEP (Flutter device) which improved with further instruction on breathing techniques. No adverse events were reported in the PEP group.	GRADE: low
	OPEP vs PEP, vibration & percussion	Any with cystic fibrosis	Flutter & Acapella	NR	18 (1)	None reported in any group	GRADE: low
Bronchiectasis							
Any adverse event	OPEP vs no ACT	Acute & stable; adults	NR	NR	NR (3)	None reported in any group	GRADE: low
Other respiratory conditions							
Withdrawal	OPEP vs no ACT	Acute COPD	Cornet	Short-term	90 (1)	No significant difference between groups	GRADE: low
In-hospital mortality	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups for survivors	GRADE: very low
Intensive care unit mortality	OPEP vs mechanical percussion	Lower respiratory tract infection	Acapella	Day 7 after chest physiotherapy	27 (1)	No significant difference between groups for survivors	GRADE: very low

Appendix 5. Systematic Reviews

Table 1. Systematic review: McIlwaine et al. (2019)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 28 **Total number of patients:** 788 **Mean participant age:** NR	**Review period:** Up to 20 February 2019 **Review purpose:** To determine the effectiveness and acceptability of PEP devices compared to other forms of physiotherapy. **Population:** Adults and children with cystic fibrosis **Included study designs:** RCTs **Included outcome measures:** Forced expiratory volume (FEV); number of respiratory exacerbations; participant preference; adverse events	This review only included RCTs. Many of the included studies had a high risk of bias due to not reporting how the randomisation sequence was generated or concealed.

Results

Included a comparison of PEP with oscillating PEP (Acapella, Flutter and Cornet) in outpatient setting.

Outcome	No. of participants (studies)	Follow-up	Finding	Quality of evidence (GRADE)
FEV1: change from baseline (% predicted)	217 (7 studies)	Single treatment to 13 months	No significant difference between treatment groups in any study.	Moderate
Number of respiratory exacerbations: requiring either IV antibiotics or hospitalisation	112 (3 studies)	1 year to 13 months	One study of 1 year duration found significantly fewer hospitalisations with PEP compared to OPEP. The other two studies found no significant differences in the number of respiratory exacerbations between groups.	Moderate
Exercise tolerance: modified shuttle test	68 (2 studies)	10 days to 1 year	No significant difference between treatment groups in either study.	Moderate
Well-being: QWB scale. CF SF-36 and Chronic Respiratory questionnaire	75 (2 studies)	1 year	No significant change from baseline between groups in QWB scale or any domain.	Low
Lung clearance index (LCI)	30 (1 study)	1 year	Mean (SD) LCI for OPEP was 0.2 (2.47). Mean LCI for PEP was 0.80 higher (1.36 lower to 2.96 higher).	Low
Adverse events	22 (1 study)	2 weeks	Five participants experienced dizziness with OPEP (Flutter device) which improved with further instruction on breathing techniques. No adverse events were reported in the PEP group.	Low

Table 2. Systematic review: Morrison & Milroy (2017)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 35 **Total number of patients:** NR **Mean participant age:** NR	**Review period:** up to 27 April 2017 **Review purpose:** To identify whether oscillatory devices, oral or chest wall, are effective for mucociliary clearance and whether they are equivalent or superior to other forms of airway clearance in the successful management of secretions in people with cystic fibrosis. **Population:** children and adults diagnosed with cystic fibrosis **Included study designs:** RCTs **Included outcome measures:** respiratory function (FEV1, FEF, FVC, ERV); sputum; exercise tolerance; quality of life; oxygen saturation; frequency of exacerbations; participant satisfaction; lung clearance index	Assessed both oral and chest wall oscillatory devices. Meta-analysis did not provide subgroup outcomes for OPEP separately. This review sought to complement previous Cochrane reviews of chest physiotherapy in people with cystic fibrosis which compared oscillatory devices with another single recognised therapy: conventional chest physiotherapy (Maine 2005), PEP (McIlwaine 2015), or ACBP (McKoy et al. 2016).

Results

Lung function

Comparison	Number of studies (n)	Follow-up	Findings
FEV1			
IPV versus Flutter	1 study (NR)	24 weeks	p=0.208
Thoracic oscillation versus Flutter	1 study (NR)		Non-significant change for either intervention
Flutter versus Cornet	1 study (NR)		Not statistically significant (p=0.35)
FEV1%			
Thoracic oscillation versus Flutter	1 study (NR)		Not statistically significant
FEF(25-75)			
IPV versus Flutter	1 study (NR)	24 weeks	p=0.126
Thoracic oscillation versus Flutter	2 studies (NR)		Studies report mixed findings
FVC			
IPV versus Flutter	1 study (NR)	24 weeks	p=0.292
Flutter versus Cornet	1 study (NR)		Not statistically significant
FVC%			
Thoracic oscillation versus Flutter	2 studies (NR)		Not statistically significant

Frequency of exacerbations

Comparison	Number of studies (n)	Follow-up	Findings
IPV versus Flutter	1 study (NR)	24 weeks	No difference

Participant satisfaction

Comparison	Number of studies (n)	Follow-up	Findings
IPV versus Flutter	1 study (NR)	24 weeks	IPV was well tolerated with 67% of participants wanting to continue using it instead of other ACTs
Thoracic oscillation versus Flutter	2 studies (NR)		In both studies, Flutter was significantly better for convenience. In one study, the comparator scored significantly higher for efficacy ($p<0.02$). Other scores showed no difference.

Exercise tolerance

Comparison	Number of studies (n)	Follow-up	Findings
Flutter versus Cornet	1 study (NR)		Not statistically significantly difference on modified shuttle walk score

Quality of life

Comparison	Number of studies (n)	Follow-up	Findings
Flutter versus Cornet	1 study (NR)		Not statistically significantly difference on CRQ

Table 3. Systematic review: Morrison & Milroy (2020)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 39 **Total number of patients:** 1,114 **Mean participant age:** range 4-63 years	**Review period:** up to August 2019 **Review purpose:** To identify whether oscillatory devices, oral or chest wall, are effective for mucociliary clearance and whether they are equivalent or superior to other forms of airway clearance in the successful management of secretions in people with cystic fibrosis. **Population:** children and adults diagnosed with cystic fibrosis **Included study designs:** RCTs and clinical controlled studies **Included outcome measures:** respiratory function (FEV1, FEF, FVC); sputum volume and weight; frequency of exacerbations; participant satisfaction	Update of previous review. Assessed both oral and chest wall oscillatory devices. Meta-analysis did not provide subgroup outcomes for OPEP separately. This updated included two additional studies of OPEP.

Results

Included below are findings which incorporate the two additional OPEP studies identified. Please see Morrison & Milroy (2017) (Table 2) for other findings.

Lung function

Outcome	Number of studies (n)	Follow-up	Findings
OPEP versus ACT			
FEF(25-75)	1 study (44)	Up to 1 week	p=0.80
FVC (% predicted)	1 study (44)	Up to 1 week	p=0.63
FEV1 (% predicted)	1 study (44)	Up to 1 week	Mean difference: 0.00 (95% CI -13.67 to 13.67)

Table 4. Systematic review: Lee et al. (2015a)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 7 **Total number of patients:** 102 **Mean participant age:** NR	**Review period:** up to November 2015 **Review purpose:** To summarise the safety and efficacy of airway clearance techniques in people with acute and stable bronchiectasis, and to determine their effects on rates of acute exacerbation, incidence of hospitalisation, and quality of life. **Population:** adults and children with acute and stable bronchiectasis **Included study designs:** RCTs comparing airway clearance techniques with no intervention, sham or coughing alone. **Included outcome measures:** rate, duration or time to acute exacerbation; hospitalisation (for stable or acute); quality of life; pulmonary function; gas exchange; symptoms; clearance and expectoration of mucus; antibiotic usage; adverse events; mortality; participant withdrawal.	Did not include studies comparing ACTs with other ACTs. Update of a previous Cochrane review. No subgroup analysis for OPEP devices, limited data obtained from in text. It is assumed that airway oscillating device refers to OPEP devices alone as extra-thoracic oscillating devices are reported separately.

Results

Exacerbation and hospitalisations
One study was identified (N=20) which found no significant difference in the frequency of exacerbations between groups at 12 weeks (five for OPEP and seven for no ACT; p=0.48).

Quality of life
One study found significantly better cough-related quality of life at 12 weeks for OPEP compared to no ACT. Whilst a second study found that it did not.

Outcome	Number of studies (n)	Follow-up	Findings
OPEP versus no airway clearance technique			
Leicester Cough Questionnaire: total score	1 study (n=20)	12 weeks	Median difference 1.3; p=0.002
Leicester Cough Questionnaire: physical	1 study (n=20)	12 weeks	p=0.002
Leicester Cough Questionnaire: psychological	1 study (n=20)	12 weeks	p<0.0001
Leicester Cough Questionnaire: social	1 study (n=20)	12 weeks	p=0.02
St. George's Respiratory Questionnaire: total score	1 study (n=20)	12 weeks	OPEP: median -7.8 (IQR -14.5 to -0.99) versus no ACT: median -0.7 (IQR -2.3 to 0.05); p=0.005
	1 study (NR)	15 days	p>0.05

Lung function
One study found OPEP significantly reduced FRC, TLC, IC/TLC ratio, and RV compared to a control immediately following the session. However, no significant difference was found for FEV1, FEV1/FVC, FVC, FEF(25-75%), IC or RV/TLC ratio.
A second study found no significant difference in FEV1, FVC or FEF(25-75%) at 12 weeks between OPEP and no ACT.
A third study found no significant difference in FEV1, FVC, or TLC compared to no ACT at 15 days.

Comparison	Number of studies (n)	Follow-up	Findings
FRC	1 study (NR)	Immediately following a session	Median difference: 30.07%; p<0.05
TLC	1 study (NR)	Immediately following a session	Median difference: 22.9%; p<0.05
	1 study (NR)	15 days	p>0.05
IC/TLC ratio	1 study (NR)	Immediately following a session	Median difference: 16.07%; p<0.05
RV	1 study (NR)	Immediately following a session	Median difference: 26.7%; p<0.05
FEV1	1 study (NR)	Immediately following a session	p>0.05
	1 study (NR)	12 weeks	Median difference: 0.00 L; p=0.7
	1 study (NR)	15 days	p>0.05
FEV1/FVC	1 study (NR)	Immediately following a session	p>0.05
FVC	1 study (NR)	Immediately following a session	p>0.05
	1 study (NR)	12 weeks	Median difference: 0.07 L; p=0.9
	1 study (NR)	15 days	p>0.05
FEF(25-75%)	1 study (NR)	Immediately following a session	p>0.05
	1 study (NR)	12 weeks	Median difference: 0.06 L; p=0.6
IC	1 study (NR)	Immediately following a session	p>0.05
RV/TLC ratio	1 study (NR)	Immediately following a session	p>0.05

Symptoms
One study found OPEP significantly improved ease of expectoration and cough frequency at 15 days compared to no ACT, but had no effect on cough severity, chest discomfort or dyspnoea.

Outcome	Number of studies (n)	Follow-up	Findings
Ease of expectoration	1 study (NR)	15 days	p>0.001
Cough frequency	1 study (NR)	15 days	P=0.003
Cough severity	1 study (NR)	15 days	p>0.05
Chest discomfort	1 study (NR)	15 days	p>0.05
Dyspnoea	1 study (NR)	15 days	p>0.05

Sputum clearance
One study found OPEP significantly increased the volume of sputum produced compared to sham therapy. A second study reported a significant increase in 24-hour

sputum volume compared with control. A third study found no significant difference in dry sputum weight after a single session between OPEP and control.

Outcome	Number of studies (n)	Follow-up	Findings
Sputum volume	1 study (NR)	NR	Mean difference: 8.40 mL (95% CI 3.40 to 13.40 mL)
	1 study (NR)	24 hours	Mean difference: 3 mL; p=0.02
Dry sputum weight	1 study (NR)	Single session	0.15 g versus 0.14 g; p>0.05

Adverse events and participant withdrawal
Three studies reported no adverse events during studies, and that all participants completed the studies, comparing OPEP to control.

Table 5. Systematic review: Lee et al. (2017)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 9 **Total number of patients:** 213 **Age range:** 46-74 years (where reported)	**Review period:** up to February 2017 **Review purpose:** to determine the effects of any type of PEP therapy compared with other ACTs on HRQOL, rate of acute exacerbations, and incidence of hospitalisation in individuals with stable or an acute exacerbation of bronchiectasis. **Population:** adults and children with stable or acute exacerbation of bronchiectasis. **Included study designs:** RCTs of PEP versus other ACT. **Included outcome measures:** HRQOL; rate, duration or time to acute exacerbation; hospitalisation for bronchiectasis; sputum volume; mucociliary clearance; lung function; symptoms; adverse events.	Included studies comparing any type of PEP to other ACT. Subgroup analysis of OPEP versus other ACT. The quality of the studies included was mixed.

Results

Quality of life

Outcome	Number of studies (n)	Follow-up	Findings
Flutter versus ACBT			
SF-36: general health	1 study	4 weeks	p=0.048
Flutter versus ACBT with gravity-assisted drainage			
Chronic respiratory disease questionnaire: total score	1 study	4 weeks	Mean difference: -0.09 (95% CI -0.37 to 0.19)
Chronic respiratory disease questionnaire: dyspnoea	1 study	4 weeks	Mean difference: 0.01 (95% CI -0.48 to 0.50)
Chronic respiratory disease questionnaire: fatigue	1 study	4 weeks	Mean difference: -0.19 (95% CI -0.82 to 0.44)
Chronic respiratory disease questionnaire: emotional function	1 study	4 weeks	Mean difference: -0.06 (95% CI -0.63 to 0.51)
Chronic respiratory disease questionnaire: mastery	1 study	4 weeks	Mean difference: -0.10 (95% CI -0.65 to 0.45)

Lung function

Outcome	Number of studies (n)	Follow-up	Findings
OPEP versus gravity assisted drainage			
FEV1	1 study	Day 2 of admission	Mean difference: 0.12 (95% CI -0.32 to 0.56)
	1 study	Day 4 of admission	Mean difference: 0.15 (95% CI -0.27 to 0.57)
	1 study	Day of discharge	Mean difference: 0.12 (95% CI -59.48 to 59.72)

FVC	1 study	Day 2 of admission	Mean difference: -0.22 (95% CI -0.81 to 0.37)
	1 study	Day 4 of admission	Mean difference: 0.20 (95% CI -0.48 to 0.88)
	1 study	Day of discharge	Mean difference: 0.12 (95% CI -0.52 to 0.76)
Flutter versus ACBT			
FEV1	1 study	4 weeks	No significant difference
FVC	1 study	4 weeks	No significant difference
Flutter versus ACBT with gravity assisted drainage			
PEFR	1 study	4 weeks	No significant difference in morning (median: -2.5; p=0.38) or afternoon session (median: -2.72; p=0.30)
Acapella versus ACBT with gravity assisted drainage			
FEV1	1 study	NR	No significant difference
FVC	1 study	NR	No significant difference
PEF%	1 study	NR	No significant difference
Acapella versus autogenic drainage			
PEFR	1 study	NR	No significant difference; p=0.87
Flutter versus slow expiration with the glottis open			
PEFR	1 study	4 treatment sessions	No significant difference; p>0.05
FEV1	1 study	1 treatment session	No significant difference
FVC	1 study	1 treatment session	No significant difference
FEV1/FVC	1 study	1 treatment session	No significant difference
FEF(25-75)	1 study	1 treatment session	No significant difference
IC	1 study	1 treatment session	No significant difference
TLC	1 study	1 treatment session	No significant difference
FRC	1 study	1 treatment session	No significant difference
RV	1 study	1 treatment session	No significant difference
RV/TLC	1 study	1 treatment session	No significant difference

Symptoms

Outcome	Number of studies (n)	Follow-up	Findings
Acapella versus ACBT with gravity-assisted drainage			
15-count breathlessness score	1 study	Single treatment session	No significant difference
Flutter versus ACBT with gravity-assisted drainage			
Fatigue	1 study	NR	Mean difference: -0.3 (95% CI -0.35 to 0.95)
Discomfort	1 study	NR	Mean difference: -0.3 (95% CI -0.82 to 0.22)
Dyspnoea (Borg score)	1 study	NR	No significant difference

Flutter versus ACBT			
Tiredness	1 study	NR	Mean difference: 0.7 (95% CI 0.15 to 1.25)
Discomfort	1 study	NR	Mean difference: 0.40 (95% CI -0.12 to 0.92)
Chronic respiratory disease questionnaire: emotional function	1 study	4 weeks	Mean difference: -0.06 (95% CI -0.63 to 0.51)
Chronic respiratory disease questionnaire: mastery	1 study	4 weeks	Mean difference: -0.10 (95% CI -0.65 to 0.45)
Dyspnoea (Borg score)	1 study	NR	No significant difference
Cough	1 study	4 weeks	No significant difference
Weakness	1 study	4 weeks	No significant difference
Breathlessness	1 study	4 weeks	No significant difference in morning (median: -0.13; p=0.36) or evening session (median: -0.04; p>0.99)
Acapella versus autogenic drainage			
Dyspnoea (Borg score)	1 study	NR	p=1.00

Sputum clearance

Comparison	Number of studies (n)	Follow-up	Findings
Flutter versus gravity assisted drainage	1 study	Day 2 of admission	Mean difference: 19.86 g (95% CI -7.95 to 47.67).
	1 study	Day 4 of admission	Mean difference: 22.46 g (95% CI -10.71 to 55.63).
	1 study	Day of discharge	Mean difference: 21.03 g (95% CI -11.29 to 53.35).
OPEP versus ACBT with gravity-assisted drainage	1 study	Single treatment session	Mean difference: 0.54 g (95% CI -0.38 to 1.46).
	1 study	Single treatment session	Mean difference: 5.60 g (95% CI 2.91 to 8.29).
	1 study	Single treatment session	Mean difference: 5.1 ml (95% CI 2.24 to 7.96).
	1 study	4 weeks	Mean difference: 7.64 g; p=0.77
OPEP versus ACBT	1 study	Single treatment session	Mean difference: -0.30 g (95% CI -1.42 to 0.82).
	1 study	Single treatment session	Mean difference: -0.60 ml (95% CI -1.87 to 0.67).
OPEP versus slow expiration with the glottis open	1 study	Single treatment session	Median: 0.15 g versus 0.38 g; p<0.05
Flutter versus slow expiration with the glottis open	1 study	Single treatment session	No difference in dry weight (p>0.05) or wet weight (p>0.05)
Acapella versus autogenic drainage	1 study	Immediately post treatment	No difference in volume (p=0.92) or weight (p=0.85)

Adverse events

One study reported the occurrence of nausea in one participant when using Flutter.

Table 6. Systematic review: Phillips et al. (2020)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 6 **Total number of patients:** 120 **Age range:** not reported	**Review period:** up to January 2018 **Review purpose:** to establish if ACTs are safe for individuals experiencing acute exacerbation of bronchiectasis. **Population:** adults and children with bronchiectasis who are experiencing an acute exacerbation and have been prescribed ACTs. **Included study designs:** case studies were excluded. **Included outcome measures:** not specified.	Included studies of ACTs in those with acute exacerbations. Not just RCTs. Studies were considered to be of strong or moderate quality. OPEP studies used Flutter or Acapella. No summary analysis or subgroup analysis of OPEP. Results reported for two studies of OPEP.

Results

One RCT (N=20) compared Acapella and two postural drainage positions with a review of the patient's usual ACT (90% ACBT; 10% PEP). This study is reported to have found no significant differences between groups in regards to any clinical outcomes. The authors notes that follow-up evaluation suggests Acapella may facilitate long-term adherence to regular airway clearance.
The second study was also an RCT (N=15) and compared breathing and coughing with gravity-assisted drainage with Flutter and with just a breathing and coughing cycle. Patient's reported Flutter to be significantly more effective than breathing control on each treatment day (day 2: p=0.016; day 4: p=0.013; day of discharge: p=0.013; overall: p=0.011). There was no significant difference between Flutter and postural drainage.

Acceptability
The authors note that both studies showed patient preference towards OPEP. One found that 7/10 participants preferred Acapella to their usual ACT (90% ACBT). The other study found that Flutter was consistently perceived to be more effective than breathing or coughing on a Likert scale on days 2, 4 and discharge following acute exacerbation (p-0.011).

Lung function
One study found no change in lung function after Acapella compared to usual ACT (90% ABCT). The second study found similar results when comparing Flutter, postural drainage with breathing and coughing, and breathing and coughing alone, at days 2, 4 or discharge.

Outcome	Number of studies (n)	Follow-up	Findings
Acapella versus other ACT			
FEV1	1 study	NR	No significant difference; p=0.13
FVC	1 study	NR	No significant difference; p=0.12
VC	1 study	NR	No significant difference; p=0.84
PEF%	1 study	NR	No significant difference; p=0.41

Flutter with breathing and coughing versus breathing and coughing alone			
FVC	1 study	2 days	No significant difference; p=0.069
	1 study	4 days	No significant difference; p=0.639
	1 study	At discharge	No significant difference; p=0.798
FEV1	1 study	2 days	No significant difference; p=0.790
	1 study	4 days	No significant difference; p=0.302
	1 study	At discharge	No significant difference; p=0.843

Symptoms

Outcome	Number of studies (n)	Follow-up	Findings
Acapella versus other ACT			
Patient perception: sputum volume	1 study	NR	p=0.91
Patient perception: sputum colour	1 study	NR	p=0.19
Patient perception: intensity of cough	1 study	NR	p=0.97
Patient perception: frequency of cough	1 study	NR	p=0.67
Patient perception: exercise tolerance	1 study	NR	p=0.17
Patient perception: fatigue	1 study	NR	p=0.69
Patient perception: sinus discharge	1 study	NR	p=0.06
Patient perception: appetite	1 study	NR	p=0.08

Sputum clearance

Both studies found OPEP improved sputum production compared to usual ACT or postural drainage with breathing and coughing but this was not statistically significant. Acapella resulted in a greater volume of sputum production compared to other ACTs but this did not reach statistical significance.

Comparison	Number of studies (n)	Follow-up	Findings
Acapella versus other ACT	1 study	NR	No significant difference in sputum volume; p=0.31
Flutter with breathing and coughing versus breathing and coughing alone	1 study	At any time point	p range: 0.123 to 0.737

Adverse events

Both studies reported not adverse events.

Table 7. Systematic review: Osadnik et al. (2012)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 28 **Total number of patients:** NR **Mean age range:** 54-72 years	**Review period:** up to October 2011 **Review purpose:** to determine whether ACTs have beneficial effects on exacerbations, hospitalisation, and HRQOL in people with acute exacerbations, or stable, COPD. **Population:** individuals diagnosed with COPD, emphysema or chronic bronchitis (bronchiectasis, asthma or cystic fibrosis without COPD excluded). **Included study designs:** RCTs with a no intervention, sham intervention, or coughing alone as control. **Included outcome measures:** rate or time to acute exacerbation; hospitalisation; resource utilisation; HRQOL; pulmonary function; gas exchange; symptoms; sputum clearance and expectoration; exercise tolerance; antibiotic use; mortality; participant withdrawal.	Included studies of ACTs in those with acute exacerbations and stable COPD. Did not include studies comparing different ACTs. Subgroup analysis of PEP but no OPEP results reported separately. Some data taken from analysis which only included data from studies of OPEP. Considerable variation in risk of bias across studies.

Results

Outcome	Number of studies (n)	OPEP used	Findings
OPEP versus no ACT – acute COPD			
Participant withdrawal	1 study (N=14)	Cornet	no significant difference (OR 3.46 95% CI 0.12 to 100.51)
OPEP versus no ACT – stable COPD			
Hospital admission	1 study (N=50)	Cornet	significantly lower for OPEP (5/25 vs 12/25; OR 0.27 95% CI 0.08 to 0.95)
Number of days hospitalised	1 study (N=50)	Cornet	no significant difference (mean: 16.2 vs 18.3; difference: -2.1 (95% CI -5.18 to 0.98)
HRQOL - SGRQ	1 study (N=NR)	Flutter	significantly better for OPEP (mean difference: -6.1; 95% CI -8.93 to -3.27)
Lung function – FEV1 (immediate)	1 study (N=NR)	Flutter	No significant difference (mean difference: 0.04; 95% CI 0.0 to 0.07)
Lung function – FEV1 (short-term)	1 study (N=90)	Cornet & Flutter (pooled)	No significant difference (mean difference: -0.06; 95% CI -0.47 to 0.35)
Lung function – VC (immediate)	1 study (N=NR)	Flutter	No significant difference (mean difference: 0.13; 95% CI -0.13 to 0.4)
Lung function – VC (short-term)	1 study (N=90)	Cornet & Flutter (pooled)	No significant difference (mean difference: -0.01; 95% CI -0.51 to 0.49)
Symptoms – breathlessness (Borg scale)	1 study (N=NR)	Flutter	significantly better for OPEP (mean difference: -0.3; 95% CI -0.53 to -0.07)
Sputum – weight (g) (immediate)	1 study (N=NR)	Flutter	No significant difference (mean difference: 0.65; 95% CI -0.86 to 2.16)
Exercise tolerance – 6-minute walk test	2 studies (N=NR)	Flutter	Significantly better for OPEP (mean difference: 12.93 (95% CI 5.98 to 19.89)

Table 8. Systematic review: Alghamdi et al. (2020)

Included studies	Inclusion criteria	Quality and other observations
Number of studies: 8 **Total number of patients:** 381 **Mean (SD) age range:** 65 (7.4) years	**Review period:** up to March 2020 **Review purpose:** to evaluate the effectiveness of OPEP devices on outcomes in people with COPD to inform clinical practice. **Population:** individuals diagnosed with COPD, stable or with acute exacerbation. **Included study designs:** RCTs. **Included outcome measures:** HRQoL; symptoms; exacerbation; lung function; exercise capacity; antibiotic use; hospital admission; acceptance; completion and drop out rates.	Identified in update search – includes 1 study not previously identified (Sethi et al. 2014) and a second study which did not meet inclusion criteria. Results relating to new study reported but discrepancies in reporting between text and graphs.

Results

Overall found that the use of OPEP devices can have a positive impact in COPD, but confidence in effect sizes is low and there is a need for further, higher quality studies.

Below are findings reported for the study included in this review not previously identified:

Outcome	Number of studies (n)	OPEP used	Findings
OPEP + usual care versus usual care			
Symptoms (change in CCQ)	1 study (N=69)	Lung Flute	Reduction in symptoms with OPEP: -0.23 versus +0.01
HRQoL (change in SGRQ)	1 study (N=69)	Lung Flute	Significantly improved with OPEP: -3.23 versus -1.85; p=0.03
Exacerbations	1 study (N=69)	Lung Flute	Significantly fewer with OPEP: 6/33 versus 14/36; p=0.03
Exercise capacity (change in 6MWD)	1 study (N=69)	Lung Flute	Improved with OPEP: +7m versus -42m

Appendix 6. Summary of primary studies

Table 1. Dwyer et al. (2017)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 24 **Country:** Australia **Mean participant age:** 30 (range 19-48) **Type of study:** randomised, controlled cross-over	**Study aim:** to evaluate respiratory flow, sputum properties and subjective responses of treadmill exercise and Flutter therapy, compared to resting breathing (control). **Population:** adults ≥ 17 years old with mild to severe cystic fibrosis lung disease (FEV1 28-86% predicted) **OPEP:** Flutter device plus forced expiratory technique – breathing through the Flutter device for 15 breaths, followed by relaxed and deep breathing, huffing and coughing according to protocol. They cycle was repeated six times. **Comparator(s)**: constant load treadmill exercise at 60% of participant's peak 02 consumption; 20 minutes of resting breathing **Included outcome measures:** respiratory flow; sputum properties; cough count; participant reported sense of chest congestion and ease of expectoration	Study was small but sufficiently powered. Analysis was per protocol.

Results

Peak expiratory flow (PEF) was significantly higher during treadmill exercise and Flutter compared to control ($p<0.01$). There were no significant differences in sputum water content. Both treadmill and Flutter resulted in significant reductions in sputum mechanical impedance compared to control, but there was no significant difference between treadmill and Flutter. There were significantly more coughs during treadmill exercise and Flutter compared to control, and during Flutter compared to treadmill. There was no difference between treadmill and Flutter in the number of spontaneous coughs during the 20-minute recovery. Treadmill exercise significantly improved subjective ease of expectoration compared to control after 20-minute recover. There was no significant difference between Flutter and control, or Flutter and treadmill. Flutter significantly improved the send of chest congestion compared to control, immediately post intervention and after 20 minutes recovery. There was no significant difference between Flutter and treadmill, or between treadmill and control.

Outcome	Control	Treadmill	Flutter	Comparison
PEF (l/s)	0.68 (SD 0.28)	1.68 (SD 0.51)	1.53 (SD 0.25)	
Coughs during intervention	2 (0-5)	4 (1-9)	24 (18-34)	P<0.01 for treadmill & Flutter compared to control
Coughs during recovery	1 (0-3)	2 (1-5)	2 (1-4)	No significant differences
Sense of chest congestion	NR	NR	NR	Flutter versus control: mean difference of 0.8 cm (95% CI 0.1 to 1.4) immediately post intervention and 0.9 cm (95% CI 0.2 to 1.7) after 20 minutes recovery

Table 2. Radtke et al. (2018)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 15 **Country:** Switzerland **Median participant age:** 23 (IQR 22-25) **Type of study:** randomised, controlled cross-over	**Study aim:** to compare a single bout of moderate intensity cycling exercise incorporating Flutter with exercise alone in adults with cystic fibrosis. **Population:** adults ≥ 18 years old with confirmed diagnosis of cystic fibrosis **OPEP:** combination of interval cycling exercise plus Flutter. Cycling was for a 4-minute interval interspersed with 2-minute resting periods during which Flutter was used. **Comparator(s)**: continuous cycling exercise at moderate intensity. Cycling exercise was at 75% of peak heart rate achieved during cardiopulmonary exercise testing. **Included outcome measures:** sputum properties; pulmonary diffusing capacity.	Study was small but well conducted. No power calculation used. Analysis was per protocol. No adjustment for multiple testing.

Results

During recovery, there was a significant difference in patient reported ease of expectoration favouring exercise alone (p=0.016). No differences in pulmonary diffusing capacity were found between the interventions except for a higher alveolar volume comparing pre- and post-exercise changes in favour of exercise alone.

The authors conclude that the addition of Flutter to moderate intensity exercise has no effect on sputum viscoelastic properties.

Outcome	Exercise alone	Exercise + Flutter	p-value
Sputum solids content (%), absolute change pre- to post-exercise (median (IQR))	0.25 (-0.1–3.5)	1.11 (-1.2-3.4)	0.967
Sputum solids content (%), absolute change pre- to 45 minutes post-exercise (median (IQR))	0.86 (0.4–1.9)	0.94 (-1.6-3.6)	0.653
Ease of sputum expectoration (cm), absolute change pre- to post-exercise (median (IQR))	0.50 (-0.2–1.7)	-0.20 (-1.6-1.3)	0.276
Ease of sputum expectoration (cm), absolute change pre- to 45 minutes post-exercise (median (IQR))	0.80 (-0.1–1.2)	-1.1 (-1.8-0.1)	0.016
Oxygen saturation (%), absolute change pre- to post-exercise (median (IQR))	0.0 (-1.5–1.0)	0.0 (-1.0-0.0)	0.983
Oxygen saturation (%), absolute change pre- to 45 minutes post-exercise (median (IQR))	0.0 (-0.8–0.5)	0.3 (-0.1-1.0)	0.378

Table 3. McCarren & Alison (2006)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 18 **Country:** Australia **Mean participant age:** 28.5 (SD 6.2) years **Type of study:** randomised, controlled	**Study aim:** to compare the physiological effects of vibration to other physiotherapy interventions used for airway clearance and relate these effects to the proposed mechanisms of secretion clearance. **Population:** individuals diagnosed with cystic fibrosis. Six (33%) had severe lung disease; eight (44%) had moderate lung disease; one (6%) had mild lung disease; and three (17%) had normal lung function. **OPEP:** Flutter; Acapella **Comparator(s)**: PEP. **Included outcome measures:** inspiratory and expiratory flow rates; participant perceived breathing effort (Borg scale for breathlessness); number of spontaneous coughs.	Study was small power calculation sample size was met. Relatively high risk of bias.

Results

There was no significant difference in the number of coughs stimulated between interventions. There were no reported adverse events during the study.

The authors conclude that these results suggest that stimulation of a cough is not a mechanism by which these physiotherapy interventions may aid secretion clearance.

Intervention	Coughs stimulated, mean (SD)
Vibration	0.7 (1.0)
Percussion	0.5 (0.9)
PEP	0.5 (0.6)
Flutter	0.4 (0.7)
Acapella	0.8 (1.0)

Table 4. Silva et al. (2017)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 40 **Country:** Australia **Mean participant age:** 63 (SD 16) years **Type of study:** randomised, controlled **Recruitment period**: March 2013 – July 2014	**Study aim:** to compare the efficacy of sputum expectoration and acceptability of Flutter and Lung Flute in adults with stable, productive bronchiectasis. **Population:** adults >18 years with stable bronchiectasis and productive of >25 mL of sputum/day attending an outpatient clinic. **OPEP:** Flutter **Comparator(s)**: Lung Flute (OPEP). **Included outcome measures:** expectorated sputum (wet and dry); acceptability and tolerability (Likert scale).	Power calculation sample size was met. Participants were requirement to meet a threshold of daily sputum production for inclusion. Unclear risk of bias.

Results

The mean weight of sputum expectorated while using the devices (T1 wet sputum weight) was significantly greater with the Flutter compared with the Lung Flute. However, the mean sputum expectorated 30 min after completion of using the devices (T2 wet sputum weight) was significantly greater with the Lung Flute compared with the Flutter. Overall, there was no significant difference in the total wet sputum weight and dry sputum weight for sputum cleared using either device.

Outcome	Flutter (mean (SD))	Lung flute (mean (SD))	Mean difference (95% CI)	p-value
Sputum weight: wet, during intervention (g)	5.10 (6.26)	3.74 (3.44)	-1.36 (-3.0 to 0.2)	p=0.038
Sputum weight: wet, 30 minutes from end of intervention (g)	0.68 (0.75)	2.02 (3.01)	1.34 (0.5 to 2.2)	p<0.001
Sputum weight: wet, total (g)	5.78 (6.47)	5.75 (0.22)	-0.03 (-1.8 to 1.8)	p=0.91
Sputum weight: dry, total (g)	0.40 (0.86)	0.22 (0.21)	0.18 (-0.5 to 0.1)	p=0.76

The subjects perceived Flutter to be significantly more useful for clearing secretions, easy to understand, and simple to use (Fig. 4). The Flutter tended to be less tiring and embarrassing to use compared with the Lung Flute; however, this was not significant. Both devices were perceived as time consuming, uncomfortable to use, and interfering with everyday life (Fig. 4). At the completion of the study, in response to a specific enquiry regarding preference, 25 preferred the Flutter, 4 preferred the Lung Flute, and 11 were non-committal.

Outcome: Likert scale	Findings
Assists with secretions	p=0.01 (favours Flutter)
Easy to understand	p=0.03 (favours Flutter)
Simple to use	p=0.01 (favours Flutter)

Tiring	p=0.10
Uncomfortable to use	p=0.94
Time consuming	p=0.57
Interferes with everyday life	p=0.60
Causes embarrassment	p=0.31

Table 5. Valente et al. (2004)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 8 **Country:** Brazil **Participant age range:** 16-73 years **Type of study:** observational, cohort **Recruitment period**: NR	**Study aim:** to explore whether Flutter alters properties related to the transport of tracheobronchial mucus. **Population:** outpatients with stable bronchiectasis with daily expectoration of >1 tablespoon of yellowish sputum. **OPEP:** Flutter **Comparator(s)**: PEP (Flutter device with orifices of protective cover closed). **Included outcome measures:** relative transport velocity; contact angle; sputum displacement during simulated cough machine.	Pilot study to obtain sample size for future study. Convenience sampling was used to identify participants. Very small sample.
Results		
A larger displacement of sputum during use of the simulated cough machine was seen after Flutter (114 mm to 146 mm) compared to after PEP (118 mm to 138 mm). It is not reported whether this was a statistically significant difference.		

Table 6. Gastaldi et al. (2015)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 15 **Country:** Brazil **Participant mean age:** 67.3 years **Type of study:** randomised, controlled **Recruitment period**: January-August 2013	**Study aim:** to determine the effect of 30 minutes of breathing exercises with a Flutter device on airways resistance and small airways function. **Population:** patients with COPD. **OPEP:** Flutter **Comparator(s)**: sham OPEP (Flutter without stainless steel ball); Flutter + bronchodilator. **Included outcome measures:** impulse oscillometry; exhaled nitric oxide; spirometry; cough and secretions.	Small sample but sample size calculation met. Unclear risk of bias.

Results

There were no significant differences compared to baseline values immediately after flutter exercises, flutter exercises with bronchodilator, or after flutter-sham intervention in FVC, FEV1, FEV1/FVC or medium expiratory flow (MEF(25-75)).
The COPD patients had significantly greater volumes of secretions with the flutter exercises compared to the flutter-sham intervention. There were also more spontaneous coughs recorded in the COPD patients during flutter exercise and flutter with bronchodilator than during flutter-sham intervention. There were no differences among purulence score.

Outcome	Flutter (mean (SD))	Flutter + bronchodilator (mean (SD))	Sham OPEP (mean (SD))	Finding
Secretion volume (g)	2.54 (1.39)	NR	1.5 (1.33)	$p<0.05$
Spontaneous coughs	3.95	3.63	1.69	NR
Purulence score	2.30 (0.82)	2.60 (1.34)	2.57 (0.79)	No difference

Table 7. Milan et al. (2019)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 91 **Country:** US **Participant mean age (SD):** 63.9 (11.5) years **Type of study:** randomised, controlled **Recruitment period**: October 2013 – October 2015	**Study aim:** to determine the effectiveness of a PEP device, with or without oscillatory mechanism, followed by 'huff coughs' in reducing hospital length of stay among individuals requiring hospitalisation for acute exacerbation of COPD. **Population:** patients aged >18 years with primary admission diagnosis of acute exacerbation of COPD, with sputum production of >1 tablespoon (15 mL) per day for at least 2 days. **OPEP:** Acapella + standard COPD management. **Comparator(s)**: sham OPEP (without oscillatory mechanism) + standard COPD management **Included outcome measures:** hospital length of stay; change in dyspnoea score to discharge or day 5; change in sputum volume to discharge or admission.	Included both an RCT and cohort study (latter not included as did not distinguish between OPEP and PEP). Focuses on patients with acute exacerbation requiring hospitalisation. Unclear risk of bias.

Results

Mean MMRC scores from day 1 to day 5 of hospitalization were similar among the PEP and OPEP groups although there was a trend toward greater improvement/lower scores in the PEP group over the initial 5 days of hospitalization compared with the OPEP group. The mean change in MMRC among all participants was not different among the groups.
Sputum production was less in the PEP group compared with the OPEP group during each day of the initial 5 days of hospitalization.
Self-reported compliance of device usage was 95% for both groups.

Outcome	OPEP	PEP	Finding
Subjective dyspnoea (MMRC scale), days 1 – 5 of hospitalisation	NR	NR	p=0.07
Sputum production	NR	NR	p<0.05
Device compliance (self-reported)	95%	95%	No difference

Table 8. Nicolini et al. (2018)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 120 **Country:** Italy **Participant mean age:** NR **Type of study:** RCT **Recruitment period**: January 2014 – June 2015	**Study aim:** to evaluate the effectiveness of two similar PEP techniques to reduce exacerbations and improve respiratory function parameters and dyspnoea and health status assessment tests in severe to very severe COPD. **Population:** patients aged ≥35 years with severe to very severe COPD (based on GOLD stage 3-4 group C-D assessment tool). Patients with exacerbation or hospitalisation of COPD within 8 weeks of recruitment were excluded. **OPEP:** Lung Flute. **Comparator(s)**: T-PEP and pharmacological therapy alone **Included outcome measures:** acceptance (Likert scale); exercise capacity (6MWT) respiratory measures (dyspnoea, cough and sputum scales) (BCSS scale, COPD Assessment Test, and MMRC Dyspnoea scale); health status assessment evaluations; respiratory function (FVC, FEV1, FEV1/FVC, total lung capacity TLC, residual volume RV, diffusing lung capacity monoxide DLCO, maximal inspiratory pressure MIP, maximal expiratory pressure MEP); arterial blood gas analysis; haematological parameters.	Only patients with severe or very severe COPD aged 35+ years. Relatively low risk of bias.

Results

Exacerbations

There was no significant difference in exacerbations between OPEP and either T-PEP or control.

There was a significant difference between OPEP and pharmacological therapy alone for lung function variables: change in total lung capacity; % change in total lung capacity; change in residual volume; and % change in residual volume. There was no significant difference in change in FVC; % change in FVC; change in FEV1; % change in FEV1; change in FEV1/FVC; change in diffusing lung capacity monoxide; change in MIP, change in MEP.

There was a significant difference in change in 6 minute walk test score, MMRC dyspnoea scale, and COPD Assessment Test scale between OPEP and control. There was no significant difference in change in Breathlessness Cough Sputum score between OPEP and control.

There were no significant differences in any change in lung function variable, 6 minute walk test score, MMRC dyspnoea scale, COPD Assessment Test scale; or Breathlessness Cough Sputum score between OPEP and T-PEP.

Both OPEP and T-PEP were accepted by patients (p=0.33).

Outcome	OPEP	T-PEP	Control	Finding
Exacerbations at 1 month	4	2	8	OPEP vs T-PEP: p=0.07; OPEP vs control: p=0.10
Exacerbations at 2 months	8	3	10	OPEP vs T-PEP: p=0.10; OPEP vs control: p=0.09

Exacerbations at 3 months	9	7	11	OPEP vs T-PEP: p=0.12; OPEP vs control: p=0.10
FVC change (mL)	417	499	372	OPEP vs T-PEP: p=0.22; OPEP vs control: p=0.18
FVC% change	11.5	15.3	13.1	OPEP vs T-PEP: p=0.24; OPEP vs control: p=0.18
FEV1 change (L)	184	163	161	OPEP vs T-PEP: p=0.18; OPEP vs control: p=0.14
FEV1% change	7.4	7.3	7.1	OPEP vs T-PEP: p=0.22; OPEP vs control: p=0.18
FEV1/FVC change	1.9	4.1	0.3	OPEP vs T-PEP: p=0.20; OPEP vs control: p=0.26
TLC change (L)	-831	-949	-684	OPEP vs T-PEP: p=0.14; OPEP vs control: p=0.02*
TLC% change	-13.6	-13.9	-11.7	OPEP vs T-PEP: p=0.26; OPEP vs control: p=0.04*
RV change (L)	-1207	-1020	-726	OPEP vs T-PEP: p=0.30; OPEP vs control: p=0.04*
RV% change	-30.4	-32.2	-21.7	OPEP vs T-PEP: p=0.18; OPEP vs control: p=0.02*
DLCO% change	3.9	4.0	3.2	OPEP vs T-PEP: p=0.68; OPEP vs control: p=0.20
MIP change (kpa)	2.0	1.7	1.6	OPEP vs T-PEP: p=0.84; OPEP vs control: p=0.40
MEP change (kpa)	2.3	2.3	2.2	OPEP vs T-PEP: p=0.36; OPEP vs control: p=0.24
6 minute walk test change (mt)	11.5	18.4	-4.8	OPEP vs T-PEP: p=0.34; OPEP vs control: p=0.01*
MMRC dyspnoea scale change	-0.4	-0.6	0.1	OPEP vs T-PEP: p=0.16; OPEP vs control: p=0.012*
COPD Assessment Test scale change	-6.4	-7.5	-1.6	OPEP vs T-PEP: p=0.14; OPEP vs control: p=0.008*
Breathlessness Cough Sputum score change	-3.1	-2.9	-3.5	OPEP vs T-PEP: p=0.24; OPEP vs control: p=0.22
Acceptance Likert scale 1-7	4274-5275	4729-5270	NA	OPEP vs T-PEP: p=0.33

Table 9. Tse et al. (2020)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 5,029 **Country:** USA **Participant mean age:** 72.4 (SD 11.1) & 72.2 (11.2) years **Type of study:** Retrospective cohort **Study period:** 2012-2019	**Study aim:** to compare healthcare resource use and severe disease exacerbations at 30 days and 12 months post-discharge in patients with COPD or chronic bronchitis treated with two of the most commonly used OPEP devices in the hospital setting. **Population:** patients with COPD or chronic bronchitis. **OPEP:** Aerobika and Acapella. **Included outcome measures:** severe exacerbations; moderate exacerbations; all cause health resource use; inpatient visits; emergency department visits; outpatient/physician office visits	Undertook multivariable analysis.

Results

In the univariate model, Acapella had significantly more patients with severe exacerbations within 30 days, and within 12 months, post-discharge than Aerobika and the mean numbers of severe exacerbations per patient were significantly higher. There was no significant difference in moderate exacerbation, with the exception of mean number per patient at 12 month. Mean length of stay per patient hospitalised with severe exacerbation was significantly longer for Acapella. There was no difference in the mean time to severe exacerbation.
Significantly more patients had one or more inpatient visit within 30 days, and within 12 month, with Acapella than Aerobika and the mean number of visits was higher. There was no difference in the mean length of stay, mean number of emergency department or outpatient/physician office visits, or number of patients with an emergency department or outpatient/physician office visit.

In the adjusted model, the odds of severe exacerbation post-discharge were significantly lower with Aerobika compared to Acapella (OR 0.80 95% CI 0.66 to 0.98; p=0.03).

Outcome	Aerobika	Acapella	p-value
Severe exacerbations			
Patients with >1 severe exacerbations at 30 days post-discharge, n (%)	68 (12.0%)	306 (17.4%)	p=0.001
Mean number of severe exacerbations per patient at 30 days post-discharge (SD)	0.1 (0.4)	0.2 (0.5)	p=0.02
Patients with >1 severe exacerbations at 12 months post-discharge, n (%)	245 (39.6%)	841 (45.3%)	p=0.01
Mean number of severe exacerbations per patient at 12 months post-discharge (SD)	0.7 (1.3)	0.9 (1.4)	p=0.01
Mean time to severe exacerbation, days (SD)	102.0 (97.5)	96.6 (97.8)	p=0.44
Mean length of stay per patient hospitalised (SD)	6.5 (3.9)	7.1 (5.4)	p=0.05
Moderate exacerbations			
Patients with >1 moderate exacerbations at 30 days post-discharge, n (%)	76 (12.3)	245 (13.2)	p=0.58
Mean number of moderate exacerbations per patient at 30 days post-discharge (SD)	0.2 (0.5)	0.2 (0.6)	p=0.37

Patients with >1 moderate exacerbations at 12 months post-discharge, n (%)	254 (41.0)	762 (41.0)	p=0.98
Mean number of moderate exacerbations per patient at 12 months post-discharge (SD)	1.0 (1.8)	1.2 (3.2)	p=0.03
Healthcare resource use			
Patients with ≥1 inpatient visit within 30 days	79 (13.9)	358 (20.3)	p<0.001
Patients with ≥1 inpatient visit within 12 months	278 (44.9)	962 (51.8)	p=0.003
Number of inpatient visits within 30 days per patient (SD)	0.16 (0.4)	0.24 (0.5)	p=0.001
Number of inpatient visits within 12 months per patient (SD)	0.9 (1.4)	1.1 (1.6)	p=0.003
Length of stay per patient with inpatient visit within 12 months (SD)	7.5 (4.9)	8.3 (7.2)	p=0.28
Patients with ≥1 ED visit	381 (61.6)	1113 (59.9)	p=0.45
Number of ED visits per patient (SD)	1.8 (2.5)	1.9 (4.4)	p=0.52
Patients with ≥1 outpatient/physician's office visit	575 (92.9)	1739 (93.6)	p=0.50
Number of outpatient/physician's office visits per patient (SD)	20.5 (22.5)	21.2 (22.1)	p=0.51

Table 10. Bellone et al. (2000)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 10 **Country:** Italy **Participant mean age:** 57.5 (SD 6) years **Type of study:** RCT **Recruitment period**: NR	**Study aim:** to compare the short-term effects for improved secretion removal of three different techniques with regard to oxygen saturation, pulmonary function, and sputum production during an acute exacerbation of chronic bronchitis. **Population:** patients with a history of chronic bronchitis for at least 3 consecutive months for the last 2 years, producing >30 mL sputum per day, affected by an acute exacerbation. **OPEP:** Flutter. **Comparator(s)**: slow expiration with the glottis open in lateral position (ELTGOL) or postural drainage. **Included outcome measures:** arterial oxygen saturation; forced expiratory volume in 1 second (FEV1) as a percentage of predicted value.	Patients had chronic bronchitis with an acute exacerbation. Very small study. Each patient received all three treatments in random order. High risk of bias.
Results		
All techniques were well tolerated. There was no significant difference in FEV1 between treatments, during treatment and up to 1 hour after. Sputum production increased significantly with all three treatments at 30 minutes after beginning treatment and 1 hour after the end of treatment.		

Table 11. Ni et al. (2018)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 27 **Country:** China **Participant mean age:** 73 (SD 11) and 68 (SD 14) years for intervention and control respectively **Type of study:** retrospective cohort study **Recruitment period**: February 2016 – July 2017	**Study aim:** to evaluate the effectiveness of OPEP in patients with lower respiratory tract infection in a respiratory intensive care unit. **Population:** patients diagnosed with lower respiratory tract infection (pneumonia, acute bronchitis, acute bronchiolitis, unspecified acute lower respiratory tract infection, bronchitis not specified as acute or chronic, influenza, other COPD with acute lower respiratory tract infection/acute exacerbation, whooping cough, Legionnaires disease, or Chlamydia psittaci infection. **OPEP:** Acapella (≥ 5 times per day, for at least 5 minutes) **Comparator(s)**: mechanical percussion (10 minutes, 4 times per day) **Included outcome measures:** daily sputum quantity and purulence, arterial blood gas analysis, O2 index, hospitalisation, mortality, use of mechanical ventilation, LOS in hospital.	Small cohort study 52% had severe pneumonia; 22% had acute exacerbation of COPD; 7% had bronchiectasis

Results

Sputum

On day 7, the sputum quantity of the OPEP group was significantly smaller compared with the MP group (P=0.001). Sputum purulence 7 days after CPT slightly improved in both groups. After 7 days of CPT, the oxygenation index of patients in the OPEP group increased from 223±86 to 322±89 (P=0.003), while that of the MP group, which had a similar level of oxygenation index at baseline, only increased to 299±117 (P=0.053). There was no difference in the duration of hospital stay, the rate of mortality in hospital, the duration of stay in intensive care among survivors or the length of hospitalization among survivors between the two groups.

Outcome	OPEP	MP	Finding
Sputum quantity at day 7 after chest physiotherapy	NR	NR	Significantly lower in OPEP group (p=0.001)
Sputum purulence at day 7 after chest physiotherapy	NR	NR	Improved in both groups
Duration of chest physiotherapy (days)	8 (SD 1)	7 (SD 1)	p=0.069
Hospital length of stay (days)	24 (SD 13)	19 (SD 8)	p=0.220
Hospital length of stay among survivors	23 (SD 12)	22 (SD 8)	p=0.220
In-hospital rate of mortality	1	0	p=0.370
Intensive care unit rate of mortality	1	0	p=0.370
Duration of stay in intensive care among survivors (days)	25 (SD 13)	20 (8)	p=0.209

Table 12. Felicio-Junior et al. (2020)

Included studies	Inclusion criteria	Quality and other observations
Total number of patients: 33 **Country:** Brazil **Participant age:** range 7 – 18 years **Type of study:** RCT **Recruitment period:** January 2016 – July 2018	**Study aim:** to analyse the efficiency of physiotherapy techniques in sputum induction and in the evaluation of pulmonary inflammation in asthmatic children and adolescents. **Population:** children and adolescents with asthma. **OPEP:** OPEP (device not reported) with forced expiration and acceleration of expiratory flow **Comparator(s)**: 3% hypertonic saline or hypertonic saline with OPEP, forced expiration, and acceleration of expiratory flow. **Included outcome measures:** spirometry; sputum induction.	Limited details available

Results

Pulmonary function
There was no significant difference between groups in FEV1, PEF or FEV1/FVC.

Sputum induction

Outcome	Hypertonic saline	OPEP	Hypertonic saline + OPEP	p-value
Sputum induction time (min), median (IQR)	14 (7-21)	10 (10-10)	17 (17-17)	p=0.001 (comparing HS+OPEP to HS and OPEP
Sputum weight (g), median (IQR)	0.37 (0.19-0.40)	0.36 (0.24-0.44)	0.41 (0.37-0.46)	p=0.020 (comparing HS+OPEP to HS

Appendix 7. Summary of included health economic studies

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Thanh et al. (2019a) **Country:** Canada **Type of economic analysis:** Cost-utility analysis using Markov model and published inputs **Perspective**: Canadian (Alberta) healthcare system perspective **Currency**: Canadian dollars (Can $) **Price year:** 2017 **Time horizon:** One year **Discounting:** Not performed because of short time horizon. **Source of funding:** Trudell Medical International (TMI) provided a grant for this study. **Potential conflict of interest:** The following COIs are	**Population**: COPD population who had recently experienced an exacerbation **Strategies considered:** 1) Aerobika device 2) No Aerobika device **Study design:** A similar Markov model from Khoudigian-Sinani et al. (2017) was used. Patients entered the model in a no-exacerbation health state. Based on one month cycles, 3 health states were considered (death, exacerbation (moderate or severe), or no exacerbation. If the patient experiences a moderate or severe exacerbation, within a month he/she could either die or revert to the no-exacerbation health state. A moderate exacerbation was defined as an emergency room (ER) visit by the patient, with no hospital admission. A severe exacerbation is defined as a patient's admission to hospital. Mild exacerbation did not require any ER visit nor hospital admission, so it was treated as no exacerbation in the model.	**Source of baseline and effectiveness data:** Model inputs were derived from the literature. No information was given on searches performed. The observational study by Burudpakdee et al. (2017) and economic analysis by Khoudigian-Sinani et al. (2017) were used to inform transition probabilities and the RR of exacerbations (based on severity) in the first month. It was assumed that there was a relative risk of 1 from month 2-12 for moderate- severe exacerbations (i.e.no further improvement in exacerbation using the Aerobika device after the first month. The probability of dying from a severe exacerbation was taken from two papers of hospitalised COPD patients (Celli 2010, Connors et al. 1996) with probability of dying with moderate/mild exacerbations based on previous studies (Anthonisen et al. 2005, Sin et al. 2005). Utility values were estimated using data from Trudell Medical International, Alberta Health Services (2018) and a published study (Anthonisen et al. 2005). Scores were calculated for COPD severity based on published Dutch severity distributions	**<u>Base case</u>** **Total costs** Aerobika: $8,141.56 No OPEP/PEP: $8,835.71 Difference: - $694.15 **QALYs** Aerobika: 0.57 No OPEP/PEP: 0.53 Difference: 0.04 **ICER** **Aerobika was the dominant strategy** **<u>OWSA</u>** The ICER was sensitive to variations in changes to costs and effects. The largest range in incremental cost was from -$2,180 to +$795 (mean -$694), meaning that the use of the Aerobika device would result in a range from $2,180 in reduced cost to an increase in $795. The largest range in the incremental outcome effect was from a reduction of 0.016 of a QALY to an increase of 0.087 (mean + 0.04). The most sensitive variable was the probability of a severe exacerbation in patients with no PEP/OPEP therapy. The second most sensitive variable was the probability of a severe exacerbation among patients	**Applicability**: Analysis was deemed to be not directly applicable as it did not consider a UK NHS perspective. There was insufficient information on the patient population (e.g. age, sex) to assess whether this is representative of a COPD population in Wales. The alternative strategies considered (e.g. other OPEP/PEP devices used) may not be reflective of treatment options/standard of care in NHS Wales/UK NHS settings. **Limitations:** The economic analysis was generally considered to be of high quality but some potentially serious limitations were identified. The time horizon is limited to a one year which would not capture the longer-term cost-effectiveness in a chronic condition population. However, given the quality of evidence available, a limited time horizon may be deemed appropriate until further evidence of longer term effectiveness is available. Data was taken from a hospitalised population of COPD patients therefore may only represent a sub-population. Whilst utilities are well documented, the lack of reporting of a systematic search and selection strategy and the

Study details	Study population and design	Data sources	Results	Quality assessment
declared by the authors: Jacobs received a grant from TMI and attended a paid workshop. Suggett was employed by TMI. McIvor received honoraria, attended advisory board, and participated in clinical trials related to TMI and other companies. Kaplan is a member of the advisory board and speaker fees from TMI and other companies.	**Analysis** The base case analysis was incremental cost per QALY gain over 1 year. Deterministic (one way), scenario (assumed impact of Aerobika on exacerbations remained for 1 year) and probabilistic sensitivity analyses (SAs) were undertaken.	(Hoogendoorn et al. 2006). Utility decrements for a month with severe or moderate exacerbations were estimated by multiplying the utility decrements per year from Rutten-van Mölken et al. (2009) with 12 as used by Samyshkin et al. (2013). Utility values used are reported. **Source of resource use and cost data:** Costs were estimated from Alberta Health Services (AHS) data and included: • **Moderate exacerbations** ER costs and emergency doctor fees. • **Severe exacerbations** ER visit that precedes the hospital admission, hospital costs, emergency doctor fees, and attending respirologist fees. The cost for a severe exacerbation was based on the average length of stay in hospital which was estimated at 9.3 days from AHS data. • **No exacerbation** Outpatient follow-up, physician visits and drugs (antibiotics and corticosteroids) from AHS cost data and Dhamane et al. (2015) • **Intervention cost** The cost of the Aerobika device that was used was $90 per patient per year (TMI data).	using the Aerobika device. **<u>Scenario analysis</u>** With exacerbations with Aerobika remaining the same (RR 0.72) for 1 year. **Costs** Aerobika= $6,712.19 No OPEP/PEP= $8,835.71 Difference -$2,123.52 **QALYs** Aerobika= 0.63 No OPEP/PEP=0.53 Difference= 0.1 ICER Aerobika remains the dominant strategy. **Probabilistic Sensitivity Analysis** The probability for the Aerobika device to be the dominant strategy was 72.2%. The probability for the Aerobika device to be cost-effective at Willingness to Pay (WTP threshold of $50,00 per QALY gained was 76.8%. The probability for the Aerobika device to be dominated was 20.8%. Due to the positive associations between the number of exacerbations and costs, and between the number of exacerbations and utility decrements, the Aerobika device	use of company data may bias the results. Some difference between US and Canadian health care systems (e.g. readmissions) have been accounted for in SA but the applicability of data inputs from the US may limit the findings. Patient tolerance/adherence to using Aerobika has not been considered. Adverse events associated with the use of Aerobika device were not included and only exacerbation-related costs of COPD were considered. This may underestimate the downstream costs and consequences associated with the use of the Aerobika device compared to relevant alternative strategies in the management of COPD. The study acknowledged the use of assumed +/-20% of base case for SA may not represent 95% CIs of parameters.

Study details	Study population and design	Data sources	Results	Quality assessment
		All costs were converted to 2017 Canadian dollars using the Bank of Canada general price index inflation calculator.	was (mostly) either dominant or dominated, reflecting that if it did not prevent exacerbations, it would be dominated it would mean more costs and more utility decrements.	
Author and year: Khoudigian-Sinani et al. (2017) **Country** USA **Type of economic analysis** Cost Effectiveness Analysis (CEA) using Markov model with inputs from published data and a real world effectiveness study. **Perspective**: US commercial payer **Currency**: US dollars (US $) **Price year:** 2016 **Time horizon:** One year **Discounting:** Not examined (not applicable as time horizon <12 months) **Source of funding:** Trudell Medical International	**Population**: The population was COPD patients who experienced an exacerbation in the previous month, or a post-exacerbation care population. **Strategies considered:** 1) Aerobika device 2) Standard of Care (no OPEP/PEP therapy) **Study design:** De Novo decision analytic model (Markov model). The Markov model consisted of three health states: (i) no exacerbation, (ii) exacerbation, and (iii) death (Figure 1). Patients with COPD entered the model in the no-exacerbation health state, and based on published probabilities, they could experience an exacerbation, stay in the same health state, or die. The Markov model used monthly cycles. **Analysis** The base case was incremental cost per exacerbations avoided per 100 patients per year.	**Source of baseline and effectiveness data:** Targeted literature searches were undertaken to obtain data inputs for transition probabilities and relative risks for exacerbation of COPD in first month/after first month. All sources of evidence were referenced. **Key evidence sources included:** An observational (real-world effectiveness) study (Burudpakdee et al. 2017) was used to inform the effectiveness (transition probabilities and relative risk) for the Aerobika device. A real world evidence study (Pasquale et al. 2012) of patients with a diagnosis of COPD (in a large US claims database (Medicare) was used to derive the probability of experiencing an exacerbation in the post-exacerbation care population. Mortality estimates were derived from 2016 US Census data estimates for the general US population. **Source of resource use and cost data:** Published sources were used to	**Base case analysis** (*based on 30-day post-exacerbation care population, as compared to the population without any PEP or OPEP therapies*) **Costs:** Aerobika device: $7,829 No OPEP/PEP: $8,382 Difference: -$553 per patient (in favour of Aerobika) **Effectiveness (number of exacerbations per patient):** Aerobika device: 0.77 No OPEP/PEP: 0.83 Difference: -0.06 (six per 100 patients) exacerbations avoided **ICER** Aerobika is the **dominant strategy** (i.e. less expensive and more effective) **OWSA** Overall, the base case finding remained robust to parameter variation with Aerobika remaining the dominant strategy in most analysis: With a 20% increase in benefit of Aerobika in first month (RR of exacerbation reduced from 0.72 to 0.58), the cost saving	**Applicability**: Analysis was considered to have limited applicability to the UK/Wales NHS due to: i) The perspective taken was not applicable to the UK NHS. ii) There was insufficient information on the patient population (e.g. age, sex) to assess whether this is representative of a COPD population in Wales. Definitions of exacerbation severity were poorly described. iii) The alternative strategies considered (e.g. other OPEP/PEP devices used) may not be reflective of treatment options/standard of care in NHS Wales/UK NHS settings. iv) Data on health outcomes (e.g. QALYs) were not considered in the study and no cost-utility analysis performed. **Limitations:** The reporting of the economic analysis was of reasonable quality against international standards but some potentially serious limitations exist (Husereau et al. 2013). The time horizon is limited to one year

Study details	Study population and design	Data sources	Results	Quality assessment
Potential conflict of interest: Khoudigian- Sidani and Kowa are employees of Quintiles IMS who received funding from Trudell Medical International to conduct study and develop paper. No other COIs are declared by the authors.	The unit of effect for the CEA was frequency of exacerbations per 100 patients per year. Deterministic sensitivity analyses were undertaken including one way sensitivity analysis (OWSA) (+/-20% around input parameters parameters) and scenario analysis testing the model's sensitivity to alternative efficacy assumptions for the device	estimate direct medical costs for each COPD health state based on Medicare populations and the real world effectiveness study. Resource use included pharmacy claims for COPD related medications, physician visits and re-hospitalisations during the first month of experiencing an exacerbation in addition to health care resources related to visiting the emergency department or hospital admission for the exacerbation itself. Unit costs were taken from US representative public sources including Medicare and Medicaid physician fee schedules, Cleveland clinic costs and Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) database. Medication unit costs were taken from Medispan based on product prescribing information. The health care resource use associated with treating an exacerbation was calculated based on and accounted for the site of care. The proportion of COPD patients with moderate-to-severe exacerbations were separated into mutually exclusive groups based on Burudpakdee et al. (2017) COPD patients with moderate	increased to $858 per patient and clinical benefit was estimated to be nine fewer exacerbations per 100 patients per year compared with the control cohort and the clinical benefit. When the benefit was reduced by 20% (RR of exacerbation increased to 0.86), cost savings were $261 with three exacerbations avoided per 100 patients per year as compared to patients with no PEP or OPEP therapy. When the benefit of the Aerobika device after the first month (months 2 to 12) was increased by 20% (RR exacerbations reduced to 0.8), cost saving increased to $1,546 per patient and clinical benefit improved by 17 fewer exacerbations per 100 patients per year. When the RR of exacerbation with the Aerobika device after the first month was increased by 20% (RR exacerbations increased to 1.2), an overall additional cost of $408 per patient and four additional exacerbations per 100 patients per year were estimated. The authors state this is unlikely as no data suggests Aerobika would lead to an increased exacerbation risk. **Scenario Analysis (using a constant average annual**	which would not capture the longer-term cost-effectiveness in a chronic condition population. However, given the quality of evidence available, a limited time horizon may be deemed appropriate until further evidence of longer term effectiveness is available. A key assumption made is Aerobika's effectiveness in avoiding an exacerbation in the first month would continue (at a similar effect) past this time period. The plausibility of this assumption would need further evidence to validate any longer-term extrapolation. The model did not account for mortality based on severity of exacerbation. As this is a significant driver of resource use and outcome in COPD populations, this could underestimate costs/outcomes. Patient tolerance/adherence to using Aerobika has not been considered. The population included only COPD patients with subsequent exacerbations who would have had an ED visit or had been readmitted to hospital, as only those patients would appear in the claims database used. Thus, these findings may only be applicable to a specific sub-group of COPD patients. Adverse events associated with the use of Aerobika device were not included and only exacerbation-related costs of COPD were considered.

Study details	Study population and design	Data sources	Results	Quality assessment
		exacerbations were assumed to have an ER visit, whereas COPD patients with severe exacerbations were assumed to be admitted to a hospital for appropriate treatment. All costs were reported in 2016 US dollars, and where appropriate, inflated to 2016 US dollars using the medical care services component of the consumer price index.	**monthly RR of exacerbation applied throughout the year):** **Costs:** Aerobika = $6,430 No OPEP/PEP = $8,352 Difference: -$1,952 **Outcome** Aerobika = 0.62 No OPEP/PEP = 0.83 Difference: 0.21 Aerobika remains the dominant strategy.	This may underestimate the downstream costs and consequences associated with the use of the Aerobika device compared to relevant alternative strategies in the management of COPD. The plausibility of the findings based on varying parameters could be challenged in the OWSA and further analysis based on precise evidence of benefit (e.g. lower/upper Confidence Intervals) would add confidence to these estimations given the recognised impact of key factors (proportion of severe exacerbations, probability of experiencing exacerbation in the first month and after the first month, and the provability of dying) affecting cost-effectiveness findings. No probabilistic sensitivity analysis was undertaken to assess the impact of joint uncertainty around costs/outcomes.
RCT: randomised controlled trial; SD: standard deviation; OPEP: oscillating positive expiratory pressure; PEP: positive expiratory pressure				

Appendix 8: Patient Submission from Cystic Fibrosis Trust

The views expressed in this submission are those of the Cystic Fibrosis Trust

Patient/Carer Group Submission Form

General Information

HTW appraisal topic	Oscillating positive expiratory pressure
Name of patient/carer group	Cystic Fibrosis Trust
Health/medical conditions represented	Cystic Fibrosis
Date of submission	30th October 2020

Health conditions and technology

1. Describe any sources you used to gather information for this submission

This submission draws on data from the following resources:

- Results from a widespread survey the Cystic Fibrosis Trust ran between March and April 2020, to gain insight into life with cystic fibrosis by those whose lives are affected by cystic fibrosis: people with the condition, families, partners, and friends (n=645).
- Data from the UK Cystic Fibrosis Registry consisting of data from 99% of people with cystic fibrosis in the UK, which is hosted and managed by the Cystic Fibrosis Trust.
- In October 2020, we also surveyed people whose lives are affected by cystic fibrosis (n=14) to gain insight on the use of OPEP as a treatment particularly for this submission.

2. What is the health condition and how does it affect the day-to-day lives of patients and their carers?

Cystic fibrosis is a genetic, life-limiting condition affecting more than 10,500 people in the UK. A wide range of progressive symptoms and co-morbidities affect multiple organs in the body and require a rigorous and burdensome medicine and physiotherapy management regime.

Living with cystic fibrosis is to live with physical and social restrictions, a rigorous medical regimen, concerns about illness and death, and uncertainties about the future. Cystic fibrosis is a progressive, life-shortening disease where respiratory symptoms of cough and shortness of breath become more severe and harder to manage with age. Data from the UK Cystic Fibrosis Registry shows that, last year, the median age at death in the UK was only 32, with the primary cause of mortality being respiratory failure. Lung infection, damage, and reduced lung capacity make it difficult to breathe and move around. Shortness of breath can affect the simplest of everyday tasks like climbing a flight of stairs and walking around your home. For many people, breathlessness also leads to experiences of panic. Progressive lung damage causes respiratory failure in cystic fibrosis leading to death or necessitating lung transplant to prolong life. Cystic fibrosis is unpredictable, and symptoms and disease

severity fluctuate. This unpredictability disrupts everyday life, making it difficult to plan anything in advance –from a day out to planning a career.

3. How is the health condition currently diagnosed and/or treated?

Cystic Fibrosis is usually diagnosed at birth through newborn screening. Newborn screening for cystic fibrosis has been done routinely in the whole of the UK since mid-2007 as part of the heel prick blood spot with testing done at 5-7 days of age. This means that more babies born after 2007 receive an early diagnosis than those born before, when diagnosis was made on the basis of clinical presentation. The latest data from the UK Cystic Fibrosis Registry shows that the median age at diagnosis for patients aged under 16 in 2019 was 22 days and a total of 137 (71.0%) out of 193 patients born in 2019 were identified by newborn screening. However, for some people diagnosis is made much later in life. 887 (14.9%) adults with cystic fibrosis in the UK Cystic Fibrosis Registry in 2019 were diagnosed at age 16 or over. In 2019, 28 people aged 16 or over were newly diagnosed with cystic fibrosis.

There is currently no cure for cystic fibrosis, but treatments can help to manage the symptoms of the disease by preventing further decline and improving quality of life. Symptoms can vary and treatment plans will be individualised. Our survey into life with cystic fibrosis further showed that people with cystic fibrosis face a heavy burden of care consisting of physiotherapy, exercise, nebulisers and antibiotics. People with cystic fibrosis (and their carers where applicable) spend an average of three to five hours administering standard maintenance therapy per day. Current treatments to address the symptoms of cystic fibrosis are time-consuming, intrusive, and indiscrete but are necessary to stay well for as long as possible. Most people with cystic fibrosis experience additional periods of acute ill health referred to as exacerbations which can lead to permanent lung damage. During an exacerbation the amount of therapy and care burden increases, meaning day to day life must be put on hold. As cystic fibrosis is progressive, the number and severity of exacerbations increases with time, meaning the more unwell a person with cystic fibrosis becomes, the more treatments they will be on – increasing this heavy burden of care even further.

4. What do patients and carers expect from the health technology?

Chest physiotherapy uses airway clearance techniques to help clear excess thick sticky mucus from the lungs. It is important to try and clear these secretions because a build-up of mucus can increase the problems with infection and inflammation. Secretions can also block the smaller airways, resulting in the lungs not being able to work effectively. People with cystic fibrosis and their carers work closely with specialist cystic fibrosis physiotherapists to develop, monitor and adapt a personalised regime. The type of airway clearance and quantity will change over time depending on symptoms, as various techniques and technologies are more suitable for different ages and at different disease stages.

Common techniques include:

- Active cycle of breathing techniques (ACBT)
- Autogenic drainage (AD)
- Intrapulmonary percussive ventilation (IPV)
- Oscillating positive expiratory pressure – Flutter, R-C Cornet, Acapella
- Positive expiratory pressure (PEP)

- High Positive expiratory pressure

The specialist physiotherapist will work in partnership with the person with cystic fibrosis to decide how much treatment is needed and how often. Once the lungs become productive, meaning the lungs are producing excess secretions, airway clearance treatments are usually needed daily and may be required up to three-four times a day if there is active infection or exacerbation. However, when a person with cystic fibrosis is well then treatment will be needed less frequently – once or twice a day. The length of each treatment session will also vary according to need. Sessions may only be 10-15 minutes when there are only small amounts of secretions, however longer treatments will be necessary if there is a lot of excess secretions to be cleared. The type of treatment will alter over time, as various techniques are more suitable for different ages and at different stages of the condition process. The physiotherapist will continue to monitor this and change treatment as necessary.

5. What difference did the health technology make to the lives of patients that have had it?

The difference OPEP makes to the lives of people with cystic fibrosis varies depending on the person. For example, in our survey on experiences of OPEP, 78% of respondents stated to have a 70-90% adherence rate of all their treatments. When a person with cystic fibrosis reduces their adherence, some have stated not to notice a difference as they will increase other medications, whereas others have said they will experience increased exacerbations and increased mucus build up. This variation in response is what makes cystic fibrosis so unique as patients can have a variation of symptoms requiring individualised treatments, including the use of OPEP.

However, it is important to note that, even though people with cystic fibrosis tend to use a variety of airway clearance technique, OPEP plays a substantial part of that regime. For example, our survey in the use of OPEP showed 72% of respondents are using OPEP as part of their regular treatment regime. The results also showed that all respondents use it because their clinicians have included OPEP in their regime and 80% of respondents preferred the use of OPEP as an airway clearance technique over others available.

The dominant message within our survey on OPEP was the importance of shared decision-making between the person with cystic fibrosis, clinicians and specialist physiotherapists, to ensure people with cystic fibrosis have some control on treatment management, particularly given the heavy treatment burden. Therefore, it is important that all people with cystic fibrosis continue to have access to an array of treatments, such as OPEP, so that they can choose the best technique for them.

6. Additional information you believe would be helpful for HTW to consider.

No additional information to add.

7. Summarise the key points of your submission in up to 5 statements.

1. Cystic fibrosis is a genetic, life-altering disease which has no cure and requires a heavy burden of treatment to manage symptoms and help people with cystic fibrosis stay well for longer.
2. Airway clearance techniques such as OPEP are a key part of a cystic fibrosis treatment regime.

3. The results of OPEP vary from person to person but there is clear evidence the inclusion of OPEP reduces the risk of exacerbation and helps with mucus clearance for some.
4. Shared decision-making between the person with cystic fibrosis and the clinicians to ensure people with cystic fibrosis have some control on treatment management is essential, particularly given the heavy treatment burden.
5. It is vital that people with cystic fibrosis continue to have access to an array of treatments, including OPEP, so that they can choose the best technique based on their needs, preferences, and circumstances.