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Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Morrison L, Milroy S

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Oscillating devices for airway clearance in people with cystic fibrosis.
Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD006842.
DOI: [10.1002/14651858.CD006842.pub5](https://doi.org/10.1002/14651858.CD006842.pub5).

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[Intervention Review]

Oscillating devices for airway clearance in people with cystic fibrosis

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2020.

Citation: Morrison L, Milroy S. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD006842. DOI: [10.1002/14651858.CD006842.pub5](https://doi.org/10.1002/14651858.CD006842.pub5).

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ABSTRACT

Background

Chest physiotherapy is widely prescribed to assist the clearance of airway secretions in people with cystic fibrosis. Oscillating devices generate intra- or extra-thoracic oscillations orally or external to the chest wall. Internally they create variable resistances within the airways, generating controlled oscillating positive pressure which mobilises mucus. Extra-thoracic oscillations are generated by forces outside the respiratory system, e.g. high frequency chest wall oscillation. This is an update of a previously published review.

Objectives

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.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and hand searches of relevant journals and abstract books of conference proceedings. Latest search of the Cystic Fibrosis Trials Register: 29 July 2019.

In addition we searched the trials databases ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Latest search of trials databases: 15 August 2019.

Selection criteria

Randomised controlled studies and controlled clinical studies of oscillating devices compared with any other form of physiotherapy in people with cystic fibrosis. Single-treatment interventions (therapy technique used only once in the comparison) were excluded.

Data collection and analysis

Two authors independently applied the inclusion criteria to publications, assessed the quality of the included studies and assessed the evidence using GRADE.

Main results

The searches identified 82 studies (330 references); 39 studies (total of 1114 participants) met the inclusion criteria. Studies varied in duration from up to one week to one year; 20 of the studies were cross-over in design. The studies also varied in type of intervention and the outcomes measured, data were not published in sufficient detail in most of these studies, so meta-analysis was limited. Few studies were considered to have a low risk of bias in any domain. It is not possible to blind participants and clinicians to physiotherapy interventions, but 13 studies did blind the outcome assessors. The quality of the evidence across all comparisons ranged from low to very low.

Forced expiratory volume in one second was the most frequently measured outcome and while many of the studies reported an improvement in those people using a vibrating device compared to before the study, there were few differences when comparing the different devices to each other or to other airway clearance techniques. One study identified an increase in frequency of exacerbations requiring antibiotics whilst using high frequency chest wall oscillation when compared to positive expiratory pressure (low-quality evidence). There were some small but significant changes in secondary outcome variables such as sputum volume or weight, but not wholly in favour of oscillating devices and due to the low- or very low-quality evidence, it is not clear whether these were due to the particular intervention. Participant satisfaction was reported in 13 studies but again with low- or very low-quality evidence and not consistently in favour of an oscillating device, as some participants preferred breathing techniques or techniques used prior to the study interventions. The results for the remaining outcome measures were not examined or reported in sufficient detail to provide any high-level evidence.

Authors' conclusions

There was no clear evidence that oscillation was a more or less effective intervention overall than other forms of physiotherapy; furthermore there was no evidence that one device is superior to another. The findings from one study showing an increase in frequency of exacerbations requiring antibiotics whilst using an oscillating device compared to positive expiratory pressure may have significant resource implications. More adequately-powered long-term randomised controlled trials are necessary and outcomes measured should include frequency of exacerbations, individual preference, adherence to therapy and general satisfaction with treatment. Increased adherence to therapy may then lead to improvements in other parameters, such as exercise tolerance and respiratory function. Additional evidence is needed to evaluate whether oscillating devices combined with other forms of airway clearance is efficacious in people with cystic fibrosis. There may also be a requirement to consider the cost implication of devices over other forms of equally advantageous airway clearance techniques. Using the GRADE method to assess the quality of the evidence, we judged this to be low or very low quality, which suggests that further research is very likely to have an impact on confidence in any estimate of effect generated by future interventions.

PLAIN LANGUAGE SUMMARY

The use of vibrating devices to help people with cystic fibrosis clear their airways of mucus

Review question

We reviewed the evidence about the effect of vibrating devices (e.g. Flutter, acapella, cornet, Quake[®], intrapulmonary percussive ventilation, high frequency chest wall oscillators (e.g. Vest[®]), VibraLung[®], MetaNeb[®], and Aerobika[®]) to help people with cystic fibrosis clear their airways of mucus. This is an update of a previously published review.

Background

People with cystic fibrosis have too much sticky mucus in their lungs which can lead to constant infection and inflammation. This damages their airways and worsens lung function over time. People with cystic fibrosis use chest physiotherapy to clear the mucus from their lungs. They can use different methods alone or in combination with others - manual techniques, breathing techniques and mechanical devices. Vibrating devices (also sometimes known as oscillators) use pressure generated either inside or outside of the body to clear the mucus.

Search date

Evidence is current to 29 July 2019.

Study characteristics

The review included 39 studies with 1114 people with cystic fibrosis aged between 4 and 63 years of age. Studies compared different physiotherapy treatments and people were selected for one treatment or the other randomly. Not many studies looked at the same types of physiotherapy over the same period of time; studies ranged in duration from two days to 13 months.

Key results

Given the differences in study design, it was difficult to combine the results from these studies in a useful way.

We did not find any clear evidence that vibrating devices were better than any other form of physiotherapy which they were compared to in these studies, or that one device was better than another. One study found that people using a vibrating device needed additional antibiotics for a chest infection more often than those using positive expiratory pressure. When recommending the most suitable method of airway clearance, physiotherapists should consider the needs of the people they are treating.

For the future, larger and longer trials are needed to measure the frequency of lung infections, preference, adherence to and general satisfaction with treatment, financial constraints should also be taken into consideration. We think adherence is important, because if people with cystic fibrosis are willing to stick to their physiotherapy regimen, there may be improvements in other outcomes such as exercise tolerance, respiratory function and mortality.

Quality of the evidence

Oscillating devices for airway clearance in people with cystic fibrosis (Review)

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Overall, we thought most studies had some design problems which might affect our confidence in some of the results. In about a quarter of studies there were concerns that not all the results were reported clearly and in about a third of the studies the reasons for people withdrawing from a trial were not clearly explained. In comparisons of different types of physiotherapy, a person and their physiotherapist will always know which treatment they are receiving and this might affect their answers to some questions, such as which treatment makes them feel better, but we only thought this was a problem in a few studies. We used a scoring system called GRADE to assess the quality of the evidence, we then judged it to be either low- or very low-quality, which suggests that further research is very likely to affect our confidence in the results in this review for of any of the interventions analysed.

SUMMARY OF FINDINGS

Summary of findings 1. Oscillating devices compared with PEP for cystic fibrosis

Oscillating devices compared with PEP for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients and hospitalised patients

Intervention: oscillating devices

Comparison: PEP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PEP	Oscillating devices ^a				
FEV₁ : % predicted Follow-up: less than 1 week to 1 year	There were no statistically significant differences between oscillating devices and PEP in terms of FEV ₁ % predicted post-intervention or change from baseline at any time point.		NA	510 (15 studies)	⊕⊕⊕⊕ very low^{c,d}	
FEF₂₅₋₇₅ : % predicted Follow-up: less than 1 week to 1 year	There were no statistically significant differences between oscillating devices and PEP in terms of FEF ₂₅₋₇₅ % predicted post-intervention or change from baseline at any time point.		NA	355 (9 studies)	⊕⊕⊕⊕ very low^{c,d}	
FVC Follow-up: less than 1 week to 1 year	There were no statistically significant differences between oscillating devices and PEP in terms of FVC post-intervention or change from baseline at any time point.		NA	362 (9 studies)	⊕⊕⊕⊕ very low^{c,d}	
Sputum: volume (mL) Follow-up: up to 1 week	The mean sputum volume in the PEP group was 8.5 mL.	The mean sputum volume in the oscillating device group was 1.8 mL lower (6.6 mL lower to 3.0 mL higher).	NA	23 (1 study)	⊕⊕⊕⊕ low^{d,e}	A 2nd study recruiting 30 participants reported that there was an increase in sputum volume when HFCWO was compared to

participants' usual ACT; however, it was not clear exactly what interventions were included in the usual ACT treatment arm.

Sputum: weight (dry or wet) (g)	3 out of 4 studies reported no statistically significant difference between oscillating devices and PEP in terms of sputum weight (g).	NA	104 (4 studies)	⊕⊕⊕⊕ low^{d,f}	
Follow-up: up to 2 weeks	1 study reported that a significantly greater weight of sputum was yielded using PEP compared to HFCWO.				
Frequency of exacerbations^b	2 out of 4 studies reported no statistically significant difference between oscillating devices and PEP.	NA	219 (4 studies)	⊕⊕⊕⊕ low^{d,f}	
Follow-up: up to one year	2 out of 4 studies reported that significantly more hospitalizations or participants requiring antibiotics in the oscillating devices groups compared to the PEP groups.				
Participant-reported satisfaction with treatment intervention	Some differences were reported between treatment groups in single domains of satisfaction questionnaires or measurement scales (in favour of or against oscillating devices).	NA	242 (7 studies)	⊕⊕⊕⊕ very low^{c,d,g}	
Follow-up: less than 1 week to 1 year	Overall across the 7 studies, no consistent differences were reported in terms of satisfaction of any treatment intervention.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACT: airway clearance technique; **CI:** confidence interval; **FEF₂₅₋₇₅:** mid-expiratory flow; **FEV₁:** forced expiratory volume at one second; **FVC:** forced vital capacity; **HFCWO:** high frequency chest wall oscillation; **IPV:** intrapulmonary percussive ventilation; **NA:** not applicable; **PEP:** positive expiratory pressure.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a The oscillating devices included in the trials under this comparison were HFCWO, flutter, IPV, acapella and cornet.

^b Frequency of exacerbations were measured as defined by Rosenfeld as a consequence of the treatment intervention (Rosenfeld 2001).

^c Downgraded twice due to serious risk of bias; many judgements of high risk of bias across the included studies due to reasons such as inadequate allocation concealment, lack of blinding of participants, clinicians and outcome assessors, incomplete outcome data and selective reporting (see [Risk of bias in included studies](#) for further information).

^d Downgraded once due to imprecision: many included studies had very small sample sizes, short treatment durations and employed cross-over designs. As results were not presented from paired analyses for these studies, we treated the cross-over trials as if they were parallel trials which is a conservative approach as it does not take into account within-patient correlation. Sensitivity analyses indicates that results were robust to this approach.

^e Downgraded once due to unclear risk of bias; the study was published as an abstract only and very limited information was available regarding the study design.

^f Downgraded once due to risk of bias; judgements of high risk of bias across some of the included studies due to reasons such as inadequate allocation concealment, lack of blinding of participants clinicians and outcome assessors, incomplete outcome data and selective reporting (see [Risk of bias in included studies](#) for further information).

^g Downgraded once due to applicability; 3 of the studies reported anecdotal findings in terms of participant satisfaction or preference for a treatment arm without numerical results to support these findings.

Summary of findings 2. Oscillating devices compared with breathing techniques for cystic fibrosis

Oscillating devices compared with breathing techniques for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients and hospitalised patients

Intervention: oscillating devices

Comparison: breathing techniques

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Breathing techniques	Oscillating devices ^a				
FEV₁: % predicted or L Follow-up: less than 1 week to 1 year	7 out of 9 studies reported no statistically significant differences between oscillating devices and breathing techniques in terms of FEV ₁ (% predicted or L). 1 study reported a significant advantage for IPV at 400 bpm compared to AD at 2 weeks. 1 study reported a significant advantage for active cycle of breathing techniques compared to HFWCO in terms of FEV ₁ (L) after 2 days.		NA	210 (9 studies)	⊕⊕⊕⊕ low^{c,d}	
FEF₂₅₋₇₅	There were no statistically significant differences between oscillating devices and breathing techniques in terms of FEF ₂₅₋₇₅ .		NA	29 (2 studies)	⊕⊕⊕⊕ very low^{e,f}	

Follow-up: 5 days				
FVC Follow-up: less than 1 week to 1 year	6 out of 8 studies reported no statistically significant differences between oscillating devices and breathing techniques in terms of FVC. 1 study reported a significant advantage for IPV at 400 bpm compared to AD at 2 weeks. 1 study reported a significant advantage for active cycle of breathing techniques compared to HFWCO in terms of FVC % predicted after 2 days.	NA	181 (8 studies)	⊕⊕⊕⊕ low^{c,d}
Sputum: volume (g) Follow-up: up to 1 month	The mean sputum volume in the breathing technique group was 3.6 g. The mean sputum volume in the oscillating device group was 0.9 g higher (1.72 g lower to 3.52 g higher).	NA	14 (1 study)	⊕⊕⊕⊕ low^{e,g}
Sputum: weight (dry or wet) (g) Follow-up: up to 2 weeks	4 out of 6 studies reported no statistically significant difference between oscillating devices and breathing technique in terms of sputum weight (g). 2 out of 6 studies reported that a significantly greater weight of sputum was yielded using breathing techniques compared to oscillating devices.	NA	114 (6 studies)	⊕⊕⊕⊕ low^{c,d}
Frequency of exacerbations^b Follow-up: NA	Outcome not reported in any study.	NA	NA	NA
Participant-reported satisfaction with treatment intervention Follow-up: up to 2 weeks	Some differences were reported between treatment groups in single domains of satisfaction questionnaires or measurement scales (in favour of or against oscillating devices). Overall across the 6 studies, no consistent differences were reported in terms of satisfaction of any treatment intervention.	NA	114 (6 studies)	⊕⊕⊕⊕ low^{c,d}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEF₂₅₋₇₅:** mid-expiratory flow; **FEV₁:** forced expiratory volume at one second; **FVC:** forced vital capacity; **HFCWO:** high frequency chest wall oscillation; **L:** litres; **MD:** mean difference; **NA:** not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a The oscillating devices included in the trials under this comparison were IPV, HFCWO, flutter and cornet.

^b Frequency of exacerbations were measured as defined by Rosenfeld as a consequence of the treatment intervention (Rosenfeld 2001).

^c Downgraded once due to risk of bias; judgements of high risk of bias across some of the included studies due to reasons such as lack of blinding of participants clinicians and outcome assessors, incomplete outcome data and selective reporting (see [Risk of bias in included studies](#) for further information).

^d Downgraded once due to imprecision: many included studies had very small sample sizes, short treatment durations and employed cross-over designs. As results were not presented from paired analyses for these studies, we treated the cross-over trials as if they were parallel trials which is a conservative approach as it does not take into account within-patient correlation. Sensitivity analyses indicates that results were robust to this approach.

^e Downgraded once due to risk of bias: the single included study was at high risk of bias due to lack of blinding and reported limited information regarding other aspects of the methodological design.

^f Downgraded once due to serious imprecision: a single cross-over study recruiting only seven participants over a 5-day period contributed to the outcome and no numerical data were available.

^f Downgraded once due to imprecision: a single cross-over study recruiting only 14 participants contributed to the outcome.

Summary of findings 3. Oscillating devices compared with conventional physiotherapy for cystic fibrosis

Oscillating devices compared with conventional physiotherapy for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients and hospitalised patients

Intervention: oscillating devices

Comparison: conventional physiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional physiotherapy	Oscillating devices ^a				
FEV₁: % predicted Follow-up: less than 1 week up to 3 years	There were no statistically significant differences between oscillating devices and conventional physiotherapy in terms of FEV ₁ % predicted post-intervention or change from baseline at any time point.		NA	363 (10 studies)	⊕⊕⊕⊕ very low^{c,d}	

FEF₂₅₋₇₅: % predicted Follow-up: less than 1 week up to 3 years	There were no statistically significant differences between oscillating devices and conventional physiotherapy in terms of FEF ₂₅₋₇₅ % predicted post-intervention or change from baseline at any time point.	NA	319 (8 studies)	⊕⊕⊕⊕ very low^{c,d}
FVC Follow-up: less than 1 week up to 3 years	There were no statistically significant differences between oscillating devices and conventional physiotherapy in terms of FVC post-intervention or change from baseline at any time point.	NA	268 (7 studies)	⊕⊕⊕⊕ very low^{c,d}
Sputum: volume Follow-up: up to 1 week	Both studies found a statistically significant advantage for the oscillating device compared to the conventional physiotherapy in terms of volume of sputum.	NA	17 (2 studies)	⊕⊕⊕⊕ low^{d,e}
Sputum: weight (dry or wet)	6 out of 8 studies reported no statistically significant difference between oscillating devices and conventional physiotherapy in terms of sputum weight (g). 1 study reported that a significantly greater weight of sputum was yielded using conventional physiotherapy compared to HFCWO. 1 study reported that a significantly greater weight of sputum was yielded using HFCWO compared to conventional physiotherapy.	NA	188 (8 studies)	⊕⊕⊕⊕ very low^{c,d}
Frequency of exacerbations^b Follow-up: less than 1 week up to 3 years	There were no significant differences between oscillating devices and conventional physiotherapy in terms of days of hospitalisation or time to next pulmonary exacerbation.	NA	262 (4 studies)	⊕⊕⊕⊕ very low^{c,d}
Participant-reported satisfaction with treatment intervention Follow-up: less than 1 week up to 3 years	Some differences were reported between treatment groups in single domains of satisfaction questionnaires or measurement scales (in favour of or against oscillating devices). Overall across the 9 studies, no consistent differences were reported in terms of satisfaction of any treatment intervention.	NA	345 (9 studies)	⊕⊕⊕⊕ very low^{c,d,f}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **FEF₂₅₋₇₅:** mid-expiratory flow; **FEV₁:** forced expiratory volume at one second; **FVC:** forced vital capacity; **HFCWO:** high frequency chest wall oscillation; **IPV:** intrapulmonary percussive ventilation; **NA:** Not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

- ^a The oscillating devices included in the trials under this comparison were HFCWO, flutter and IPV.
- ^b Frequency of exacerbations were measured as defined by Rosenfeld as a consequence of the treatment intervention (Rosenfeld 2001).
- ^c Downgraded twice due to serious risk of bias; many judgements of high risk of bias across the included studies due to reasons such as inadequate allocation concealment, lack of blinding of participants, clinicians and outcome assessors, incomplete outcome data and selective reporting (see [Risk of bias in included studies](#) for further information).
- ^d Downgraded once due to imprecision: many included studies had very small sample sizes, short treatment durations and employed cross-over designs. As results were not presented from paired analyses for these studies, we treated the cross-over trials as if they were parallel trials which is a conservative approach as it does not take into account within-patient correlation. Sensitivity analyses indicates that results were robust to this approach.
- ^e Downgraded once due to unclear risk of bias; limited information was available regarding the methodological designs of the 2 studies.
- ^f Downgraded once due to applicability; 4 of the studies reported anecdotal findings in terms of participant satisfaction or preference for a treatment arm without numerical results to support these findings.

Summary of findings 4. Oscillating devices compared with different oscillating devices for cystic fibrosis

Oscillating devices compared with different oscillating devices for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients and hospitalised patients

Intervention: oscillating devices

Comparison: a different oscillating device

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oscillating devices ^a	Oscillating devices ^a				
FEV₁ Follow-up: less than 1 week up to 3 years	5 out of 6 studies showed no statistically significant differences between oscillating devices in terms of FEV ₁ at any time point. 1 study showed that participants treated with IPV at a higher frequency showed a significantly higher change from baseline in FEV ₁ % predicted compared to AD at 2 weeks.	NA	320 (6 studies)	⊕⊕⊕⊕ very low^{c,d}		
FEF₂₅₋₇₅ Follow-up: less than 1 week up to 3 years	There were no statistically significant differences between oscillating devices in terms of FEF ₂₅₋₇₅ at any time point.	NA	211 (3 studies)	⊕⊕⊕⊕ very low^{c,d}		

FVC Follow-up: less than 1 week up to 3 years	4 out of 5 studies show no statistically significant differences between oscillating devices in terms of FVC at any time point. 1 study showed that participants treated with IPV at a higher frequency showed a significantly higher change from baseline in FVC % predicted compared to AD at 2 weeks.	NA	290 (5 studies)	⊕⊕⊕⊕ very low^{c,d}
Sputum: volume Follow-up: NA	Outcome not reported.	NA	NA	NA
Sputum: weight (dry or wet) Follow-up: 6 days	The results of the study showed that wet and dry sputum weight in the IPV group was significantly greater than in the HFCWO group.	NA	24 (1 study)	⊕⊕⊕⊕ low^{d,e}
Frequency of exacerbations^b Follow-up: 24 weeks	There were no statistically significant differences between oscillating devices in terms of frequency of hospitalisations or need for home intravenous therapies.	NA	16 (1 study)	⊕⊕⊕⊕ very low^{f,g}
Participant-reported satisfaction with treatment intervention Follow-up: less than 1 week up to 3 years	Some differences were reported between treatment groups in single domains of satisfaction questionnaires or measurement scales (in favour of or against oscillating devices). Overall across the 5 studies, no consistent differences were reported in terms of satisfaction of any treatment intervention.	NA	265 (5 studies)	⊕⊕⊕⊕ very low^{c,d}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEF₂₅₋₇₅**: mid-expiratory flow; **FEV₁**: forced expiratory volume at one second; **FVC**: forced vital capacity; **HFCWO**: high-frequency chest wall oscillation; **IPV**: intrapulmonary percussive ventilation; **NA**: not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a The oscillating devices included in the trials under this comparison were HFCWO, flutter, IPV and cornet.

^b Frequency of exacerbations were measured as defined by Rosenfeld as a consequence of the treatment intervention (Rosenfeld 2001).

^c Downgraded twice due to serious risk of bias; many judgements of high risk of bias across the included studies due to reasons such as lack of blinding of participants, clinicians and outcome assessors, incomplete outcome data and selective reporting (see [Risk of bias in included studies](#) for further information).

d Downgraded once due to imprecision: many included studies had very small sample sizes, short treatment durations and employed cross-over designs. As results were not presented from paired analyses for these studies, we treated the cross-over trials as if they were parallel trials which is a conservative approach as it does not take into account within-patient correlation. Sensitivity analyses indicates that results were robust to this approach.

e Downgraded once due to unclear risk of bias; the study was potentially at risk of bias due to the administration of the interventions and limited information was available regarding the study design.

f Downgraded once due to serious risk of bias; the study was at risk of attrition bias and selective reporting bias.

g Downgraded once due to imprecision: the study recruited only 16 participants and numerical data were not available for the outcome.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a common inherited life-limiting genetic disorder. The genetic defect causes mucus hypersecretion within the airways leading to airway obstruction and mucus plugging (Zach 1990). Airway damage and progressive loss of respiratory function is a consequence of persistent infection and inflammation within the lungs (Cantin 1995; Konstan 1997).

Description of the intervention

Chest physiotherapy is currently implemented at initial diagnosis. It is recommended that it should be carried out for the maintenance of a clear chest with an additional recognition for altered or more aggressive therapies during times of respiratory exacerbation. Dependent on the age of the individual, chest physiotherapy will traditionally take the form of manual therapies. Conventional manual therapies would require the assistance of another person to perform the techniques of percussion and vibrations, with the addition of postural drainage when this was felt to add to the technique. With the advent of a more modern approach to physiotherapy, self-administered techniques are more frequently used. These self-administered techniques do not necessitate postural drainage or indeed the assistance of another person. They can be done in a sitting position (if preferred) and use different methods of breathing or different devices to assist mucus clearance. Oscillatory devices are designed to interrupt the expiratory airflow. These devices are either intra- or extra-thoracic. Intra-thoracic oscillatory devices are placed in the mouth and provide resistance during exhalation which results in the airways vibrating thus loosening the mucus. Extra-thoracic oscillatory devices, such as an inflatable vest attached to a machine, vibrate at variable frequencies and intensities as set by the operator to ensure the individual's comfort and associated concordance. Fuller descriptions of all the interventions to be compared in the review can be found below in [Types of interventions](#).

In this review we have considered the use of oscillation and oscillatory devices as a means of airway clearance and the consequent impact this type of intervention has on the individual with CF and in particular when compared with other recognised forms of airway clearance.

How the intervention might work

Respiratory infections are the primary cause of morbidity and mortality in CF and therefore chest physiotherapy is considered to be an important treatment for the assistance and clearance of the sticky mucus found within the airways of people with CF.

Oscillations, or interruptions in expiratory airflow have been postulated to mechanically reduce the viscoelasticity of sputum and enhance mucociliary clearance (Newbold 2005). Oscillations, both internally and externally, have also been considered to improve airway patency by preventing spontaneous compression through the introduction of alternating positive pressure where the consequent vibration loosens mucus allowing ease of expectoration (Oermann 2001; Pryor 1994).

Why it is important to do this review

Other Cochrane Reviews have considered the benefits of different forms of chest physiotherapy in people with CF (Main 2005; McIlwaine 2019; McKoy 2016; McCormack 2017). They compare oscillatory devices with another recognised single therapy; conventional chest physiotherapy (Main 2005), positive expiratory pressure (PEP) (McIlwaine 2019), active cycle of breathing techniques (ACBT) (McKoy 2016) and autogenic drainage (AD) (McCormack 2017). It is the intention of this review to complement the information previously provided. This review will examine the effect and acceptability of oscillatory devices when compared to all other techniques including comparing types of oscillatory device currently used for airway clearance.

This is an updated version of previous reviews (Morrison 2007; Morrison 2009; Morrison 2014).

OBJECTIVES

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 CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCT's.

Types of participants

Children (aged up to 16 years) and adults (16 years and above) with any degree of disease severity, with defined CF, diagnosed clinically and by sweat or genetic testing. Trials with participants enrolled during a period of stability or during a pulmonary exacerbation were both considered.

Types of interventions

Oscillatory devices, both oral and chest wall, for airway clearance compared with another recognised airway clearance technique either as a single technique (e.g. oscillation versus active cycle of breathing technique (ACBT)) or in conjunction with another recognised airway clearance technique (e.g. oscillation and ACBT versus ACBT alone).

Interventions of variable duration would be considered and separated according to term of intervention. Single treatment interventions (where the therapy technique was used only once in the comparison) were not considered.

Specific techniques considered for comparison are likely to fall in to one of the following categories:

1. Oscillatory devices

Devices which have an oscillatory component which consider intra- or extra-thoracic oscillations.

Intra-thoracic oscillations are generated orally and created using variable resistances within the airways generating controlled oscillating positive pressure which mobilises respiratory

secretions. When the oscillation frequency approximates the resonance frequency of the pulmonary system, endobronchial pressure oscillations are amplified and result in vibrations of the airways. These vibrations loosen mucus from the airway walls. The intermittent increases in endobronchial pressure reduce the collapsibility of the airways during exhalation, increasing the likelihood of clearing mucus from the tracheobronchial tract. The airflow accelerations increase the velocity of the air being exhaled, facilitating the movement of mucus up the airways (Konstan 1994). Exhalation through these devices generates both oscillations of positive pressure in the airways and repeated accelerations of expiratory airflow that have been shown to result in improved sputum clearance (Rogers 2005).

The devices frequently employed for this purpose are:

a. Flutter

A small plastic device containing a large ball bearing which repeatedly interrupts the outward flow of air (Konstan 1994; Pryor 1999).

b. Acapella

A flow operated oscillatory PEP device, which uses a counterweighted plug and magnet to generate the oscillatory resistance (Volsko 2003).

c. Cornet

A horn-shaped tube which houses a rubber inner tube. The degree of rotation of this inner tube reflects the resistance generated. As the individual exhales through the horn the inner tube unfurls generating a rhythmic bending and unbending of the inner tube within the horn throughout the expiration phase (Pryor 1999).

d. Quake[®] (Thayer Medical, Tucson, Arizona, USA)

This device oscillates a column of air in both inspiratory and expiratory phases of respiration. It does not rely on an oscillating valve like the Flutter and the acapella, as it uses a manually turned cylinder that fits within another cylinder. Airflow occurs only when slots within the two cylinders line up. Therefore, the airflow is interrupted at regular intervals as the user turns the crank. The rate at which the device is cranked will determine the frequency of the flow interruption. Since the resulting vibration is not determined by the patient's rate of flow, the Quake[®] theoretically may be more helpful for patients with severe obstructive lung disease who are unable to generate high peak expiratory flow rates.

e. Intrapulmonary percussive ventilation (IPV)

This provides continuous oscillation to the airways via the mouth (Homnick 1995).

f. Extra-thoracic oscillations (HFCWO)

Extra-thoracic oscillations are generated by forces external to the respiratory system, e.g. high frequency chest wall oscillation (HFCWO) (Warwick 1991). External chest wall oscillations are applied using an inflatable vest attached to a machine which vibrates at a variable frequencies and intensities as set by the operator to ensure the individual's comfort and associated concordance. This type of device can also be called the Vest[®] or Hayek Oscillator.

g. The VibraLung[®]

The VibraLung[®] is an acoustic percussor, where sound waves are applied directly to the tracheobronchial tract at frequencies that cover the range of resonant frequencies of the human tracheobronchial tract (5 to 1,200 Hz). This causes a vibration within the airways and mucus directly, instead of indirectly through the chest wall. Additionally, the VibraLung[®] incorporates positive expiratory pressure (PEP) through its mouthpiece design with the inclusion of two tiny holes to provide resistance to exhalation (Wheatley 2018).

h. Metaneb[®]

The MetaNeb[®] System is a pneumatic compressor system which delivers continuous high frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP) to facilitate the clearance of mucus from the lungs, provide aerosol delivery and lung expansion therapy. Flow, pressure and percussive rate are all adjustable (Patel 2013).

i. Aerobika[®]

The Aerobika[®] is a hand-held oscillating positive expiratory pressure (OPEP) device. When the individual exhales through the device, intermittent resistance creates a unique pressure – oscillatory and dynamic - which expands the airways, helping move the mucus to the upper airways where it can be coughed out. The Aerobika[®] can be used in combination with a nebuliser, which is considered to enhance adherence to therapies and may enhance drug deposition.

2. Positive expiratory pressure (PEP)

Positive expiratory pressure is another well-recognised and well-utilised clearance method. Devices can be used to open up and recruit obstructed lung, allowing air to move behind secretions and assist in mobilising them. Breathing out against a slight resistance (10 to 20 cm H₂O) prevents the smaller bronchial tubes from collapsing down and thus permits the continuing upward movement of any secretions (McIlwaine 2019). Masks, mouthpieces or a novel Bubble PEP system offer more choice when considering this approach.

Hi-PEP is a modification of PEP which involves the full forced expiration against a fixed mechanical resistance usually between 80 to 140 cm H₂O (Prasad 1993).

3. Breathing techniques

When the individual is considered to be moving toward independence and chooses not to use a device, the techniques frequently adopted are AD and the active cycle of breathing technique (ACBT).

a. AD

This term describes a series of breathing exercises devised by the Belgian physiotherapist Jean Chevaillier. The aim is to dislodge and collect mucus from the lungs and then clear these secretions by breathing at various lung volumes (Chevaillier 1984; Schöni 1989). There are three phases - the Unstick, Collect and Evacuate when breathing at low, mid and high lung volumes to mobilise, collect and expectorate secretions respectively.

b. ACBT

This consists of three breathing techniques: breathing control is used between other techniques to allow relaxation; thoracic (chest) expansion exercises with the emphasis on inspiration, expiration being quiet and relaxed; and the forced expiration technique or huff is used to mobilise and clear secretions. One or two forced expirations are combined with a period of breathing control. A huff from high lung volume (when a breath has been taken in) will clear secretions from the upper airways and a huff from mid to low lung volume will clear secretions from the lower more peripheral airways (Pryor 1999; Webber 1986; Webber 1990).

4. Conventional chest physiotherapy

Conventional therapy techniques typically consisting of techniques such as modified postural drainage, percussion and manual vibrations or shakings are likely to have been introduced in infancy, or if the initial diagnosis was made in childhood (Prasad 1993). They may also include huffing and directed cough (Main 2005). If the diagnosis of CF was made during adolescence or indeed adulthood, many people prefer to use techniques which enable independence from an operator and which can easily be fitted around an active lifestyle.

As a consequence of many different descriptions of therapy techniques it was considered by the authors that certain manual therapies could be combined and considered as one 'type' of therapy. For this reason we have grouped the techniques of postural drainage and percussion (PD&P), postural drainage and clapping (PD&C) and postural drainage percussion and vibration (PDPV) under the term conventional physiotherapy (CPT), for unless otherwise stated we have assumed that CPT is a derivative of, or comparable to, the other terms used in the grouping.

5. Exercise

Where an individual with CF has few respiratory symptoms, exercise can often be the treatment of choice as a means of airway clearance or as an adjunct to other techniques. It has been recognised as contributing to enhanced quality of life (QoL) and improvements in functional exercise tolerance in people with chronic respiratory diseases such as CF. In addition exercise has been shown to increase respiratory muscle endurance, increase sputum expectoration and preserve respiratory function in some individuals with CF, where a higher level of aerobic fitness also correlated with a decreased risk of mortality (Radtke 2017; Webb 1995).

Types of outcome measures

Primary outcomes

1. Respiratory function
 - a. forced expiratory volume at one second (FEV₁)
 - b. mid-expiratory flow (FEF₂₅₋₇₅)
 - c. forced vital capacity (FVC)
 - d. expiratory reserve volume (ERV) or reserve volume (RV)

Secondary outcomes

1. Sputum
 - a. volume
 - b. weight (dry or wet)

2. Exercise tolerance (as measured by recognised standard exercise tests e.g. walk tests, step tests or cycle ergometry)
3. Quality of life (QoL) indices, e.g. CF QOL questionnaire
4. Level of oxygen saturation in response to treatment
5. Frequency of exacerbations (as defined by Rosenfeld (Rosenfeld 2001)) as a consequence of the treatment intervention
6. Participant reported satisfaction with treatment intervention
7. Lung clearance index (LCI)

Search methods for identification of studies

There are no restrictions regarding language or publication status.

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the term: 'oscillating devices'.

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

Date of last search of the Cystic Fibrosis Trials Register: 29 July 2019.

We also searched the relevant clinical trials databases clinicaltrials.gov/ and [WHO ICTRP](http://www.who.int/clinicaltrials/ctcp/) using the terms 'cystic fibrosis' AND 'oscillation'. Date of the latest search: 15 August 2019.

Data collection and analysis

Selection of studies

Two authors (up to 2017: LM and JA; after 2017: LM and SM) independently reviewed all citations and abstracts identified by the search to determine which papers assessed should be included. If disagreement had occurred, the authors planned to seek resolution by consensus.

Data extraction and management

Both authors (up to 2017: LM and JA; after 2017: LM and SM) independently performed data extraction and recorded data on forms developed for this purpose. If disagreement had occurred, the authors planned to seek resolution by consensus.

We planned to group outcome data those measured at one, three, six, 12 months and annually thereafter. If outcome data were recorded at other time periods, then we planned to consider examining these as well. We have subsequently considered these time points and felt that to combine data measured at two weeks with data measured at four weeks was inappropriate. Therefore, we have split the original proposed time point of one month and reported data at up to two weeks (Arens 1994; Braggion 1995; Darbee 2005; Davies 2012; Dingemans 2018a; Gondor 1999; Grzincich 2008; Hare 2002; Klufft 1996; Milne 2004; Osman 2010; Patel 2013; Phillips 2004; Pike 1999; Varekojis 2003a; Warwick 1990;

West 2010; Wheatley 2018) and at over two weeks and up to one month (Homnick 1998; Padman 1999a).

We have considered studies identifying interventions of varying duration separately; we considered those of one to 12 weeks as short-term; those over 12 weeks and up to 24 weeks medium-term; and those over 24 weeks as long-term. We did not consider single-treatment interventions, as it is unlikely that an individual can be instructed in the most appropriate usage of such devices or treatment techniques in a single session. We have identified four multiple-arm studies which consider more than one oscillatory technique when compared with an alternative physiotherapy technique. In order to achieve a comparison we have set up 'dummy' study ID's which allow the data from the study to be entered more than once on the same graph (Dingemans 2018b; Modi 2010b; Padman 1999b; Varekojis 2003b). In addition, there are other studies which consider two or more therapies. Due to the limitations of the analysis we are able to carry out in RevMan 5, the participants in the control groups will appear in more than one comparison, i.e. be counted twice, and we would caution the reader to consider this when interpreting the graphs.

Assessment of risk of bias in included studies

Cochrane Reviews incorporate a recommended approach for assessing risk of bias in included studies. It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). Each domain includes one or more specific entries in a 'Risk of bias' table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

In order to establish the risk of bias in the included studies, the two authors (up to 2017: LM and JA; after 2017: LM and SM) independently assessed the methodological rigour and quality of selected studies and reported on the six domains as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and incorporated the criteria on quality assessment described by Jüni (Jüni 2001).

Generation of allocation sequence

We considered this as adequate, and a low risk of bias, if a computer algorithm or a similar process based on chance was used to randomise participants to treatment groups. We identified this as inadequate, and a high risk of bias, if sequences which could be attributed to prognosis, degree of disease severity, age etc were employed. We considered this unclear, and thus the risk of bias was also be unclear, where the generation of allocation sequence has not been identified.

Concealment of allocation

We considered concealment of allocation adequate where it was not possible for the investigators to foresee the allocation of participants to a particular treatment group, e.g. centralised or pharmacy-controlled randomisation, pre-numbered or coded identical containers administered serially to participants, on-

site locked computer system, or sequentially numbered, sealed, opaque envelopes. This means the study has a low risk of bias. We considered the concealment of allocation inadequate if the investigator was able to predict the allocation, e.g., alternation; the use of case record numbers, dates of birth or day of the week; thus the study has a high risk of bias. We graded this (and the risk of bias) as unclear if the concealment of allocation has not been described.

Blinding

We reported on the degree of blinding employed in each study. Given the treatment interventions and the specific devices for chest clearance which we have considered in this review, blinding of the investigator and participants was not possible: however, blinding of the person analysing the data was possible. The risk of bias is likely to be lower when these aspects of the trial are blinded, but frequently when the study compares the use of a device this is not practically possible.

Incomplete outcome data and intention-to-treat analysis

We described the completeness of outcome data for each main outcome and commented on attrition and exclusions from the study. If there was a discrepancy between total numbers randomised and numbers in each intervention group we reported on these and any reasons given for this occurrence.

We reported on whether the original investigators employed an intention-to-treat analysis (analysis based on the initial treatment allocation, not on the treatment eventually administered). We assessed whether the numbers and reasons for dropouts and withdrawals in all intervention groups were described or whether it was specified that there were no dropouts or withdrawals. If information is lacking on missing data, the risk of bias will increase.

Selective reporting

We considered the possibility that selective reporting influences the number of published articles and for this reason have also included abstracts and articles of non-English language in our review. Following translation, we have included these articles in the review and entered data into the meta-analysis where available.

We considered there to be selective reporting, if statistically non-significant results were selectively withheld from publication. The most common reasons for non-publication of results are 'lack of clinical importance' or lack of statistical significance. Therefore, meta-analyses excluding unpublished outcomes are likely to overestimate intervention effects. We have tried where possible to include all identified outcomes within the meta-analysis whether they demonstrated statistical significance or not and consequently reducing the likelihood of selective reporting within this review.

Within this review we have highlighted those references where selective reporting may have occurred. Examples of this include where we were unable to compare the original protocol of the study with the final paper and so we were unable to determine whether exclusions had occurred. Additionally, there were articles which identified particular variables in their outcome measures; however, these were not fully reported in their results. In these instances we have highlighted the discrepancies in the tables [Characteristics of included studies](#) and reported within the text of the review.

Other potential sources of bias

We considered that external bias could also influence the number of published articles and again this can be noted from the tables [Characteristics of included studies](#). It is apparent that funding may have been sought, or indeed researchers identified, to consider mechanical or other devices, and their benefits, when compared to other techniques that do not necessitate potentially expensive equipment. This fact may limit the frequency of studies that include expensive equipment as research may be limited due to lack of funding streams.

Measures of treatment effect

For binary outcome measures, we planned to seek data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the individual was later thought to be ineligible or otherwise excluded from treatment or follow up. We aimed to calculate a pooled estimate of the treatment effect for each outcome across studies using relative risk where appropriate.

For continuous outcomes, we recorded either mean relative change from baseline for each group or mean post-treatment or intervention values and their standard deviations (these will be presented separately). If standard errors were reported, we planned to calculate the standard deviations if possible. We calculated a pooled estimate of treatment effect by calculating the mean difference.

Unit of analysis issues

When conducting a meta-analysis combining results from cross-over trials we planned to use the methods recommended by Elbourne ([Elbourne 2002](#)). However, only limited data were available and we entered the first-arm data only from one trial ([Oermann 2001](#)); for the remainder we treated the cross-over trials as if they were parallel trials. Elbourne states that this approach will produce conservative results as it does not take into account within-patient correlation ([Elbourne 2002](#)). Also each participant appears in both the treatment and control group, so the two groups are not independent.

This review comprises data from both parallel and cross-over studies, in the analysis of the data we have combined the results from both types of trial. In order to minimise the carry-over effect from one arm to another, we have included only the data from the first arm of the cross-over trial where possible as suggested by Curtin ([Curtin 2002a](#)); although taking data from the first arm of the trial reduces carry-over it may offer a less efficient treatment estimate consequently leading to selection bias.

There were several studies which examined multiple treatment arms where more than one device was compared to conventional chest physiotherapy ([Modi 2010a](#); [Padman 1999a](#); [Varekojis 2003a](#)). We created duplicate references for each of these studies to enable data from both types of oscillatory device to be entered into the analysis. There was one paper where oscillatory devices were compared with the "usual" airway clearance technique (which encompassed a number of alternative therapies); however, we did not consider it meaningful to extract these data for inclusion in the analysis ([Osman 2010](#)). One further paper compared five different devices and again we were not able to extract the data in a clinically relevant way to be included in the analysis ([Pryor 2010](#)).

A further consideration noted in the study by Varekojis was that the data collected referred to the number of sputum samples rather than number of participants included in the study ([Varekojis 2003a](#)). This does accurately reflect how the comparison influenced sputum expectorated by participants, particularly as the number of samples compared were not equal. There were 24 participants in this study with six sets of sputum data anticipated for each treatment option; however, some of the sputum cups were contaminated by hematemesis, one dried prior to wet weight being measured and one sputum cup was lost prior to weighing, leading to a discrepancy in terms of sputum samples across the intervention groups i.e. 142 compared to 143.

Dealing with missing data

If data were missing from the original trial reports, we planned to seek clarification from the authors. In the instance of a discrepancy between data in abstracts and the published article we sought clarification from the author and acted appropriately when considering data analysis.

Assessment of heterogeneity

The greater the consistency between the primary studies in a meta-analysis, the more generalisable are the results. Heterogeneity refers to the genuine differences between studies rather than those that occur by chance. We planned to test for heterogeneity using the I^2 statistic ([Higgins 2003](#)). The values of I^2 lie between 0% to 100%, and we planned to use a simplified categorization of heterogeneity where we judge heterogeneity as low if the I^2 value is up to 25%, moderate up to 50% and high up to 75% ([Higgins 2003](#)). If this value were to be greater than 75% we would consider heterogeneity as extremely high.

Assessment of reporting biases

Many of the papers measured the outcome variables routinely and often during clinic visits. In the analysis of the papers, where possible, we have included the appropriate time points; however, it was often the case that measurements were recorded on completion of the study and it is these data that have been included in the tables of analyses. We examined the papers to assess when outcome variables were measured and which time points were reported. We recorded the data for each time point reported and noted if data were not presented for any of the outcomes. We looked for sponsorship of the trials by companies and whether this had been acknowledged in the papers. Furthermore, we noted if adverse events which could be a direct consequence of the use of the oscillating devices were reported in these papers.

Data synthesis

We analysed data using a fixed-effect model, but if we had included sufficient studies for each outcome (at least four) and we had identified significant heterogeneity (where heterogeneity was 50% or greater), we planned to use a random-effects model in the final analysis of the data.

Subgroup analysis and investigation of heterogeneity

There were insufficient combined data in the meta-analysis for each comparison and outcome to allow for any of the planned subgroup analysis. If we had included a sufficient number of studies in the review and had identified moderate or high degrees of

heterogeneity between studies in the meta-analyses, we planned to investigate this by performing subgroup analysis of the following:

1. children (up to 16 years) compared to adults;
2. different treatment regimens (frequency per day and duration of treatment sessions) and concomitant medications (e.g. the use of bronchodilators or hypertonic saline);
3. participants with acute exacerbations compared to those with stable disease.

Sensitivity analysis

We also planned to perform the following sensitivity analyses to assess how robust the results of our meta-analysis are:

1. study quality i.e. RCT compared to quasi-RCT;
2. differing baseline characteristics of studies (specifically disease severity as measured by FEV₁ and defined as severely (FEV₁ < 45% predicted), moderately (FEV₁ > 46% to < 65% predicted) and minimally affected (FEV₁ > 65% predicted)).

The studies we included in the review were a mixture of cross-over and parallel designed studies. In a post hoc change we decided to perform a sensitivity analysis including and excluding the studies with a cross-over design to assess whether the study design had an effect on the results.

Summary of findings tables

In a post hoc change in line with current Cochrane guidance, at the 2017 update we added a summary of findings table for each comparison presented in the review. We selected the following seven outcomes to report (chosen based on relevance to clinicians and consumers):

1. FEV₁
2. FEF₂₅₋₇₅

3. FVC
4. Sputum volume
5. Sputum weight (dry or wet)
6. Frequency of exacerbations (as defined by Rosenfeld ([Rosenfeld 2001](#))) as a consequence of the treatment intervention
7. Participant reported satisfaction with treatment intervention

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

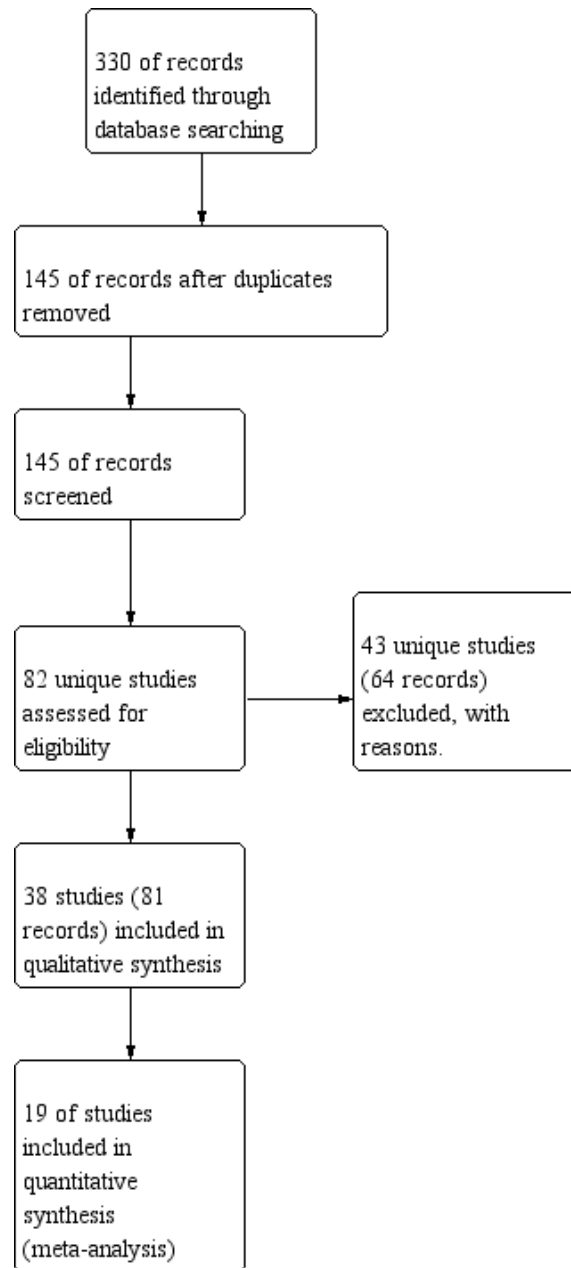
RESULTS

Description of studies

Results of the search

A total of 330 references were identified from searches of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register combined with studies identified through attendance at international conferences. Searches of the international trials databases did not provide any further relevant studies for inclusion in this review. After initial consideration, those studies obviously not relevant to the review question or duplicated were discounted, leaving 145 references to 82 studies requiring closer inspection. Following further examination, 43 studies (64 references) were excluded, details of which can be found in the tables ([Characteristics of excluded studies](#)). There are 39 studies (81 references) included in the review, details of which are provided in the tables and summarised in the text below ([Characteristics of included studies](#)). These are summarised in a study flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

Of the included studies, 11 were published as abstracts only (Davies 2012; Giles 1996; Gotz 1995; Grzincich 2008; Hare 2002; Lyons 1992; Marks 2001; Patel 2013; Pike 1999; Prasad 2005; Warwick 1990), with only two of these providing data that could be included in the meta-analyses (Giles 1996; Grzincich 2008).

Trial design

A cross-over design was used in 22 studies and the remaining 17 studies used a parallel design. A total of 18 studies were generated by research carried out in the USA and 16 of these were single centre. The UK generated eight single-centre studies, and the remaining 10 studies came from Europe, Canada, South Africa and Australia. In addition there were five multicentre studies, two from

the USA, one from Canada, one from Spain and Belgium and finally one from Germany. Study duration varied widely ranging from two days (Braggion 1995) up to 2.8 years (Modi 2010a); duration was unspecified in four studies analysed (Hansen 1990; Khan 2014; Patel 2013; Warwick 1990).

Participants

The 39 included studies involved a total of 1114 participants and the numbers in each trial varied from four (Dingemans 2018a) to 166 (Modi 2010a). Participant age (when identified) varied from four years to 63 years of age; on closer inspection 19 of the studies included children younger than 16 years of age. 10 studies did not describe their gender split, and in the 29 studies which did, 20 of them had a greater number of male participants. There

were 16 studies which did not identify whether participants were in a stable condition or experiencing an exacerbation. In the 23 studies that did report this factor, ten studies included participants who were deemed stable at the time of study initiation and 13 studies included participants who were admitted to hospital for the management of clinical exacerbations.

Interventions

As a consequence of many different descriptions of therapy techniques, it was considered by the authors that certain manual therapies could be combined and considered as one 'type' of therapy. For this reason we have grouped the techniques of PD&P, PD&C and PDPV under the term CPT. Unless otherwise stated we have assumed that CPT is a derivative of, or comparable to, the other terms used in the grouping.

There were 12 studies which failed to identify the frequency of interventions performed on a daily basis (Darbee 2005; Gondor 1999; Grzincich 2008; Hansen 1990; Khan 2014; Milne 2004; Oermann 2001; Patel 2013; Prasad 2005; Pryor 2010; San Miguel Pagola 2016; Warwick 2004). Where this was reported, the most common frequency of treatment interventions was twice daily with a range of one to four times daily. Where there were treatment comparisons, these were done at the same time of day and the same frequency of interventions occurred.

Outcomes measured

Once again the diversity of outcomes measured was great. However, the most frequently used clinical outcome measure was respiratory function (34 studies included respiratory function parameters in their outcome data), followed by sputum weight (19 studies) and individual satisfaction (13 studies).

Excluded studies

A total of 43 studies were excluded.

The authors consider it unlikely that an individual can be instructed in the appropriate usage of therapy devices or treatment techniques in a single session and consequently 22 studies were excluded using this criteria (Borka 2012; Dosman 2003;

Dunn 2013; Dwyer 2017; Elkins 2004; Elkins 2005; Fainardi 2011; Grosse-Onnebrink 2017; Hartsell 1978; Kempainen 2007; Konstan 1994; Lagerkvist 2006; Lindemann 1992; Marks 1998; Marks 2004; McCarren 2006; Natale 1994; Newhouse 1998; Radtke 2018; Scherer 1998; Stites 2006; Van Ginderdeuren 2008). Despite best efforts in specifying appropriate search terms 13 studies were excluded on the grounds that they did not concern either the population under review (Cegla 1993; Clinkscale 2012) or indeed the types of devices we were comparing on this occasion (Cantin 2005; Jarad 2010; Kraemer 1996; Kirkpatrick 1995; Leemans 2018; Morris 1982; NCT02600039; NCT01923753; Salh 1989; Skopnik 1986; Webber 1984). One study was excluded as a consequence of incomplete data being reported in the abstract and the authors not being available for a response to requests for the missing data (Roos 1987). A further study was excluded as it did not contain any of the outcome measures we had identified as useful to this review (Majaesic 1996). One study of hypertonic saline in conjunction with acapella was excluded as the only difference between treatment groups was the timing of hypertonic saline administration (O'Neil 2017). One study was excluded as it did not recruit and was withdrawn (NCT03261219). The remaining four studies were excluded as (following translation of the full papers) were not RCTs (Amelina 2014; Orlik 2000a; Orlik 2000b; Orlik 2001).

Risk of bias in included studies

Further details can be found in the risk of bias sections of the Characteristics of included studies tables.

Allocation

Considering the risk of bias graphs (Figure 2; Figure 3), we can determine that approximately 10% of the published studies had a high risk of allocation bias. This was apparent where there was no clear evidence that the allocation sequence could not be compromised by those entering participants into the studies. Methods of allocation were frequently omitted or described as alternate, and means of randomisation, concealment and sequence generation were not clearly identified. Approximately a further 85% of published studies had an unclear risk of bias, leaving only 5% of studies with a low risk of allocation bias.

Figure 2. Risk of bias: review authors' judgments about each risk of bias item presented as percentages across all included studies.

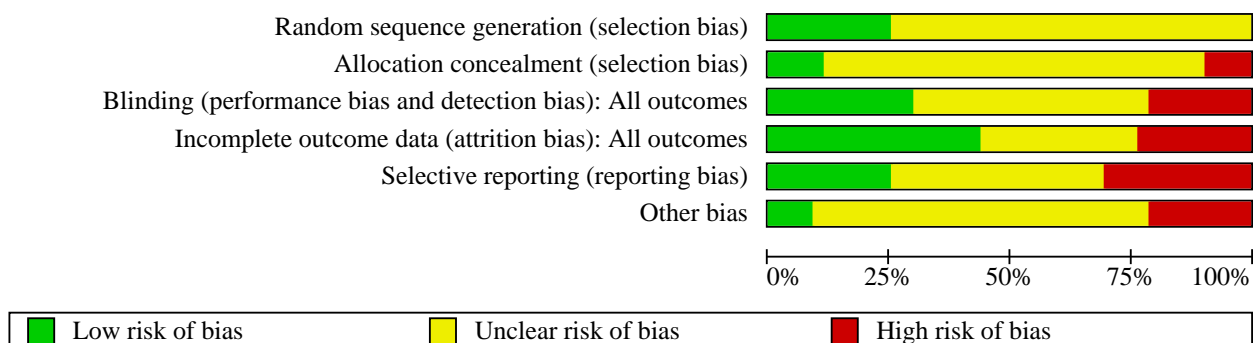


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
App 1998	?	?	-	+	?	?
Arens 1994	?	?	-	+	?	?
Braggion 1995	+	?	-	-	-	?
Darbee 2005	+	-	?	?	?	?
Davies 2012	?	?	-	?	?	?
Dingemans 2018a	?	?	+	+	+	?
Dingemans 2018b	?	?	+	+	+	?
Giles 1996	?	?	?	?	-	?
Gondor 1999	?	?	+	-	?	?
Gotz 1995	?	?	-	?	?	?
Grzincich 2008	?	?	?	?	?	?
Hansen 1990	?	?	?	?	-	?
Hare 2002	?	-	?	?	-	?
Homnick 1995	?	?	?	-	?	+
Homnick 1998	?	-	?	+	-	+
Khan 2014	?	?	?	+	?	?
Kluft 1996	?	-	?	+	+	?
Lyons 1992	?	?	?	?	?	?
Marks 2001	?	?	?	-	-	?
McIlwaine 2001	?	?	+	+	-	?
McIlwaine 2013	+	+	+	+	+	+
Milne 2004	?	?	-	+	?	+
Modi 2010a	+	?	?	-	+	-
Modi 2010b	+	?	?	-	+	-
Newbold 2005	+	+	+	+	+	-
Oermann 2001	?	?	?	+	-	?
Quinn 2010	+	?	+	+	?	-

Figure 3. (Continued)

Oermann 2001	?	?	?	+	-	?
Osman 2010	+	?	+	+	?	-
Padman 1999a	?	?	?	-	-	?
Padman 1999b	?	?	?	-	-	?
Patel 2013	?	?	?	-	?	?
Phillips 2004	?	+	+	+	?	-
Pike 1999	?	?	+	?	?	?
Prasad 2005	?	?	-	+	-	-
Pryor 1994	?	?	+	+	?	?
Pryor 2010	+	?	+	-	-	?
San Miguel Pagola 2016	+	+	?	+	?	?
van Winden 1998	?	?	+	+	?	?
Varekojis 2003a	?	?	?	?	+	-
Varekojis 2003b	?	?	?	?	+	-
Warwick 1990	?	?	-	?	?	?
Warwick 2004	?	?	-	?	+	-
West 2010	+	+	+	+	+	?
Wheatley 2018	+	?	?	?	-	?

Generation of sequence

Nine studies were judged to have a low risk of bias (Braggion 1995; Darbee 2005; McIlwaine 2013; Modi 2010a; Newbold 2005; Osman 2010; Pryor 2010; West 2010; Wheatley 2018). Randomisation according to Latin square design described by Williams (Williams 1949) was used in only one study (Braggion 1995). Darbee used a coin toss to decide which group the first participant was allocated to (Darbee 2005). A random numbers table and block randomisation were used in only one study which used sealed envelopes to conceal allocation; the envelopes were opened in sequence, which may itself be a form of allocation bias (Newbold 2005). A computer-generated randomisation table was used in two studies (McIlwaine 2013; Osman 2010), a random number generator was used in one study (Wheatley 2018) and electronic randomisation in a further study (Modi 2010a). In one study, the allocation sequence was generated by placing 36 pieces of paper (18 PEP mask and 18 acapella) in double-sealed envelopes one of which was opened for each enrolled participant by a research assistant not otherwise involved with the study and then the envelope was discarded (West 2010).

The remaining 30 studies had an unclear risk of bias.

Concealment of allocation

We judged five studies to have a low risk of bias (McIlwaine 2013; Newbold 2005; Phillips 2004; San Miguel Pagola 2016; West 2010). The McIlwaine study used a process of central allocation by an independent statistician, following which the allocation sequence was sent to the study co-ordinator, thus reducing the risk of bias significantly (McIlwaine 2013). The four remaining studies used sealed opaque envelopes to conceal allocation (Newbold 2005; Phillips 2004; San Miguel Pagola 2016; West 2010). Four studies were judged to have a high risk of bias (Darbee 2005; Hare 2002; Homnick 1998; Klufft 1996). Darbee used a coin toss to decide which

group the first participant was allocated to, thereafter allocation was by alternation i.e. could be foretold; therefore we judged there to be a high risk of bias from this method (Darbee 2005). The other three studies with a high risk of bias also used alternate allocation (Hare 2002; Homnick 1998; Klufft 1996). In the remaining 30 studies allocation concealment was not discussed and we judged these to have an unclear risk of bias.

Blinding

As the therapies being compared require participant participation and on occasion the inclusion of a device, it is not possible to blind participants and the clinicians who are implementing the treatments to the treatment group. However, it is possible to blind those individuals collecting data and assessing outcomes. Of the 39 studies available for analysis, only 11 studies identified that blinding of some or all of the outcome assessors or investigators had taken place and hence were judged to have a low risk of bias (Gondor 1999; McIlwaine 2001; McIlwaine 2013; Newbold 2005; Osman 2010; Phillips 2004; Pike 1999; Pryor 1994; Pryor 2010; van Winden 1998; West 2010). Of the remaining 28 studies, 19 were characterised as unclear on the subject of blinding, principally as this had not been discussed throughout the paper (Darbee 2005; Dingemans 2018a; Giles 1996; Grzincich 2008; Hansen 1990; Hare 2002; Homnick 1995; Homnick 1998; Khan 2014; Klufft 1996; Lyons 1992; Marks 2001; Modi 2010a; Oermann 2001; Padman 1999a; Patel 2013; Varekojis 2003a; San Miguel Pagola 2016; Wheatley 2018); nine studies had not used any recognisable means of blinding assessors and were judged to have a high risk of bias (App 1998; Arens 1994; Braggion 1995; Davies 2012; Gotz 1995; Milne 2004; Prasad 2005; Warwick 1990; Warwick 2004).

Incomplete outcome data

Incomplete data were essentially due to participant dropout. Reasons for withdrawal were given in 16 studies, which we judged

to have a low risk of bias (App 1998; Arens 1994; Dingemans 2018a; Homnick 1998; Khan 2014; Klufft 1996; Mcllwaine 2001; Mcllwaine 2013; Milne 2004; Newbold 2005; Oermann 2001; Osman 2010; Phillips 2004; Pryor 1994; van Winden 1998; West 2010). Principally this was reported as being: due to chest infections leading to withdrawal by the investigators (App 1998; Mcllwaine 2001; Mcllwaine 2013; Oermann 2001); early discharge and consequent incomplete data collection (Osman 2010; West 2010); and failure to comply with the treatment regimen (Arens 1994; Klufft 1996; Mcllwaine 2001; Mcllwaine 2013; Newbold 2005). In the remaining 23 studies, reasons for any withdrawals that occurred were not given, leading to a potentially higher risk of bias.

Selective reporting

Many of the papers measured the outcome variables routinely and often during clinic visits. In the analysis of the papers, where possible, we have included the appropriate time points. However, it was often the case that measurements were recorded on completion of the study and it is these data that have been included in the tables of analyses. The authors found occasionally that some parameters, e.g. blood oxygen measurements, were taken but were not commented upon in the published paper. We thought 13 studies had the potential for selective reporting, where information had been collected but no further comments were made, e.g. when days lost from work or school was identified as being an outcome variable but was not reported in the results (App 1998; Braggion 1995; Giles 1996; Hansen 1990; Hare 2002; Homnick 1998; Marks 2001; Modi 2010a; Mcllwaine 2001; Oermann 2001; Padman 1999a; Prasad 2005; San Miguel Pagola 2016;). Furthermore in one study by Mcllwaine, adherence to the regimen of less than 85% was considered suboptimal and led to participants being withdrawn (Mcllwaine 2001). In another study, measurements were performed at the participants' homes and all the assessments apart from the lung function test were self-administered, with participants submitting their home diary to the assessor at the end of each treatment arm. In this case there is an opportunity for reporting bias as we are relying on the accuracy of documentation provided by the participant (San Miguel Pagola 2016).

Other potential sources of bias

The possibility of bias due to order of the treatments was unlikely as in all of the studies where a cross-over occurred, the order of treatment interventions were randomised or alternated. Study fatigue is always a consideration when using small populations such as those with CF; and indeed one study by Newbold identified this as a reason why some participants declined to enter into the study (Newbold 2005). However, as the majority of the studies included in this review are short term, one might surmise that there was little opportunity for study fatigue to impact upon adherence and this was not an outcome we chose to measure.

The possibility of publication bias is an important point to consider. The impact of this is that published studies may not be truly representative of all valid studies undertaken, and this bias may distort meta-analyses and systematic reviews of large numbers of studies. The problem may be particularly significant when the research is sponsored by entities that may have a financial interest in achieving favourable results.

With regards to the intervention, when specific devices were used, there was some evidence of sponsorship by way of provision of equipment by the manufacturers and this may be considered as a

source of bias. However, this did not necessarily favour the device over other modalities. The original authors in the seven studies where this occurred, acknowledged the manufacturers for their sponsorship (Darbee 2005; Gondor 1999; Hare 2002; Mcllwaine 2013; Modi 2010a; Osman 2010; Padman 1999a). There were few reported incidences of adverse reactions to the therapy regimens implemented, and in the unlikely event of an adverse event occurring, it was not found to have occurred as a consequence of the device under scrutiny. This may be due to the safety of these devices or indeed may reflect reporting bias; however, we are unable to reach a firm conclusion about this. One paper also reports that a natural competition between two different therapists was created leading to the potential that the data could be skewed depending on how competitive or enthusiastic the therapists were (Warwick 2004).

In two studies there were differences in participant characteristics (Osman 2010; West 2010). One study reported that the measured levels of oxygen saturation were higher at baseline in the HFCWO group than in the group using their 'usual' airway clearance techniques, which could be a potential source of bias as groups were not balanced at the beginning of the intervention (Osman 2010). In the West study, there were clear differences at baseline for age, FEV₁, and exercise performance; participants allocated to the PEP arm of the study were older, had a greater FEV₁ and exercise ability than those in the acapella arm (West 2010). These discrepancies were attributed to the smaller than proposed sample size. In addition, where the studies included children under 16 years of age, it is a possibility that parental influence may have occurred as there appeared to be no measures in place to eliminate or reduce this possibility.

With regards to the reported results, three papers had a discrepancy between number of participants and a greater number of data sets collected (Homnick 1998; Pryor 2010; Varekojis 2003a). Whilst the papers acknowledged this fact, it may have led to duplication of data and a consequent skewing of results.

Effects of interventions

See: **Summary of findings 1** Oscillating devices compared with PEP for cystic fibrosis; **Summary of findings 2** Oscillating devices compared with breathing techniques for cystic fibrosis; **Summary of findings 3** Oscillating devices compared with conventional physiotherapy for cystic fibrosis; **Summary of findings 4** Oscillating devices compared with different oscillating devices for cystic fibrosis

In the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings are provided within the tables (Summary of findings table 1; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Oscillating devices versus PEP

A total of 15 studies reported on this comparison (Braggion 1995; Darbee 2005; Davies 2012; Gotz 1995; Grzincich 2008; Mcllwaine 2001; Mcllwaine 2013; Newbold 2005; Oermann 2001; Osman 2010; Padman 1999a; Prasad 2005; Pryor 2010; van Winden 1998; West 2010). When comparing oscillatory devices with PEP, there were studies which used PEP alone as the control and other studies where oscillatory treatments were compared to treatment

regimens which may also have included PEP, e.g. two studies compared two different oscillating devices (HFCWO, Flutter or Cornet) to PEP (Osman 2010; Pryor 2010). A number of different oscillating devices were used in this comparison: five used HFCWO (Braggion 1995; Darbee 2005; Grzincich 2008; Mcllwaine 2013; Osman 2010); five used flutter (Mcllwaine 2001; Newbold 2005; Osman 2010; Pryor 2010; van Winden 1998); one used IPV (Gotz 1995); one used acapella (West 2010) and two used cornet (Prasad 2005; Pryor 2010). The Padman study was comprised of three arms comparing flutter to PEP and CPT, but in this section we present only the data from the comparison of flutter and PEP (Padman 1999a).

The Pryor study compared flutter, cornet, PEP, ACBT and AD; however, due to the multiple comparators we have not included the data in our meta-analysis. Three studies compared an oscillating device to 'usual airway clearance technique' which included several comparator interventions combined and we found it difficult to breakdown the data meaningfully and therefore have not included these data in our meta-analysis (Davies 2012; Khan 2014; Osman 2010).

One study measured outcomes pre- and post-treatment at admission and at discharge (mean number of days in hospital was nine) (Darbee 2005). We have reported the post-treatment values at discharge and entered these under the 'over one week and up to two week' time point.

The quality of the evidence is presented in [Summary of findings 1](#).

Primary outcomes

1. Respiratory function

a. FEV₁

A total of 15 studies (510 participants) reported on this outcome (very low-quality evidence); however, only nine had data that could be entered into the meta-analysis (Braggion 1995; Darbee 2005; Grzincich 2008; Mcllwaine 2001; Mcllwaine 2013; Newbold 2005; Padman 1999a; van Winden 1998; West 2010) and six reported information we were only able to include narratively (Davies 2012; Gotz 1995; Khan 2014; Osman 2010; Prasad 2005; Pryor 2010).

Four studies reported post-intervention data for FEV₁ per cent (%) predicted (Braggion 1995; Darbee 2005; Grzincich 2008; van Winden 1998). Grzincich recorded FEV₁ pre and 30 minutes post each treatment intervention during a three-day study period (Grzincich 2008). Braggion evaluated the time points of up to one week in their analysis for HFCWO compared with PEP (Braggion 1995). Darbee also compared HFCWO and PEP and reported data at hospital discharge (average duration nine days) (Darbee 2005). Another study evaluated FEV₁ % predicted when comparing flutter and PEP at over two weeks and up to one month (van Winden 1998). None of these were statistically significant (Analysis 1.1).

Five studies reported FEV₁ % predicted as the change from baseline (Mcllwaine 2001; Mcllwaine 2013; Newbold 2005; Padman 1999a; West 2010). One study reported data collected at up to two weeks (West 2010). One study reported data at over two weeks and up to one month (Padman 1999a). Only three studies published data which could be combined and which evaluated FEV₁ % predicted as change from baseline at one year (Mcllwaine 2001; Mcllwaine 2013; Newbold 2005). There were no statistically significant changes

identified for the change from baseline in FEV₁ % predicted at any of the time points evaluated in the meta-analysis (Analysis 1.2).

There were six studies which did not have data available for inclusion in our meta-analysis and which reported FEV₁ narratively (Davies 2012; Gotz 1995; Khan 2014; Osman 2010; Prasad 2005; Pryor 2010). The paper by Gotz considered the comparison of IPV with PEP for a period of two months; the study investigators felt IPV was not superior to PEP when FEV₁ was evaluated using a repeated measures analysis of variance, but there were no data given to support this finding (Gotz 1995). Prasad compared the cornet to PEP and the primary outcome measured was FEV₁ (Prasad 2005). However, there were no statistically significant differences identified despite a small increase in FEV₁ % predicted from baseline in both treatment arms (PEP 2.2% and cornet 4.3%) over the 12-month study period. In concurrence with this finding, the Pryor study (n = 75) compared five different therapy techniques over a 12-month period and found no statistically significant differences among any of the treatment modalities in the primary outcome of the change from baseline in FEV₁ % predicted (P = 0.35); the authors also noted that there was significant decline across the entire study population over the 12-month period (P = 0.02) (Pryor 2010). Three studies comparing HFCWO to 'usual ACT' reported on FEV₁ % predicted (Davies 2012; Khan 2014; Osman 2010). Two studies reported that there was no significant change in FEV₁ between groups using HFCWO or their normal ACT (Davies 2012; Osman 2010); the third study (paper written in Russian with data translated) suggested that there was a change in FEV₁ using HFCWO as compared to control, but this was not identified as significant (Khan 2014).

b. FEF₂₅₋₇₅

Nine studies (355 participants) reported on this outcome (very low-quality evidence) (Braggion 1995; Darbee 2005; Grzincich 2008; Mcllwaine 2001; Mcllwaine 2013; Newbold 2005; Padman 1999a; Pryor 2010; van Winden 1998); we were able to enter data from eight of these into the analyses, but one study did not report data we could enter into our analysis (Pryor 2010).

Two studies evaluated the time points of up to one week in their analysis and considered FEF₂₅₋₇₅ % predicted for HFCWO compared with PEP, but there were no statistically significant results (Braggion 1995; Grzincich 2008). One further study also measured FEF₂₅₋₇₅ % predicted, with no statistical differences between flutter and PEP after one week and up to two weeks of treatment (Darbee 2005); the same was true of a fourth study which reported at two weeks of treatment (van Winden 1998) (Analysis 1.3).

Five studies reported on the change from baseline in FEF₂₅₋₇₅ % predicted; none of these results were statistically significant (Analysis 1.4). One study reported no statistically significant differences between PEP and acapella after 10 days of treatment when evaluating FEF₂₅₋₇₅ % predicted (West 2010), when analysed in this review at the 'up to two weeks' time point. One of these showed no statistical differences between PEP and flutter at over two weeks and up to one month (Padman 1999a). In three studies no significant difference in the mean change or annual rate of change was found when FEF₂₅₋₇₅ was measured at one year and compared between PEP and flutter (Mcllwaine 2001; Mcllwaine 2013; Newbold 2005). The main publication for

the later McIlwaine study reported that FEF₂₅₋₇₅ % predicted was trending downwards in the HFCWO group, but increased again between visit 5 (at 9 months) and visit 6 (at 12 months). The researchers found 30 out of 46 participants in the HFCWO group required antibiotics for a pulmonary exacerbation during this time, which they suggested could be a treatment effect and may be the reason for the (statistically non-significant) increase in FEF₂₅₋₇₅ % predicted (McIlwaine 2013).

One study reported no statistically significant differences between the treatment modalities of PEP and oscillatory devices of either flutter or cornet when evaluating FEF₂₅₋₇₅ (Pryor 2010).

c. FVC

Nine studies (362 participants) reported on this outcome (very low-quality evidence) (Braggion 1995; Darbee 2005; Grzincich 2008; McIlwaine 2001; McIlwaine 2013; Newbold 2005; Pryor 2010; van Winden 1998; West 2010); eight studies were included in our meta-analysis, but again there were no data from the Pryor paper available to enter into our analysis (Pryor 2010).

Two studies evaluated the time points of up to one week in their analysis and considered FVC % predicted for HFCWO compared with PEP; there were no statistically significant changes (Braggion 1995; Grzincich 2008). Further studies showed no significant differences in FVC % predicted between flutter and PEP after over one week and up to two weeks of treatment (Darbee 2005) or after two weeks and up to one month (van Winden 1998) (Analysis 1.5).

The remaining four studies in our meta-analysis reported on the change from baseline in FVC % predicted (McIlwaine 2001; McIlwaine 2013; Newbold 2005; West 2010). West compared PEP and acapella and reported data at up to two weeks (West 2010). The remaining three studies compared PEP and flutter and we found no significant difference in the mean change or annual rate of change (McIlwaine 2001; McIlwaine 2013; Newbold 2005) (Analysis 1.6). We initially analysed these data using a fixed-effects analysis, but identified a high degree of heterogeneity ($I^2 = 71\%$). As stated in our methods, we re-analysed the data using a random-effects analysis, but in both cases the result was not statistically significant. As for FEV₁, close contact and phone calls from study coordinators may also have contributed to increased adherence identified in the later McIlwaine study and this high adherence may explain the increase in FVC % predicted in both groups from their baseline measurements (McIlwaine 2013).

Finally, Pryor reported no statistically significant difference between any of the treatment modalities for FVC (Pryor 2010).

d. expiratory reserve volume (ERV) or reserve volume (RV)

One study reported on this outcome, but did not provide data we were able to enter into the tables (Pryor 2010).

The investigators found no statistically significant difference between the treatment modalities in the parameter of RV as a percentage of total lung capacity (Pryor 2010).

Secondary outcomes

1. Sputum

a. volume

Two studies (53 participants) reported on this outcome (Grzincich 2008; Khan 2014). Only one study (23 participants) provided data for analysis (Grzincich 2008); sputum was collected following each treatment session when HFCWO was compared with PEP but results were not statistically significant (low-quality evidence) (Analysis 1.7). The second study (30 participants) reported that there was an increase in sputum volume when HFCWO was compared to participants' usual ACT; however there were no data included and we are unaware of what interventions were included in the usual ACT treatment arm (Khan 2014).

b. weight (dry or wet)

Four studies (104 participants) reported on this outcome (low-quality evidence); only one (22 participants) had data for analysis (West 2010), the remaining three did not provide any data to enter (Braggion 1995; Davies 2012; Osman 2010). When West compared PEP to acapella this was found to clear more sputum; however, this was not statistically significant (Analysis 1.8). These data, as with any wet sputum data, may not be clinically relevant as frequently wet sputum is mixed with salivary secretions and consequently may be misinterpreted as a greater volume and or weight of sputum collected. This is a point which is true for all wet weight sputum collected and not specific to this particular paper. Two studies of the studies which did not present data reported no statistical difference in the wet or dry weight of sputum expectorated when HFCWO was compared with PEP (Braggion 1995) or 'usual' airway clearance (Davies 2012). The remaining study was of a short duration (up to one week) and the investigators reported that a significantly greater weight of sputum was yielded when using usual ACT (which included PEP) ($P < 0.001$) compared to HFCWO (Osman 2010).

2. Exercise tolerance

Two studies reported on this outcome (Pryor 2010; West 2010). West assessed exercise performance by measuring the % change in distance achieved in the modified 10 m shuttle test (West 2010). Data showed no difference between treatments at up to two weeks (Analysis 1.12); however, the authors reported that 13 out of 22 participants had an improvement in exercise performance of greater than 10%, which they considered to be clinically significant. We were unable to enter data in the meta-analysis for the second study (Pryor 2010). The study compared both cornet and flutter as oscillatory devices to PEP (and breathing techniques of AD and ACBT which will be discussed later in this review) and there were no statistical differences reported for exercise tolerance using the modified shuttle walk test (Pryor 2010).

3. QoL

Four studies reported on QoL indices (McIlwaine 2013; Newbold 2005; Prasad 2005; Pryor 2010). We able to enter data from the McIlwaine and Newbold studies into our analysis (McIlwaine 2013; Newbold 2005).

The McIlwaine study did not demonstrate a statistically significant difference in any domain evaluated (McIlwaine 2013). The Newbold study demonstrated that there were no significant differences between flutter and PEP in either of the two QoL scores utilised, which were the Quality of Well-being Scale (QWBS) and the

Chronic Respiratory Disease Index Questionnaire (CRQ) (Newbold 2005) (Analysis 1.9). One study comparing the cornet against PEP reported that there was a significant correlation between changes over 12 months in all parameters in the QWBS where current health was assessed, but no correlation when retrospective health over the previous 12 months was evaluated (Prasad 2005). The authors suggested the use of a more sensitive measure when evaluating perceived changes, particularly when children are considered (Prasad 2005). In the final study the investigators found no statistically significant differences among the treatment modalities in QoL indices (Pryor 2010).

4. Level of oxygen saturation in response to treatment

Interpretation of oxygen saturation is done using a finger probe and is most frequently written as SaO₂; however, some studies have recorded this as SpO₂, for ease of clarity we will be consistent in our reporting and use the abbreviation of SaO₂ for oxygen saturation values. Five studies reported on this outcome, but none of these had data available for analysis (Darbee 2005; Gotz 1995; Osman 2010; Padman 1999a; van Winden 1998).

The Darbee paper reported % SaO₂ but only within group differences and not between group data, thus we were not able to enter this into our analysis (Darbee 2005). The paper stated that PEP breathing was associated with increases in SaO₂ during treatment ($P < 0.00004$), but HFCWO therapy resulted in decreases in SaO₂ ($P < 0.00004$) (Darbee 2005). One study evaluated the value of IPV compared with PEP and found there to be no significant difference between the two techniques when considering the change in SaO₂ (Gotz 1995). Padman reported that the level of oxygen saturation remained over 95% in all participants; those in the PEP group had a tendency towards a further increase, although neither result was identified as statistically significant (Padman 1999a). The Osman paper measured the change in SaO₂ where measured data were higher in the HFCWO arm at baseline, during treatment and 30 minutes following treatment (however these were not significant) and as a consequence of their study grouping multiple comparators (breathing exercises, flutter, PEP and CPT) when compared with HFCWO, we felt it was difficult to breakdown the data meaningfully and so have not included the data in the meta analysis (Osman 2010). The fifth study found no significant difference in transcutaneous SaO₂ either before, immediately after or 30 minutes after completion of the physiotherapy treatments of PEP or flutter (van Winden 1998). There was some evidence of desaturation to under 92% identified in one participant using the PEP and six participants using the flutter; in all but one of these participants this episode of desaturation lasted less than two minutes.

5. Frequency of exacerbations

Four studies (219 participants) reported on the frequency of exacerbations (low-quality evidence) (Mcllwaine 2001; Mcllwaine 2013; Newbold 2005; Prasad 2005); two of which had data which could be entered into our analysis (Mcllwaine 2013; Newbold 2005).

The Newbold study found no significant difference in the mean number of hospitalizations owing to pulmonary exacerbations when flutter was compared with PEP ($P = 0.2$) (Newbold 2005) (Analysis 1.10). In the later study by Mcllwaine, the number of pulmonary exacerbations per participant was reported as 1.14 in the PEP group as compared to 2.0 per participant in the HFCWO group ($P = 0.007$) (Mcllwaine 2013). Additionally in this study,

whilst the overall incidence was low, the number of pulmonary exacerbations requiring IV antibiotics in the HFCWO group was three times more than the PEP group (19 as compared to 6). After contact with the study investigators, we have received data that can be entered into our analysis for the number of participants experiencing an exacerbation requiring antibiotics. Significantly fewer participants in the PEP group than in the HFCWO group required antibiotics for a pulmonary exacerbation, OR 4.10 (95% CI 1.42 to 11.84); however, this result was no longer significant when considering just IV antibiotics (Analysis 1.11).

In an earlier study comparing flutter and PEP, Mcllwaine suggested a statistically significant difference between the two groups in hospitalizations for a decline in pulmonary function; there were five hospitalizations in the PEP group and 18 in the flutter group ($P = 0.03$) (Mcllwaine 2001). We were not able to enter these data in the meta-analysis as it is not clear how many individuals experienced these hospitalizations. It is important to state that these hospitalizations did not occur until at least the sixth month of this year-long study and there was a disproportionate number of participants using the flutter being admitted. Despite this being the case, there were no further withdrawals from the study because of significant clinical deterioration (Mcllwaine 2001). The fourth study found no difference in pulmonary exacerbations requiring antibiotics when the cornet was compared with PEP over a 12-month study period (Prasad 2005).

6. Participant-reported satisfaction with treatment intervention

Seven studies (242 participants) reported on this outcome (very low-quality evidence) (Braggion 1995; Mcllwaine 2013; Osman 2010; Padman 1999a; Prasad 2005; van Winden 1998; West 2010). Only one (22 participants) had data available for our analysis (West 2010).

West reported on user satisfaction using a five-point scale to rate their satisfaction with aspects of efficacy, convenience, comfort, and overall satisfaction (West 2010). There was no significant difference between acapella and PEP (Analysis 1.13).

Osman reported on participant satisfaction based on comfort, efficacy, preference and frequency of urinary leakage; as a consequence of their study grouping multiple comparators (breathing exercises, flutter, PEP and CPT) when compared with HFCWO. We felt it was difficult to breakdown the data meaningfully and so have not included the data in the meta analysis (Osman 2010). However, in this paper 17 participants (55%) who completed the study, expressed a preference for their usual ACT over HFCWO (Osman 2010).

Tolerance to the treatments of HFCWO and PEP were discussed in the paper by Braggion, who referred to the results as good, but without statistical or other evidence to support this finding (Braggion 1995). Similarly in the paper by Mcllwaine, participant satisfaction based on comfort, independence and flexibility showed no difference in the comfort and independence parameters, but PEP scored more highly when considering flexibility ($P > 0.001$) (Mcllwaine 2013). When flutter was compared to PEP in the study by Padman, all participants reported they felt better and ease of expectoration was cited as having improved, although there were no data provided to support this finding (Padman 1999a). Prasad compared the cornet to PEP, with no significant changes in parameters over the year-long study or

indeed between treatment groups (Prasad 2005). One child in each group withdrew, with the reasons given being the device was either too difficult to clean or they preferred their original device. There was no correlation in the decision to continue with the device at the end of the study. The remaining study reported finding no statistical differences in satisfaction between the techniques of flutter and PEP (van Winden 1998).

7. LCI

Only one study reported on this outcome (Prasad 2005). Despite no statistical evidence of effect of the treatment, the authors felt that LCI was a more sensitive measure of abnormal lung function and further studies should be directed at the clinical relevance of LCI as an outcome measure when conventional outcomes appear normal (Prasad 2005).

Oscillating devices versus breathing techniques

Nine studies reported on this comparison (App 1998; Dingemans 2018a; Dingemans 2018b; Milne 2004; Osman 2010; Phillips 2004; Pike 1999; Pryor 1994; Pryor 2010; San Miguel Pagola 2016). Again, a variety of oscillating devices were employed: three studies compared flutter to breathing techniques (App 1998; Milne 2004; Pike 1999); two studies compared HFCWO to breathing techniques (Osman 2010; Phillips 2004); one study compared acapella (OPEP) to AD (San Miguel Pagola 2016); and one study compared two different frequencies of IPV in combination with AD to AD alone (Dingemans 2018a; Dingemans 2018b). In the Osman paper, as a consequence of their study grouping multiple comparators (breathing exercises, flutter, PEP and CPT) when compared with HFCWO, we felt it was difficult to breakdown the data meaningfully and so have not included the data in the meta-analysis (Osman 2010). The earlier Pryor study compared flutter combined with ACBT to ACBT alone (Pryor 1994) and the later Pryor study compared flutter, cornet, PEP, ACBT and AD and reported no statistically significant differences between the techniques for any outcome (Pryor 2010).

One study presents some data as median values and interquartile (IQR) ranges which we are not able to include in our analysis and we present these results narratively (San Miguel Pagola 2016).

The quality of the evidence is presented in [Summary of findings 2](#).

Primary outcomes

1. Respiratory function

a. FEV₁

Nine studies (210 participants) reported on this outcome (low-quality evidence) (App 1998; Dingemans 2018a; Dingemans 2018b; Milne 2004; Osman 2010; Phillips 2004; Pike 1999; Pryor 1994; Pryor 2010; San Miguel Pagola 2016).

Absolute post-treatment values

We were able to analyse the values for FEV₁ % predicted at up to one week from one study (San Miguel Pagola 2016). Results from the paper showed that lung function remained stable during the intervention and the data analysed after the five-day intervention showed no significant differences between combined acapella and AD therapy and AD alone (Analysis 2.1).

Change from baseline

Two studies reported on the change from baseline in FEV₁ % predicted (App 1998; Dingemans 2018a; Dingemans 2018b). When analysed the data from the Dingemans study did not show a significant difference between either high-frequency IPV or low-frequency IPV and AD at over one week and up to two weeks (Analysis 2.2). However, in the published paper Dingemans reported that participants treated with IPV at a higher frequency showed a significant improvement in FEV₁ compared to AD ($P < 0.05$), while AD demonstrated greater improvement in lung function in FEV₁ % predicted when compared to the lower frequency IPV ($P < 0.05$); this suggests that the IPV frequency may influence the efficacy of IPV as a therapeutic option (Dingemans 2018a; Dingemans 2018b). The difference in the original results and our analysis may be due to the fact that this was a cross-over study while the investigators would have been able to analyse the data more appropriately. We were able to enter data from the App study for FEV₁ % predicted at the time point 'over two weeks and up to one month' into our analysis (App 1998), and these showed no significant results when comparing oscillation with AD (Analysis 2.1).

Five of the studies were of short duration and reported results up to one week, but no data were available for analysis. The Milne study found no statistical difference between flutter and ACBT (Milne 2004). Osman reported that there was no significant change in FEV₁ between groups using HFCWO or their normal ACT (Osman 2010). In the study comparing HFCWO to ACBT, Phillips reported statistically significant results for FEV₁ (L) ($P = 0.03$) in favour of ACBT (Phillips 2004). The study by Pike did not report any significant differences between treatments for pulmonary function (Pike 1999). The earlier Pryor study showed no statistical differences between ACBT and flutter and ACBT combined (Pryor 1994).

The later study by Pryor, which was 12 months in duration, found no statistical differences between treatment techniques of ACBT, AD, cornet, flutter and PEP when considering FEV₁ ($P = 0.35$) during the study period (Pryor 2010).

b. FEF₂₅₋₇₅

Two studies (29 participants) reported absolute values for this outcome after treatment (very low-quality evidence) (Milne 2004; San Miguel Pagola 2016). We were able to analyse the data from one study for FEF₂₅₋₇₅ % predicted at "up to one week" in our analysis (San Miguel Pagola 2016). Results from the paper showed that lung function remained stable during the intervention and our analysis showed that there were no significant differences when comparing combined therapy (acapella plus AD) with usual care (AD alone) (Analysis 2.3).

Milne reported that no statistical difference was found between flutter and ACBT at the same time point (Milne 2004).

c. FVC

Eight studies (181 participants) reported on this outcome (low-quality evidence) (App 1998; Dingemans 2018a; Dingemans 2018b; Milne 2004; Phillips 2004; Pike 1999; Pryor 1994; Pryor 2010; San Miguel Pagola 2016), but we were only able to analyse data from three of these (App 1998; Dingemans 2018a; Dingemans 2018b; San Miguel Pagola 2016).

Absolute post-treatment values

One cross-over study reported absolute values for FVC % predicted at the time point "up to one week" ([San Miguel Pagola 2016](#)). Baseline data presented in the paper showed that lung function remained stable during the intervention and our analysis showed no significant difference between combined therapy (acapella plus AD) with usual care (AD alone) ([Analysis 2.5](#)).

The later study by Pryor found no statistical differences between treatment techniques of ACBT, AD, cornet, flutter and PEP at 12 months ([Pryor 2010](#)). In a short duration study Phillips compared HFCWO with the breathing techniques of ACBT and reported statistically significant results for FVC in favour of ACBT ([Phillips 2004](#)). Milne in a short duration study of four days demonstrated no significant differences between treatments for pulmonary function ([Milne 2004](#)).

Change from baseline

We were able to analyse data from two studies ([App 1998](#); [Dingemans 2018a](#); [Dingemans 2018b](#)).

At over one week and up to two weeks, Dingemans reported data for low-frequency IPV versus AD ([Dingemans 2018a](#)) and high-frequency IPV versus AD ([Dingemans 2018b](#)). Our analysis shows a significantly higher increase in FVC % predicted for AD compared to low-frequency IPV, MD -5.60 (95% CI -9.45 to -1.75), but a higher increase in FVC % predicted for high-frequency IPV compared to AD, MD 4.40 (95% CI 1.11 to 7.69) ([Analysis 2.5](#)). These findings agree with the suggestion made in the paper that the IPV frequency may influence the efficacy of IPV as a therapeutic option ([Dingemans 2018a](#); [Dingemans 2018b](#)).

At one month App found no significant changes at the end of the one-month study period when comparing flutter and AD in a cross-over study ([Analysis 2.5](#)). The investigators did, however, identify a tendency towards improvement of up to 6.5% from baseline in both groups, but attributed this to non-specific improvement or the possibility of a training effect ([App 1998](#)).

Pryor and Osman in the remaining short duration studies demonstrated no significant difference in change from baseline in any pulmonary function parameters ([Osman 2010](#); [Pryor 1994](#)).

The remaining short duration study by Pike did not report absolute post treatment values or change from baseline but only provided P values which did not demonstrate statistical significance for any pulmonary function parameters ([Pike 1999](#)).

d. ERV or RV

No studies reported on this outcome.

Secondary outcomes

1. Sputum

a. volume

One study (14 participants) reported on this outcome and provided data to enter into the analysis (low-quality evidence) ([App 1998](#)).

App considered the use of flutter and AD, but there was no statistically significant difference between the two techniques, despite acknowledging a tendency for expectorated sputum

volume to be greater following treatment with the flutter regardless of therapeutic order ([Analysis 2.6](#)).

b. weight (dry or wet)

Six studies (114 participants) reported on this outcome (low-quality evidence) ([Milne 2004](#); [Osman 2010](#); [Phillips 2004](#); [Pike 1999](#); [Pryor 1994](#); [San Miguel Pagola 2016](#)); but data were only available for the analysis from one study ([Milne 2004](#)).

The Milne data showed no significant difference in sputum weight in the short-term study when flutter was compared to ACBT ([Analysis 2.7](#)).

In the study by Phillips, it was stated that the weight of expectorated sputum was greater with sessions of ACBT than with HFCC, but this was not significant at the 24-hour time point ([Phillips 2004](#)).

Pike also considered the outcome of wet sputum weight ([Pike 1999](#)). Using the cross-over paired t-test and McNemar's Chi² test for statistical analysis, they found no significant differences between treatments of flutter and ACBT when measuring wet sputum weight. As with the Pryor study, one of the monitored sessions was in supine ([Pike 1999](#); [Pryor 1994](#)). It is not clear whether the participants had previously carried out their flutter therapy prior to adopting this position. It is not possible to use flutter in a postural drainage position other than sitting unless adaptations were made, and the implementation of adaptation was not apparent from the study methodology. Pryor considers the variables of ACBT alone versus ACBT with flutter ([Pryor 1994](#)). They report that there was a significant increase in the weight of sputum expectorated ($P < 0.001$) when ACBT alone was used. The remaining study was of a short duration (up to one week) and the investigators demonstrated that a significantly greater weight of sputum was yielded when using usual airway clearance techniques (of which included breathing techniques) ($P < 0.001$) compared to HFCWO ([Osman 2010](#)).

The San Miguel Pagola study reported median (IQR) values for sputum expectoration ([San Miguel Pagola 2016](#)). The paper states that during nebulisation with hypotonic saline and hyaluronic acid sputum expectoration was greater with combined therapy (acapella with AD) than AD alone, median difference 1.8 mL (95% CI 0.2 to 6.2). However, both interventions led to similar sputum expectoration during AD, during the session evaluated as a whole (nebulisation period and AD period combined) and the subsequent 24 hours ([San Miguel Pagola 2016](#)).

2. Exercise tolerance

One study reported on this outcome and found no statistical differences between treatment techniques of ACBT, AD, cornet, flutter and PEP when considering modified shuttle walk scores ([Pryor 2010](#)).

3. QoL

One study reported on this outcome and found no statistical differences between treatment techniques of ACBT, AD, Cornet, Flutter and PEP when considering the QoL score of CRQ and Short Form-36 ([Pryor 2010](#)).

4. Level of oxygen saturation in response to treatment

Two studies reported on this outcome, but neither had any data available for analysis ([Osman 2010](#); [Pike 1999](#)). In the cross-over

trial with two treatments per day, Pike reported that there was no statistically significant difference in SaO₂ between treatments (flutter or ACBT) (Pike 1999). The Osman paper measured the change in SaO₂ where measured data were higher in the HFCWO arm at baseline, during treatment and 30 minutes following treatment; however, these were not significant. As previously stated, due to the study design we felt it was difficult to breakdown the data meaningfully and so have not included the data in the analysis (Osman 2010).

5. Frequency of exacerbations as a consequence of the treatment intervention

There were no studies reporting on this outcome for this comparison.

6. Participant reported satisfaction with treatment intervention

Six studies (114 participants) of short duration (up to two weeks) reported on this outcome (low-quality evidence), but none had any data which we could enter into our analysis (Milne 2004; Osman 2010; Phillips 2004; Pike 1999; Pryor 1994; San Miguel Pagola 2016).

Milne considered satisfaction and whether participants were likely to change their preferred therapy following the study period; there were no statistical differences in satisfaction between the techniques and approximately 45% chose to continue with flutter either independently or in conjunction with ACBT (Milne 2004). Osman considered participant satisfaction in terms of comfort, efficacy and urinary leakage; however, these data are from combined interventions and we were unable to breakdown the data meaningfully in order to include it in our meta-analysis (Osman 2010). The investigators in the Osman study identified that 55% of their study population preferred their normal ACT compared to HFCWO; in this study the normal ACT was either ACBT or AD 83% of control participants (Osman 2010). Phillips found that all participants in their cohort of 10 found the technique of ACBT to be comfortable (Phillips 2004). In the same study, 40% of participants found the HFCWO to be comfortable, but difficult to clear secretions (80%); however, all participants felt ACBT made it easier to clear secretions (Phillips 2004). Participant preference was reported in the Pike study, with 100% recommending ACBT and 55% flutter ($P < 0.008$) (Pike 1999). Comfort and convenience were considered in the Pryor study, with the addition of effect on breathlessness and if the participants were likely to change their regimen based on preference (Pryor 1994). Here participants found both treatments easy to use but most preferred ACBT due to helpfulness at clearing secretions. The three participants who did indicate a preference for flutter had discontinued within the month following completion of the study (Pryor 1994). In the final study, at the end of each treatment arm, participants completed a self-administered Likert-type scale for domains such as ease of expectoration, improvement in symptoms and preferred intervention (San Miguel Pagola 2016). In addition, participants reported their tolerance of hypertonic saline and hyaluronic acid in a home diary each day, by registering the presence and severity of haemoptysis, cough, throat irritability and saltiness. Although no differences were observed in the Leicester Cough Questionnaire score, the total Cough and Sputum Assessment Questionnaire score and the sputum symptoms domain score improved for combined therapy compared with usual care. Investigators also reported that participants showed a significant preference for combined therapy, median value 3.5 points (95% CI 1.0 to 5.5) ($P >$

0.05); this was mainly related to a reduction in adverse effects from hypertonic saline and hyaluronic acid (San Miguel Pagola 2016).

7. LCI

No studies reported on this outcome.

Oscillating devices versus conventional physiotherapy

A total of 16 studies reported on this comparison (Arens 1994; Braggion 1995; Giles 1996; Gondor 1999; Hansen 1990; Hare 2002; Homnick 1995; Homnick 1998; Kluft 1996; Lyons 1992; Modi 2010a; Padman 1999b; Osman 2010; Varekojis 2003a; Warwick 1990; Warwick 2004). There were three studies considering multiple treatment arms where more than one oscillatory device was compared to conventional chest physiotherapy (Modi 2010a; Padman 1999a; Varekojis 2003a). For each of these studies a duplicate reference was created to enable data from both types of oscillatory device to be entered into the analysis.

Six studies compared HFCWO to CPT (Arens 1994; Braggion 1995; Hansen 1990; Kluft 1996; Warwick 1990; Warwick 2004); three studies compared flutter to CPT (Giles 1996; Gondor 1999; Homnick 1998); and two studies compared IPV to CPT (Hare 2002; Homnick 1995). Four further studies compared multiple oscillating devices and CPT (Modi 2010a; Osman 2010; Padman 1999b; Varekojis 2003b). One study compared flutter, HFCWO and PD&P (Modi 2010a; Modi 2010b); another study compared flutter, PEP and CPT (Padman 1999a; Padman 1999b); the third study compared IPV, HFCWO and PD&P (Varekojis 2003a; Varekojis 2003b). These three studies presented data for different oscillating devices compared to a single arm of conventional physiotherapy and these data will be presented separately in this review as follows: flutter versus PD&P (Modi 2010a), HFCWO versus PD&P (Modi 2010b), flutter versus PEP (Padman 1999a), flutter versus CPT (Padman 1999b), IPV versus PD&P (Varekojis 2003a) and HFCWO versus PD&P (Varekojis 2003b). As a consequence of the Osman study grouping multiple interventions (breathing exercises, flutter, PEP and CPT) when compared with HFCWO, we have not included the results in the meta-analysis (Osman 2010).

The quality of the evidence for this comparison is presented in [Summary of findings 3](#).

Primary outcomes

1. Respiratory function

a. FEV₁

A total of 10 studies (363 participants) reported 11 data sets on this outcome (very low-quality evidence) (Arens 1994; Braggion 1995; Giles 1996; Gondor 1999; Hare 2002; Homnick 1995; Homnick 1998; Modi 2010a; Modi 2010b; Osman 2010; Padman 1999b).

Four studies reported on absolute post treatment values for FEV₁ % predicted which we entered into our analysis (Braggion 1995; Giles 1996; Gondor 1999; Homnick 1995). These were reported at different time points and we were only able to combine data for the time point 'up to one week' (Analysis 3.1). Braggion compared FEV₁ % predicted for HFCWO compared with CPT and reported data at the time point of 'up to one week' but found no statistically significant differences between groups (Braggion 1995). The Gondor paper presents absolute data at day 7 and day 14 for this outcome, neither of which showed a significant difference

between groups in our analysis (Analysis 3.1). However, the Gondor paper reports that there was a significant improvement in FEV₁ in both treatment groups over the two-week treatment period, with the flutter group having a significantly higher increase from baseline by day 7 than the CPT group; further increases in FEV₁ from day 7 to the end of treatment were not significant and the investigators did not find any statistical difference between the treatment groups (Gondor 1999). Giles also reported this outcome and demonstrated no significant difference between flutter and CPT during or after the treatment periods (Giles 1996). The Homnick data also showed no significant differences in FEV₁ % predicted between IPV and CPT at the end of the six-month study period (Homnick 1995).

Hare noted significant improvements from admission to discharge in the IPV group for FEV₁, but data were not provided to support this claim (Hare 2002). In the later Homnick study, investigators found no significant differences between flutter and CPT in % predicted FEV₁ (Homnick 1998).

Two studies reported data on the change in FEV₁ % predicted from baseline which we were able to enter into the analysis (Arens 1994; Padman 1999b). Arens reported data for the change from baseline in FEV₁ % predicted at time points of 'up to one week' and 'over one week and up to two weeks' for the comparison between HFCWO and CPT (Arens 1994); Padman reported data for this outcome at 'over two weeks and up to one month' (Padman 1999b). Analysis showed no significant differences between treatment groups at any time point (Analysis 3.2).

Osman reported that there was no significant change in FEV₁ between groups using HFCWO or their normal ACT (Osman 2010). As already stated, these data are from several comparator interventions combined and not included it in our meta-analysis.

In the Modi study, no differences were identified between the three therapies (PD&P, FD, HFCWO) in FEV₁ % predicted (Modi 2010a; Modi 2010b). The data presented in the paper can not be analysed here as they report longitudinal decline in respiratory function as % predicted from baseline adjusted for BMI rather than a post intervention or change from baseline measure of lung function.

b. FEF₂₅₋₇₅

Eight studies (319 participants) reported nine data sets on this outcome (very low-quality evidence) (Arens 1994; Braggion 1995; Gondor 1999; Hare 2002; Homnick 1995; Homnick 1998; Modi 2010a; Modi 2010b; Padman 1999a). Only five had data suitable for analysis; of these, four presented data for absolute values of FEF₂₅₋₇₅ % predicted (Braggion 1995; Gondor 1999; Homnick 1995) (Analysis 3.3) and two presented change data (Arens 1994; Padman 1999a) (Analysis 3.4).

Two studies evaluated FEF₂₅₋₇₅ % predicted at the time point of up to one week (Braggion 1995; Gondor 1999). There were no statistically significant differences when comparing HFCWO with CPT (Braggion 1995), or when comparing flutter with CPT (Gondor 1999). The combined results also showed no significant difference (Analysis 3.3). In the earlier Homnick study, no significant differences were noted between IPV and CPT at the end of the six-month study period (Homnick 1995).

Arens reported on the change from baseline in FEF₂₅₋₇₅ % predicted; the analysis did not show any statistically significant differences between HFCWO and CPT at either up to one week or over one week and up to two weeks (Arens 1994). Padman presented data for the time point over two weeks and up to one month which were similarly non-significant (Analysis 3.4).

Two studies did not present data which could be entered into the meta-analysis (Hare 2002; Homnick 1998). Significant improvements were described in the Hare study from hospital admission to discharge in the IPV group for FEF₂₅₋₇₅, but data were not provided to support this claim when IPV was compared with CPT (Hare 2002). The later Homnick study reported no significant difference in FEF₂₅₋₇₅ % predicted at hospital discharge after admission for an exacerbation (Homnick 1998).

In the Modi study no statistically significant differences were identified between PD&P and FD or PD&P and HFCWO for FEF₂₅₋₇₅ % predicted however with FD and HFCWO there was considered to be a significant difference P=0.035 (Modi 2010a; Modi 2010b). The data presented in the paper can not be analysed here as they report longitudinal decline in respiratory function as % predicted from baseline adjusted for BMI rather than a post intervention or change from baseline measure of lung function.

c. FVC

Seven studies (268 participants) reported eight data sets for this outcome (very low-quality evidence) (Braggion 1995; Giles 1996; Gondor 1999; Hare 2002; Homnick 1995; Homnick 1998; Modi 2010a; Modi 2010b). Four of which had data suitable for analysis (Braggion 1995; Giles 1996; Gondor 1999; Homnick 1995).

Two studies evaluated FVC % predicted at up to one week in a comparison of HFCWO and CPT (Braggion 1995) and flutter and CPT (Gondor 1999). When entered into our meta-analysis the data show no significant differences between treatment groups (Analysis 3.5). In the study by Giles, there was no significant difference between flutter and CPT during or after the treatment period of over two weeks and up to one month (Giles 1996). In the earlier Homnick study, no significant differences were noted between IPV and CPT at the end of the six-month study period (Homnick 1995).

The later Homnick study compared flutter to CPT and reported no significant difference in FVC % predicted at hospital discharge after admission for an exacerbation (Homnick 1998). Hare compared IPV to CPT and also noted no significant difference between treatment groups at the end of the treatment period (Hare 2002).

In the Modi study, no differences were identified between the three therapies (PD&P, FD, HFCWO) in FVC % predicted (Modi 2010a; Modi 2010b). The data presented in the paper can not be analysed here as they report longitudinal decline in respiratory function as % predicted from baseline adjusted for BMI rather than a post intervention or change from baseline measure of lung function.

d. ERV or RV

Three studies reported on this outcome (Arens 1994; Hare 2002; Homnick 1998). Data were only available from the Arens study for the change from baseline at time points of 'up to one week' and 'over one week and up to two weeks' (Arens 1994). There was no significant difference for RV when comparing HFCWO and CPT at either time point (Analysis 3.6).

The remaining two studies reported on time points of 'up to two weeks' (Hare 2002; Homnick 1998). In the Hare study, significant improvements were noted from admission to discharge in the IPV group for RV, but again no data were supplied to support this finding (Hare 2002). In the study by Homnick, no significant differences were found between flutter and CPT, although RV improved significantly in each group from baseline to discharge (Homnick 1998).

Secondary outcomes

1. Sputum

a. volume

Two studies (17 participants) of short duration with time points of 'up to one week' reported on this outcome, but data were not suitable to enter into our analysis (low-quality evidence) (Hansen 1990; Lyons 1992).

Hansen compared the HFCWO with CPT and reported a statistical difference in the volume of mucus cleared in favour of HFCWO ($P < 0.001$) (Hansen 1990). In the Lyons paper, the authors report the only statistically significant variable was sputum volume, where less sputum was produced on the "flutter only" day ($P = 0.0015$) (Lyons 1992). The suggestion therefore made by the authors is that flutter cannot be substituted for CPT.

b. weight (dry or wet)

Eight studies (188 participants) reported nine sets of information on this outcome (very low-quality evidence) (Arens 1994; Braggion 1995; Giles 1996; Kluft 1996; Osman 2010; Varekojis 2003a; Varekojis 2003b; Warwick 1990; Warwick 2004). There are two sets of data from the Varekojis study, one for IPV compared to PD&P (Varekojis 2003a) and one for HFCWO compared to PD&P (Varekojis 2003b). Six data sets were available to enter into the analysis from five studies (Arens 1994; Giles 1996; Kluft 1996; Varekojis 2003b; Warwick 2004).

Five studies presented six sets of data for up to one week for both dry (Analysis 3.7) and wet sputum weight (Analysis 3.8). There were no overall significant differences between oscillating devices and CPT for either outcome at this time point (Analysis 3.7; Analysis 3.8). Although not significant in our analysis, Kluft reported a significant result in favour of HFCWO in the published paper for dry weight ($P < 0.01$, using a Wilcoxon signed rank test) (Kluft 1996). The results from the Kluft study for wet sputum weight significantly favoured oscillating devices compared to CPT when entered into our analysis, MD 3.90 g (95% CI 0.08 g to 7.72 g) (Kluft 1996). When the duration of sampling was further analysed it would appear that the sputum was collected over a six-day period (Kluft 1996), yielding a greater sampling period than the other studies in the comparison which were collected over a 1-hour to a 24-hour period. One study reported sputum weights at over one week and up to two weeks (Warwick 2004); and only one further study reported sputum weights over two weeks (Giles 1996).

The remaining three studies do not have data available to enter into the meta-analysis. The first of these studies, no data were provided, but the investigators noted that there was no significant difference in sputum weight (either wet or dry) between the HFCWO group or the CPT group when measured at the end of the treatment period (Braggion 1995). The second study was of a short duration (up to one week) and the investigators demonstrated that a significantly greater weight of sputum was yielded when

using breathing techniques ($P < 0.001$) compared to HFCWO (Osman 2010). However, as a consequence of this study using multiple comparators we found it difficult to break down the data meaningfully and have not included the data in the meta-analysis. In the remaining study, Warwick measured both wet and dry sputum weight following treatments of either CPT and HFCWO in his 1990 abstract. He found that there was no statistical difference ($P = 0.221$) for the wet weights but a significant difference for dry weights ($P = 0.046$) favouring the HFCWO in the 13 pairs of samples analysed (Warwick 1990).

2. Exercise tolerance

One study reported on this outcome using the six-minute walk test (Gondor 1999). The analysis showed no significant differences between treatment groups when walk distance was evaluated after two weeks of treatment (Analysis 3.9).

3. QoL

The Modi study reports health-related QoL for 12 domains in the CFQ (Modi 2010a; Modi 2010b). The ITT analysis of data from the final questionnaire revealed a mean (SD) difference between treatment groups only in the domain of 'Body Image' (PD&P = 87.9 (3.1), flutter = 82.6 (3.4), HFCWO = 78.2 (3.1), $P = 0.03$). The change in each CFQ domain from baseline to the first or fifth assessment after randomization, and the change from baseline to the final CFQ assessment obtained (ITT analysis) only showed a difference in the 'Social' domain at the final assessment. However, after correcting for multiple comparisons in the CFQ analyses, these results were non-significant. The CFQ 'Respiratory Domain' score was positively correlated with the overall satisfaction score in the Treatment Satisfaction Survey (TSS) at the final assessment point ($R = 0.23$, $P < 0.006$).

4. Level of oxygen saturation in response to treatment

Four studies reported on this outcome (Arens 1994; Gondor 1999; Osman 2010; Padman 1999b), but only one provided data which could be entered into our analysis (Arens 1994). Data from both time points, up to one week and over one week and up to two weeks, did not favour either treatment (Analysis 3.10). However, the clinical relevance of this result is questionable as frequently activities such as ACTs correspond with a transient decrease in SaO_2 and there is no suggestion that it did not return to normal pre-treatment values within a reasonable time period (e.g. 20 minutes).

Gondor monitored SaO_2 during the study period and reported no significant differences between treatment with either flutter or CPT (Gondor 1999). Padman reported that SaO_2 was higher than 95% in all participants, with no statistical difference between treatments (Padman 1999b). The Osman paper measured the change in SaO_2 during treatment and 30 minutes following treatment; SaO_2 levels were higher in the HFCWO arm at baseline, however, the differences between groups were not significant (Osman 2010). As already stated, the study grouped multiple comparators (breathing exercises, flutter, PEP and CPT) to compare with HFCWO and so we have not included the data in the meta-analysis.

5. Frequency of exacerbations as a consequence of the treatment intervention

Four studies (262 participants) reported on this outcome, with three providing data for analysis on the number of days of hospitalisation (very low-quality evidence) (Arens 1994; Gondor 1999; Homnick

1995; Modi 2010a; Modi 2010b). Our analysis showed no significant difference between oscillating devices or CPT at either 'up to one week' or 'over one week and up to two weeks' (Analysis 3.11). The Modi study reported no significant difference in the time to next pulmonary exacerbation across the comparators (Modi 2010a; Modi 2010b).

6. Participant reported satisfaction with treatment intervention

Nine studies (345 participants) with 11 separate comparisons reported on this outcome (very low-quality evidence) (Arens 1994; Braggion 1995; Giles 1996; Hare 2002; Homnick 1995; Modi 2010a; Modi 2010b; Osman 2010; Padman 1999b; Varekojis 2003a; Varekojis 2003b). We were only able to enter data from the Varekojis study and the Modi study in our analysis for this outcome (Modi 2010a; Modi 2010b; Varekojis 2003a; Varekojis 2003b).

In the short term, Varekojis looked at the comparisons of IPV and PD&P (Varekojis 2003a) and HFCWO and PD&P (Varekojis 2003b). There was no statistical difference reported by the investigators in either treatment arm compared to PD&P when participant satisfaction was measured by Friedmans test. Similarly, our analysis also showed no significant difference between groups (Analysis 3.12). Conversely, when Modi reported on the long-term treatment satisfaction (up to three years) looking at subsets of comfort, convenience and efficacy as well as overall satisfaction, significant differences were found for all measures favouring both flutter and HFCWO over PD&P (Analysis 3.13). When the investigators carried out sub-analysis of the data according to age, they found that oscillating devices gave adolescent participants a degree of independence from their care givers which may have impacted on their improved preference over PD&P. It should be noted that the last reported TSS scores were associated with participant withdrawal from the study, indicating individuals with lower TSS were more likely to withdraw. (Modi 2010a; Modi 2010b).

Arens reported participant satisfaction from the HFCWO arm of the trial only; 88% (22 participants) in this treatment group expressed satisfaction with this technique and requested this therapy in the management of further exacerbations (Arens 1994). Braggion discussed tolerance to the treatments of HFCWO and PD&P and referred to the results as "good", but without statistical or other evidence to support this finding (Braggion 1995). Giles reported that flutter was preferred by participants based on comfort and convenience (Giles 1996). In the paper by Hare, participants in the IPV group were reported to be generally satisfied with the device (Hare 2002). Homnick evaluated participant satisfaction in the IPV group (the questionnaire was not given to the CPT group) and reported that all eight respondents would continue to use the IPV device if given the opportunity (Homnick 1995). In the Padman study, it was reported that participants felt they were in control of all their therapies, felt physically better and mucus was more easily expectorated with no preference given to any modality (Padman 1999b). The Osman study considered participant satisfaction in terms of comfort, efficacy and urinary leakage; however, these data are from combined interventions and we felt we were unable to breakdown the data meaningfully therefore have not included this data in the meta-analysis. Investigators reported that 55% of the study population preferred their normal ACT compared to HFCWO (Osman 2010).

7. LCI

No studies reported on this outcome.

Different oscillating devices compared

Eight studies (10 data sets) compared different oscillating devices (Dingemans 2018a; Dingemans 2018b; Marks 2001; Modi 2010a; Modi 2010b; Oermann 2001; Osman 2010; Pryor 2010; Varekojis 2003a; Varekojis 2003b; Wheatley 2018). One study compared two different frequencies of IPV (Dingemans 2018a; Dingemans 2018b). One study compared flutter and IPV (Marks 2001); three data sets compared flutter to HFCWO (Modi 2010a; Modi 2010b; Oermann 2001; Osman 2010); one study compared flutter to cornet (Pryor 2010); one study compared IPV and HFCWO (Varekojis 2003a; Varekojis 2003b); and the final study compared HFCWO with the VibraLung® (Wheatley 2018). In order to avoid making this review more complicated, we have only listed below the outcomes for which we have any information. As a consequence of the investigators of the Osman study grouping several interventions (breathing exercises, flutter, PEP and CPT) when compared with HFCWO, we were unable to breakdown the data meaningfully and therefore have not included the results in the meta-analysis; however, we would suggest that the reader consider the previous sections for general statements on relevant results within this paper (Osman 2010). The Wheatley study had a complex study design with the HFCWO being used across all arms of the study, but combined with the VibraLung® in the intervention arm. There were limited data available, only as median data and IQR ranges and for few participants (small number of participants recruited with limited completions). It should be noted that this was a complex study design where efficacy and safety of VibraLung® was also evaluated, with the HFCWO also used for some of the treatments during the VibraLung® arm which make the data difficult to qualify (Wheatley 2018).

A summary of the quality of the evidence for these comparisons is presented in the tables; quality was judged to be either low or very low (Summary of findings 4).

Flutter compared to IPV

Primary outcomes

1. Respiratory function

a. FEV₁

Marks reported no significant difference (P = 0.208) at the end of the 24-week treatment period (Marks 2001).

b. FEF₂₅₋₇₅

Marks reported no significant difference (P = 0.126) at the end of the 24-week treatment period (Marks 2001).

c. FVC

Marks reported no significant difference (P = 0.292) at the end of the 24-week treatment period (Marks 2001).

Secondary outcomes

5. Frequency of exacerbations as a consequence of the treatment intervention

No difference was reported between groups when frequency of hospitalisations or need for home intravenous therapies was considered (Marks 2001).

6. Participant-reported satisfaction with treatment intervention

Marks reported that IPV was well-tolerated with 67% of participants wanting to continue using it instead of other ACTs (Marks 2001).

Flutter compared to HFCWO

Primary outcomes

1. Respiratory function

a. FEV₁

Three reported on this outcome (Modi 2010a; Oermann 2001; Osman 2010). Modi reported non significant change over the 12 months period between the different comparators (Modi 2010a). Oermann was a cross-over trial and we have presented data from the first arm of the trial only (at one month) (Oermann 2001). Oermann reports absolute values for FEV₁ % predicted and the analysis shows these were not statistically significant, although tending to favour flutter (Analysis 4.1). The Osman study reported that no statistically significant change in FEV₁ % predicted was observed within or between either regimen of HFCWO or usual ACTs when compared with baseline (data not able to be meaningfully analysed in this review) (Osman 2010).

b. FEF₂₅₋₇₅

Oermann also reported on FEF₂₅₋₇₅ % predicted and again we have presented first-arm data only (Oermann 2001). Absolute values for FEF₂₅₋₇₅ % predicted were not statistically significant, although again tending to favour flutter (Analysis 4.2). The Modi study reported that there was considered to be a significant difference in FEF₂₅₋₇₅ between FD and HFCWO ($P = 0.035$) (Modi 2010a).

c. FVC

Oermann reported on this outcome with data for FVC % predicted and we have presented only data from the first arm of the trial (Oermann 2001). Results for FVC % predicted were not statistically significant, but tended to favour flutter (Analysis 4.3). Modi reported a non significant change over the 12 months period between the different comparators (Modi 2010a).

Secondary outcomes

4. Level of oxygen saturation in response to treatment

One study reported on this outcome but, as stated above, we have not been able to include any data in the meta-analysis (Osman 2010).

6. Participant-reported satisfaction with treatment intervention

Three studies reported on this outcome (Modi 2010a; Modi 2010b; Oermann 2001; Osman 2010), but we were only able to enter data into the analysis for one of these (Modi 2010a; Modi 2010b). Modi reported on differences between flutter and HFCWO regarding treatment satisfaction (Modi 2010a; Modi 2010b) with results clearly favouring flutter for convenience, whilst all other scores showed no difference, but the strong result for convenience means that the overall score is just significant in favour of flutter. Oermann also conducted a participant satisfaction survey considering efficacy, convenience and comfort. Whilst no significant difference was found between therapies for comfort, flutter was found to score significantly more for convenience ($P < 0.02$), as was seen in the

Modi study, and HFCWO scored highest for efficacy ($P < 0.02$) (Oermann 2001). However, the investigators also reported that 13% of participants preferred their pre-study therapy regimen of PD&P because of familiarity with the technique (Oermann 2001). Osman considered participant satisfaction in terms of comfort, efficacy and urinary leakage; the study identified that 55% of their study population preferred their normal ACT compared to HFCWO (Osman 2010).

Flutter compared to Cornet

Primary outcomes

1. Respiratory function

a. FEV₁

Pryor reported no statistical differences between treatment techniques of flutter and cornet when considering FEV₁ ($P = 0.35$) (Pryor 2010).

c. FVC

Pryor found no statistical differences between flutter and cornet for FVC (Pryor 2010).

Secondary outcomes

2. Exercise tolerance

Pryor used the modified shuttle walk score and found no statistical differences between flutter and cornet (Pryor 2010).

3. QoL

Pryor used the CRQ to assess QoL and found no statistical differences between flutter and cornet (Pryor 2010).

IPV compared to HFCWO

Secondary outcomes

1. Sputum

b. weight (dry or wet)

In the Varekojis study, the investigators collected 142 sputum samples from the IPV group and 143 samples from the HFCWO group. The paper states that the wet sputum weight in the IPV group was significantly greater than in the HFCWO group ($P < 0.05$, by Tukey's honest significant difference test) (Varekojis 2003a; Varekojis 2003b). However, on inspection of the data it became apparent that this evaluation was based on the number of samples in the analysis rather than the number of participants and their relevant corresponding sputum samples. The number of samples compared were not equal; 24 participants were included in the study with six sets of sputum data anticipated for each treatment option. However, some of the sputum cups were contaminated by hematemesis (vomiting of blood), one dried prior to wet weight being measured and one sputum cup was lost prior to weighing, which accounts for the discrepancy in terms of sputum samples across the intervention groups.

6. Participant-reported satisfaction with treatment intervention

Using a Friedmans test comparing the HFCWO and IPV, Varekojis reported no significant difference in preference between the techniques (Varekojis 2003b).

High-frequency IPV compared to low-frequency IPV

One study (four participants) reported on this comparison, in order to compare the two frequencies of IPV the study was duplicated so that one referred to the 200 bursts per minute (bpm) frequency and the second to the 400 bpm frequency (Dingemans 2018a; Dingemans 2018b).

Primary outcomes

1. Respiratory function

a. FEV₁

Dingemans reported that participants treated with IPV at a higher frequency (400 bpm) showed a significant higher change from baseline in FEV₁ % predicted compared to IPV at the lower frequency (200 bpm), MD 6.70 % predicted (95% CI 2.74 to 10.66) (Analysis 5.1; Dingemans 2018a; Dingemans 2018b).

c. FVC

Dingemans reported that participants treated with IPV at a higher frequency (400 bpm) showed a significant higher change from baseline in FVC % predicted compared to IPV at the lower frequency (200 bpm), MD 10.00 % predicted (95% CI 5.13 to 14.87) (Analysis 5.2; Dingemans 2018a; Dingemans 2018b).

VibraLung[®] compared to HFCWO

Wheatley presented data in terms of median and IQR range. It should be noted that this was a complex cross-over study design where the efficacy and safety of the VibraLung[®] were also evaluated. HFCWO was also used for some of the treatments during the VibraLung[®] arm which make the data difficult to qualify (Wheatley 2018).

Primary outcomes

1. Respiratory function

a. FEV₁

Wheatley presented median (IQR) values of 57 (47 to 69), but found no statistical difference between the VibraLung[®] and HFCWO (Wheatley 2018).

b. FEF₂₅₋₇₅

Wheatley presented median (IQR) values of 27 (18 to 26); the only difference between treatment arms was seen during the second arm (7 to 11 days), where participants using the HFCWO had a greater median increase in FEF₂₅₋₇₅ than those with the VibraLung[®]; however, this was not reported to be statistically significant.

Secondary outcomes

1. Sputum

b. weight (dry or wet)

In the Wheatley study, on days 1 to 5 there was no statistical difference between VibraLung[®] or HFCWO in sputum weight (either wet or dry) - in wet weight (P = 0.73) and for dry weight (P = 0.91); similarly for days 7 to 11 for wet weight (P = 0.3) and for dry weight (P = 0.69) (Wheatley 2018). However the VibraLung[®] was

considered to be as effective as the HFCWO when considering ease of expectoration and was well tolerated.

Metaneb[®] compared to HFCWO

Primary outcomes

1. Respiratory function

a. FEV₁

In the Patel study 18 participants were randomised to Metaneb[®] and 14 participants randomised to HFCWO, with 32 participants completing the study (Patel 2013). Investigators reported mean values (but without corresponding SDs) for each group for FEV₁ % predicted at baseline and at 14 days (Patel 2013). In the HFCWO group there was an increase in mean FEV₁ % predicted of 3.5% compared to an increase in the Metaneb[®] group of 4.73%; but there was no evidence of statistical significance. It should be noted that further data were requested from the authors, but thus far there has been no response to this request.

Secondary outcomes

6. Participant-reported satisfaction with treatment intervention

All participants in the Patel study completed the satisfaction survey; 75% felt that HFCWO was effective and 72.7% agreed that Metaneb[®] was effective. In the HFCWO group, 50% of participants reported chest pain or discomfort and increased coughing spells; whereas in the Metaneb[®] group, 9% felt some discomfort or increased coughing. Of those who completed the study, 87.5% on HFCWO and 100% on Metaneb[®] were satisfied with the treatment received and would like to continue with it in the future (Patel 2013).

DISCUSSION

Summary of main results

The initial aim of this review was to determine whether oscillatory devices as used in CF are effective for airway clearance and, if so, are they equivalent to, or superior to other recognised airway clearance techniques or devices. Outcomes included pulmonary function, sputum weight and volume, individual preference, QoL measures and the number of hospitalisations per study period. The frequency of exacerbations was identified as an outcome and analysed as "days of hospitalizations" throughout the literature reviewed. Single-treatment studies were excluded. There were no relevant studies identified through the search process that compared exercise with any form of oscillatory device, or indeed where the Quake[®] or Aerobika[®] were included as comparisons with any other form of airway clearance. We have also not yet been able to include any significantly meaningful data from studies of the newer devices (Acapella[®], Metaneb[®] and VibraLung[®]). None of the intended subgroup analyses were possible due to either the small numbers of studies or to insufficient detail allowing the separating of subgroup data within any study.

There were no significant differences between participants on enrolment to studies when considering demographics, spirometry, anthropometrics and clinical scores. Most studies identified improvements in outcome measures from the beginning to the end of the study periods, although between-group differences were most frequently not significant. Where there have been small

but significant changes in secondary outcome variables, such as sputum volume or weight, this has not been wholly in favour of oscillatory devices. Sputum weight and volume may be considered to be somewhat misleading as an outcome variable as some individuals have difficulty expectorating and have a tendency to swallow their secretions. This can therefore significantly alter the results obtained.

It is the authors' opinion that oscillatory devices can be effective in clearing secretions, but despite evidence showing improvement in sputum volume, there is no statistically significant evidence to suggest that the use of these devices is superior to other physiotherapy techniques when respiratory function is the primary outcome in the short term. A study by Newbold compared flutter with PEP in a 13-month intervention and found there to be no statistical differences in respiratory function or health-related QoL over the study period (Newbold 2005). In the most recent study looking at HFCWO versus PEP over a 12-month period, results significantly favour the use of PEP over HFCWO when considering the number of exacerbations requiring antibiotics (but not those specifically requiring intravenous antibiotics) occurring in each group (McIlwaine 2013). When comparing the different types of oscillatory devices, there have generally been no statistical differences noted between any of the primary or secondary outcomes evaluated; the exception being a recent short-term study comparing different frequencies of IPV which found that the higher frequency led to better lung function outcomes. On occasion, there were reported preferences for flutter over HFCWO; however, these did not reach statistical significance. It would appear therefore that oscillatory devices are a recognised therapy, but they are not superior to any other form of airway clearance or that one device is superior to another. It should also be acknowledged that longer-term studies are essential when considering the differences between alternative airway clearance therapies.

Overall completeness and applicability of evidence

The literature appears to be representative of the airway clearance techniques available to participants with CF. Apart from the lack of evidence with regard to either Quake[®], Aerobika[®] or exercise, all therapy techniques are included, with recognition that alternative devices are still in development (e.g. the Acapella[®], the Metaneb[®] and VibraLung[®]) and we await further information before being able to fully present these options. The literature also includes representation from both children and adults with mild to severe disease. Oscillatory devices have been compared with each other and all other recognised airway clearance techniques.

A total of 20 studies involved flutter as a comparison, 17 studies included HFCWO, six included IPV, two included cornet, one each included Acapella[®], Metaneb[®] and VibraLung[®]. There were no studies comparing, Quake[®] with any other treatment. These are more recently developed devices and that may account for the limited, or lack of, literature evaluating the efficacy of these devices. These devices may be included in future comparative studies as the variety of treatment options become more readily available for all people with CF.

Most studies have been short-term and the literature recognises that short-term studies demonstrating improved sputum clearance have not demonstrated preservation of respiratory function, decreased morbidity or shown improved QoL over the

long term (Varekojis 2003a; Varekojis 2003b). Modi was unable to identify differences in clinical effectiveness as measured by FEV₁ decline over the duration of this three-year study; however, perceived effectiveness as suggested by treatment satisfaction and convenience may lead to better adherence and result in long-term improvements (Modi 2010a; Modi 2010b). In 2004, Milne also reported that in short-term studies, it would be unlikely that changes, if they existed, would be apparent in single-treatment days (Milne 2004). Whilst we did not include studies where one treatment session was compared with another, we did include those studies where a single day of treatment was included, if the therapy was conducted more than once during that day.

The greater the consistency between the primary studies in a meta-analysis, the more generalisable are the results. Heterogeneity refers to substantial differences between studies rather than those that occur by chance. We planned to test for heterogeneity using the I² statistic (Higgins 2003); however, due to the limited data available for meta-analysis, testing for heterogeneity was not always appropriate or possible.

Three instances of moderate to high heterogeneity were identified in our analysis. In the test for subgroup differences in the analysis, an I² value of 59% was calculated for the comparison oscillating devices versus PEP for the change from baseline in mid-peak expiratory flow (FEF₂₅₋₇₅) (% predicted) between one study lasting one month (Padman 1999a) and three studies with a study period of one year (McIlwaine 2001; McIlwaine 2013; Newbold 2005); we believe this is due to the difference in study duration (Analysis 1.4). Between the same three studies, a value for I² of 71% was calculated for the change from baseline in FVC (% predicted) when we analysed the data using a fixed-effect model (McIlwaine 2001; McIlwaine 2013; Newbold 2005). We re-analysed these data using a random-effects model, but the result remained statistically not significant (Analysis 1.6). These studies seem to be very diverse; however, due to the low number of studies, we were unable to investigate the causes of these instances of heterogeneity further.

Of the studies reviewed, 30 were less than three months in duration; and of these, 13 were considered to be of less than one-week duration.

It is recognised that four of the studies have multiple treatment arms and in the analysis we have considered each treatment separately (Dingemans 2018a; Dingemans 2018b; Modi 2010a; Modi 2010b; Padman 1999a; Padman 1999b; Varekojis 2003a; Varekojis 2003b). It is potentially possible to conduct a multiple-treatment analysis where all the treatments are assessed simultaneously across studies; however, it was not within the capabilities of the authors to conduct such an analysis, but this should be considered in future studies to ensure clarity of the meta-analysis. Two of the studies included in the 2020 update have compared oscillatory devices with 'usual' airway clearance techniques, but the data for each individual technique were not identifiable and the authors were not able to extract data for analysis.

Quality of the evidence

The review authors assessed the quality of the evidence using the GRADE criteria (see below) and identified the following limitations which all highlight the need for further good quality RCTs.

Methodological quality of included studies

For the purposes of this review we have included only RCTs and quasi-RCTs, which are the highest quality of research studies available. This has led to the inclusion of 39 individual studies, one third of which were published only as abstracts, thus limiting the amount of salient information we were able to retrieve from them with respect to methodology and data available for analysis.

Few studies were considered to be of relatively high methodological quality, and therefore at a low risk of bias, e.g. where there was definite evidence of allocation concealment and blinding of some of the researchers (Newbold 2005; Phillips 2004; McIlwaine 2013; West 2010). Only four studies reported blinded allocation to treatment, it is not possible to blind the participants to the physiotherapy interventions included in this review; however, in nine studies there was evidence that those researchers who were collecting lung function or sputum samples or performing other relevant testing were blinded to the treatment intervention. The potential for a high risk of bias due to lack of blinding in all these studies cannot be excluded.

A sensitivity analysis for those outcomes where data from parallel studies were compared with data from cross-over studies was performed (Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.7; Analysis 3.8). The results, however, remained non-significant and we conclude that the results are therefore robust.

Small numbers

There were relatively small numbers of participants enrolled in the included studies (range 4 to 166) and 50% of those studies included children. We appreciate the hypotheses by Newbold that adults have "fixed damage" and therefore less potential improvement as a consequence of CPT and that also the mean rate of decline in adults tends to be slower (Newbold 2005). This may have an impact on the accuracy of evidence when measuring the effect of a device on lung function irrespective of the duration of the study.

Inconsistency in study design

The included studies employed different interventions and outcome measures and therefore many could not be combined for inclusion into the meta-analysis. As CPT is delivered by a therapist it must be considered that differences in technique delivery may have an impact on results achieved. This factor is most apparent in the Warwick study where competition between therapists was encouraged (Warwick 2004).

Applicability to present day practice

10 of the included studies were conducted over 20 years ago. Applicability of the results to present day practice may be compromised due to changes in population characteristics and interventions, including more aggressive management of lung infection and improvements in antibiotics.

Quality of evidence

The quality of the evidence was assessed using the GRADE methodology and four summary of findings tables were generated (one for each comparison presented) (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4). All of the included studies were graded as having low or very low-quality evidence. Downgrading of evidence occurred

for a number of reasons including small sample size, short duration of treatment and the use of a cross-over design rather than a parallel design. There were also inadequacies noted in allocation concealment, a lack of blinding and incomplete data which suggested a high risk of bias. Anecdotal evidence and limited information on some of the intervention methodology further downgraded the evidence. This low or very low-quality evidence suggests that if further research was conducted and resolution of these inadequacies existed then results would significantly influence the confidence in the estimate of effect of the interventions.

Potential biases in the review process

Several of the studies reported that they had received funding from the manufacturers of specific devices. In particular Hill-Rom (manufacturers of the Vest[®]) sponsored three studies (Darbee 2005; Modi 2010a; Osman 2010). Two of the studies evaluating flutter were provided with the devices by Scandipharm (Gondor 1999; Padman 1999a); and one intrapulmonary percussive ventilation (IPV) study was provided with the equipment by Vortran Ltd (Hare 2002). One study comparing HFCWO and PEP were loaned or provided with the devices respectively (McIlwaine 2013).

The risk of bias due to the carry-over effect is also a major problem of combined design meta-analysis on the assumption that the first period is devoid of bias, but this may lead to a biased subset of studies in a meta-analysis and it is the price of a less efficient treatment estimate (Curtin 2002b). There is a possibility that this type of bias may have occurred in our meta-analyses since the pooled data includes 11 studies of a cross-over design and six of a parallel design. In addition, whilst the studies have considered treatment of participants when they are in a "stable" state and generally excluded participants who have had an increase in symptomology (either before inclusion or during the study) it is possible that participants have had different disease severity or levels of anxiety associated to their disease. As stated by Curtin, "such differences in study populations could be a source of heterogeneity in the treatment effect which is not caused by the design but confounded by it" (Curtin 2002a). As there were insufficient studies with data to allow sub-group analysis it is not possible to further investigate the issue of heterogeneity.

Two studies reported flutter therapy in the supine position, but no supportive evidence was given to suggest how this was achieved (Pike 1999; Pryor 1994). Under normal circumstances, the manufacturers' guidelines are to use the flutter in a sitting position.

In his 1998 study, Homnick also suggested that the sample size of each comparison group should be 219 participants to achieve 80% power when considering FEV₁ as a quality primary outcome variable (Homnick 1998). With this factor in mind, all of the studies included in this review would be under-powered and consequently any evidence of no improvement should be regarded with some caution, as the issue of power is more important when the findings are of no difference between interventions.

One particular study reported that when some of the eligible participants were approached regarding entry to the study, they felt that they were happy with their current therapy regimen and on occasion they felt they had been over-studied (Newbold 2005).

Adherence to therapies has a major impact upon outcome measures; however, few of the studies considered this as a factor when evaluating the treatment intervention. Only those participants who adhered to twice-daily treatment (based on diary records) at a level of 85% were included in the Mcllwaine study (Mcllwaine 2001). Although we did not specifically address adherence as an outcome measure, we did consider other subjective parameters such as QoL indices, tolerance and participant-reported satisfaction, all of which ultimately impact upon a person's adherence to the therapy in question. Interest in participating in a study due to perceived effectiveness of a treatment, may have led to improved adherence and treatment satisfaction (Mcllwaine 2013). Close contact and phone calls from study coordinators may also have contributed to increased adherence identified in the Mcllwaine study; and the high adherence may explain the significant increase in percent predicted FEV₁ in both groups from their baseline measurements, which was reported in the paper (no data provided) (Mcllwaine 2013).

One further point is the pooling of data between adults and children. Monitoring of the flutter technique is more challenging in children than adults, where the child may be less sensitive to the requirement for adjusting the gradient of the flutter to enable optimum oscillation. This could therefore reflect a difference in outcome if, in children, the treatment is not being optimised because of lack of understanding of the technique. However, if in practice children and adults are treated the same, a random-effects analysis will be appropriate to give the average treatment effect across all adults and children.

Agreements and disagreements with other studies or reviews

The literature recognises that there is little, if any, evidence to support the use of one airway clearance technique or device over another. The findings of this review agree with the previous Cochrane Reviews which looked at PEP physiotherapy, CPT and other breathing techniques in people with CF (Mcllwaine 2019; Main 2005, McCormack 2017; McKoy 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Individual preference continues to be a factor when introducing a airway clearance technique or therapy adjunct, such as an oscillatory device. It is also important to consider the impact the device may have on the individual at particular stages of their disease. It would appear no single treatment technique is suitable for everyone and the therapist delivering airway clearance should be well-educated in all aspects of airway clearance and associated therapy techniques. This would enable the appropriate selection and inclusion of airway clearance techniques or devices into the management of the individual. As there is no appreciable difference between the devices or therapies used in airway clearance, the healthcare provider should consider a cost-benefit analysis for individuals based on financial burdens and possible insurance cover where appropriate. In particular, where the frequency of

exacerbations was shown to be increased whilst using the Vest[®] when compared to positive expiratory pressure (PEP) therapy in the recent Mcllwaine study (Mcllwaine 2013), this may have significant resource implications for the individual and the healthcare provider. Individual preference and acknowledgement of personal health beliefs are also important, as is age-appropriateness of the therapy techniques, which may have a considerable impact on concordance with therapies suggested or offered.

Implications for research

Many of the studies included quality of life scales and satisfaction questionnaires; however, few incorporated measures of adherence. When there is no marker of superiority between airway clearance techniques, it may be prudent to include time to next exacerbation, frequency of exacerbations, individual preference, adherence to therapy and general satisfaction with treatment as potential outcome measures in further studies of these techniques. As a consequence of adherence to therapy, we may then see improvements in other parameters such as exercise tolerance and respiratory function.

Most of the studies reviewed were of short duration i.e. less than three months (n = 26), and of these 10 were of less than or up to one week duration. Only nine studies were of longer duration, which in this review extended to 2.8 years (Modi 2010a). The remaining four studies had an unclear or unspecified duration. This would suggest for the future researcher that longer-term studies would add more weight to the perceived benefit of airway clearance techniques or therapy devices or both. It has been suggested in adherence literature that the introduction of new novel therapies increases the individual adherence for up to a three-month "honeymoon" period after which time the individual tends to resort to previous levels of adherence. This should be considered by the designers of future studies when deciding on the duration of their study. More adequately-powered long-term RCTs (parallel or cross-over in design) need to be included in this review before clinically valuable information can be gained with regard to treatment efficacy and safety.

ACKNOWLEDGEMENTS

The review authors would like to acknowledge the previous contribution of Jennifer Agnew who was part of the original review team.

The review authors would like to acknowledge the patient assistance of our Managing Editors, Mrs Nikki Jahnke (without whose invaluable support this review would not have reached completion), Miss Tracey Remington, and our editor, Professor Alan Smyth.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

App 1998

Study characteristics	
Methods	RCT. Cross-over design. Duration: 4 weeks. Location: multicentre in Germany.
Participants	17 participants initially randomised. 3 drop outs reported (1 for time reasons and the other 2 for acute chest exacerbation), therefore 14 (6 males, 8 females) analysed (7 in each treatment group). Age range 4 - 41 years, mean (SD) 19.6 (10.3) years. Participants had a positive diagnosis of CF by means of sweat test or clinical history or both.
Interventions	Flutter versus AD twice daily for 4 weeks.
Outcomes	Respiratory function (FEV ₁ , FVC) and sputum volume.
Notes	This paper also considered the implications of the flutter on sputum viscoelasticity but this was not an outcome measured in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract states randomised cross-over design; however the methodology does not report any details of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Abstract does not report any details of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and clinicians.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 3 dropouts occurring after randomisation; 1 for time reasons and the other 2 for acute chest exacerbation. ITT not discussed.
Selective reporting (reporting bias)	Unclear risk	Blood oxygen saturations were taken, but there are no data to support a change in this parameter if it were to have occurred during the study or as a consequence of the intervention.
Other bias	Unclear risk	None identified.

Arens 1994

Study characteristics	
Methods	RCT.

Arens 1994 (Continued)

Parallel design.
Location: single centre in USA.
Duration: 2 weeks, follow up not stated.

Participants	50 (32 males, 18 females) participants randomised. Age range 16.9 - 24.9 years. Participants with CF and an acute exacerbation who had been admitted to hospital.
Interventions	HFCWO for 30 min 3x daily in sitting whilst receiving nebuliser. CPT 30 min 3x daily in 6 different PD positions, following 15 min of nebuliser. 25 participants randomised to each treatment group. Treatment 2 weeks in duration.
Outcomes	Respiratory function (VC, FEV ₁ , FEF and RV), sputum weight in g both wet and dry at 1 hour and 24 hours. Participants reported satisfaction with technique and % change in SaO ₂ . Outcome measurements taken at admission, 7 days and 14 days.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported how sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of assessors or participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 dropouts were identified and this was due to failure to comply with the therapy regimen.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare original trial protocol with final paper.
Other bias	Unclear risk	None identified.

Braggion 1995

Study characteristics

Methods	RCT. Cross-over design (1-day washout between treatments). Location: single centre in Italy. Duration: 2 days for each of 3 treatments with 1 rest day in between treatment 1 and 2. No follow up reported.
Participants	16 (8 males, 8 females) participants. Mean (SD) age 20.3 (4) years, range 15 - 27 years. All participants had FEV ₁ >40%, sputum volume >30 ml/day and were accustomed to ACTs.

Braggion 1995 (Continued)

Mean (SD) Schwachmann score 65.1 (11).
Mean (SD) Crispin Norman score 18.5 (4.3).

Interventions	3 interventions: PD (specific PD positions were not identified); PEP; HFCWO. 15 min saline nebulised prior to treatment. 2 treatments per day for 2 days, then rest 1 day; next intervention for 2 days, then 1 rest day; then the final intervention. Each session lasting 50 min (not clear if this included the 15 min of nebulisation).
Outcomes	RFTs (FEV ₁) 30 minutes pre- and post-treatment, wet and dry sputum weight collected in 50 min of treatment and 30 min following. Only spontaneous coughs were allowed and the number of cough manoeuvres were counted and documented. Each treatment was scored for efficacy and tolerance by participant and for tolerance by therapist (method of efficacy or tolerance scoring was not defined).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised according to Latin square design described by Williams.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of participants or assessors not performed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals had not been discussed
Selective reporting (reporting bias)	High risk	Efficacy and tolerance for the treatments were scored by the participant, and tolerance was also scored by the physiotherapist. These were then referred to as good but with no further evaluation of this score made.
Other bias	Unclear risk	None identified.

Darbee 2005

Study characteristics

Methods	Quasi-RCT. Cross-over design. Location: single centre in USA. Duration: average length of hospital stay was 11 days (range 9 - 15 days); no follow-up reported.
Participants	15 participants (8 males, 7 females). Aged at least 7 years, mean (SD) age 17.5 (4.2) years. Participants were admitted to hospital for acute exacerbation. All participants performed HFCWO 1 - 3 times daily as outpatients before admission, but none had performed PEP.

Darbee 2005 (Continued)

Interventions	PEP versus HFCWO. Both treatments were alternated within 48 hours of hospital admission and then reversed prior to discharge. Treatment lasted 30 minutes.
Outcomes	RFTs and SaO ₂ measured before and after every intervention. Each intervention was only done twice i.e. day 1 or 2 following admission then day -1 or -2 prior to discharge.
Notes	Average length of hospital stay was 11 days (range 9 - 15 days). 3 participants discharged while still receiving intravenous antibiotics, for these participants the final measurement was taken within 48 hours of the final dose of antibiotic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to treatment order by numbering them consecutively, 1 through 15, at study entry. On the basis of a coin toss at admission, participant 1 and all odd-numbered participants were randomly assigned to perform HFCWO on day 1 and PEP breathing on day 2, and even-numbered participants performed PEP breathing on day 1 and HFCWO on day 2. At discharge, participants received treatment in the order opposite the treatment order at admission.
Allocation concealment (selection bias)	High risk	Used alternation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare original trial protocol with final abstract.
Other bias	Unclear risk	The authors thanked Hill-Rom for providing the Vest [®] device.

Davies 2012
Study characteristics

Methods	RCT. Parallel design. Location: single centre in UK. Duration: median length of stay for controls was 14 days, median length of stay for HFCWO group was 13 days.
Participants	36 participants with CF admitted to hospital with an acute infective pulmonary exacerbation. Mean (SD) age: HFCWO group 25.8 (7.3) years; control group 29.8 (1.7) years.

Davies 2012 (Continued)

Sex: 23 (64%) males.

Interventions

Intervention: HFCWO (device was the Vest[®], Hill Rom Model 205), participants paused to huff and cough as necessary.

Control: usual airway clearance techniques (including ACBT, AD, PEP, manual techniques or oscillating PEP), further details not given.

Treatment given 4x daily - 2x supervised by a physiotherapist and 2x carried out independently.

Outcomes

FEV₁, FVC, length of hospital stay and sputum weight.

Additional reference to this study also considered FEF₂₅₋₇₅.

Notes

Abstracts only and entry on clinicaltrials.gov (NCT01057524) available - no full paper. Further breakdown of data has been requested for inclusion in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded. Difficult to blind participants to a device trial, but assessors not blinded either and no reasons given for this.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No drop outs mentioned or missing data discussed.
Selective reporting (reporting bias)	Unclear risk	All parameters stated as recorded were discussed over the 2 abstracts, but no full paper.
Other bias	Unclear risk	Not discussed but there is a possibility of involvement of the manufacturers in provision of the Vest [®] devices for the 36 participants.

Dingemans 2018a

Study characteristics

Methods

RCT.

Cross-over design.

Location: single centre in Belgium.

Duration: approximately 9 months.

Participants

4 participants with CF. Admitted for administration of IV antibiotics for respiratory exacerbation.

Dingemans 2018a (Continued)

Interventions	<p>3 different techniques. Each regimen was 30-minute treatments of the randomised intervention 2x daily over 5 - 10 days in hospital. This was followed by a washout of 3 months during which participants continued with AD.</p> <p>Intervention 1: AD alone.</p> <p>Intervention 2: IPV at medium frequency (200 bpm) combined with AD.</p> <p>Intervention 3: IPV at high frequency (400 bpm) combined with AD.</p>
Outcomes	<p>Sputum for bacterial load- considering biofilm behaviour.</p> <p>FEV₁ percentage change from baseline in FEV1 % predicted.</p> <p>FVC percentage change from baseline in FVC % predicted.</p>
Notes	This study ID refers to the 200 bpm frequency data of the paper. Intervention 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised but sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was stated, laboratory staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs but only 4 participants included in trial.
Selective reporting (reporting bias)	Low risk	All parameters (lung function, bacterial load and gene expression) identified and recorded were discussed.
Other bias	Unclear risk	None identified.

Dingemans 2018b
Study characteristics

Methods	<p>RCT.</p> <p>Cross-over design.</p> <p>Location: single centre in Belgium.</p> <p>Duration: approximately 9 months.</p>
Participants	4 participants with CF. Admitted for administration of IV antibiotics for respiratory exacerbation.
Interventions	3 different techniques. Each regimen was 30-minute treatments of the randomised intervention 2x daily over 5 - 10 days in hospital. This was followed by a washout of 3 months during which participants continued with AD.

Dingemans 2018b (Continued)

Intervention 1: AD alone.

Intervention 2: IPV at medium frequency (200 bursts per minute -bpm) combined with AD.

Intervention 3: IPV at high frequency (400 bursts per minute-bpm) combined with AD.

Outcomes	<p>Sputum for bacterial load- considering biofilm behaviour.</p> <p>FEV₁ percentage change from baseline in FEV1 % predicted.</p> <p>FVC percentage change from baseline in FVC % predicted.</p>
Notes	<p>THIS DUPLICATE REFERENCE HAS BEEN CREATED TO ALLOW DATA FOR BOTH FREQUENCIES of IPV TO BE ENTERED IN THE ANALYSIS.</p> <p>This study ID refers to the 400 bpm frequency section of the study INTERVENTON 3.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised but sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was stated, laboratory staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs but only 4 participants included in trial.
Selective reporting (reporting bias)	Low risk	All parameters (lung function, bacterial load and gene expression) identified and recorded were discussed.
Other bias	Unclear risk	None identified.

Giles 1996
Study characteristics

Methods	<p>RCT.</p> <p>Cross-over design (2-week washout period).</p> <p>Location: single centre in USA.</p> <p>Duration: 4 weeks of treatment followed by 2-week washout and then 4 weeks of alternative treatment; follow-up not stated.</p>
Participants	<p>14 participants.</p> <p>Age and sex of the participants was unspecified, but as parents were also questioned it would suggest they were concerned with a paediatric population.</p>
Interventions	<p>PD&P versus flutter.</p> <p>2x daily for 15 min each treatment.</p>

Giles 1996 (Continued)

Outcomes Participant preference, wet and dry sputum weight, FVC and FEV₁ were measured pre-study baseline and at the end of each treatment period. Sputum collected on the last treatment of each treatment period.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed.
Selective reporting (reporting bias)	High risk	Parents were also questioned therefore it may be reasonable to assume that they may have influenced the children's decision as to preference.
Other bias	Unclear risk	Abstract only.

Gondor 1999
Study characteristics

Methods	RCT. Parallel design. Location: single centre in USA. Duration: length of hospital stay (2 weeks).
Participants	23 participants enrolled, 3 participants excluded due to being discharged prior to 14 days of inpatient stay. Data from 20 participants (11 males, 9 females) with CF, enrolled on admission to hospital. Age 5 - 21 years.
Interventions	2-week intervention of either flutter (n = 12) or CPT (n = 8). Frequency during the day was not specified.
Outcomes	SaO ₂ , exercise tolerance (as measured by the 6MWD) and FEF, FVC and FEV ₁ were measured at entry, day 7 and day 14.
Notes	20 participants included but two of them refused to walk so the data are from 18 participants – but the paper does not state which group(s) the two belonged to who dropped out, so "n" is unknown for each group in this outcome. Data have been recorded in the analysis using the numbers originally in each group therefore there may be bias attributed to one or other group as it is not clear which participants would not perform the walk test.

Gondor 1999 (Continued)

SaO₂ was monitored during admission but no other data were reported for this parameter, apart from P < 0.05 by day 14.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Pulmonary function and exercise technicians were blinded as to which treatment interventions the participants were receiving.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded due to being discharged prior to 14 days of inpatient stay, therefore not all their data were collected.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare original trial protocol with final paper. Additionally the lung function parameters are not identified and may not be those frequently observed. SaO ₂ was monitored during admission but no other data were reported for this parameter, apart from P < 0.05 by day 14.
Other bias	Unclear risk	Scandipharm Pharmaceuticals were thanked by the authors for providing the flutter valves.

Gotz 1995
Study characteristics

Methods	RCT. Cross-over design (2-week washout between treatment arms). Location: single centre in Austria. Duration: 2x 4-week treatment periods with 2-week washout in between.
Participants	7 participants. Age and sex of the participants was not identified.
Interventions	2x daily IPV versus 2x daily PEP. 2x 4-week periods of treatment, 2-week washout between where there was no PT.
Outcomes	FEV ₁ , PO ₂ . Measured before, 10, & 40 min after first treatment of the day once per week.
Notes	Abstract only, full paper not published as yet. Due to carryover effect the analysis was confined to the first treatment period; therefore this was analysed NOT as a cross-over but a parallel study.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Gotz 1995 (Continued)

Random sequence generation (selection bias)	Unclear risk	Described as randomised, method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data not reported, only generalised conclusions made.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare trial protocol with the published abstract. No full paper available to exclude selective reporting bias.
Other bias	Unclear risk	Abstract only.

Grzincich 2008
Study characteristics

Methods	RCT. Parallel design Duration: first 3 days of hospitalisation for an exacerbation.HFCWO or PEP
Participants	23 participants (12 females). Mean age 25 years.
Interventions	HFCWO at setting of 20 Hz for 30 minutes compared with 30 minutes of PEP for the first 3 days of treatment.
Outcomes	FEV ₁ , FVC and FEF ₂₅₋₇₅ were assessed pre and 30 minutes post intervention. Sputum volume was collected after each intervention.
Notes	Abstract only, full paper not published as yet. No identification how many participants were randomised to each treatment. There were no statistical data given but reference made to state $P < 0.05$ was significant but this was not attributed to any result.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.

Grzincich 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed; data provided but significance not statistically represented.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare original trial protocol with final paper. Additionally a P value was suggested in the abstract but not attributed to any specific outcome measured.
Other bias	Unclear risk	Abstract only. Details of methodology are scarce

Hansen 1990
Study characteristics

Methods	RCT. Cross-over design. Location: single centre in USA. Duration: not defined.
Participants	5 participants. Age and sex of participants not stated.
Interventions	HFCWO versus CPT. 30 sessions of each therapy lasting same duration, but duration of treatment was not defined.
Outcomes	Sputum weight. Primarily looking at the pressure and frequencies generated by the vest and the mucus collection was an aside. Measured before and after duration of intervention (30 days).
Notes	In addition a gentleman not wanting to be included in the study used the Vest [®] for 12 months and experienced a significant increase in his RFTs and restoration of ventilation to the upper lobes of his chest on scanning.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed.
Selective reporting (reporting bias)	High risk	Only reporting of respiratory function was descriptive of the man not included in the study.

Hansen 1990 (Continued)

Other bias	Unclear risk	None identified.
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Hare 2002
Study characteristics

Methods	Quasi-RCT (alternate assignment). Parallel design. Location: single centre in USA. Duration: 2 weeks.
Participants	14 participants (10 males, 4 females). Age 8 - 28 years. All participants admitted to hospital for 2-week course of IV antibiotics, acute. No complications identified, no difference between groups in terms of clinical score, but clinical score not defined.
Interventions	Percussive device (IPV) versus CPT, not stated how many participants were randomised to each treatment group 4 times per day for 2 weeks.
Outcomes	FVC, FEV ₁ and FEF ₂₅₋₇₅ and RV. Participant-reported satisfaction was noted. Measurements taken at admission and discharge.
Notes	Abstract only, no full paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no further details given.
Allocation concealment (selection bias)	High risk	Alternate assignment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed.
Selective reporting (reporting bias)	High risk	Clinical score was used as an outcome measure but no clear definition of this parameter given. Significant differences were suggested but no data provided to support this.
Other bias	Unclear risk	Supported by Vortran Medical Technology 1, Inc., Sacramento, CA.

Homnick 1995

Study characteristics

Methods	RCT. Parallel design. Location: single centre in USA. Duration: total study period of 180 days - 30-day run in (participant kept a daily log of CPT and aerosol treatment administered) followed by 150 days of treatment.
Participants	20 participants stratified by Schwachmann score and randomised to standard treatment or IPV. 4 dropped out, 16 participants (8 from each group (5 males, 3 females)) completed trial. IPV group mean (range) age: 12 (5 - 24) years. CPT group mean (range) age 10 (5 - 18) years. Participants were well matched to CF severity index, Schwachmann score. Mild to moderate disease severity.
Interventions	IPV at least 2x per day compared to standard manual CPT at least 2x daily (included manual percussion for 2 min in each of 10 PD positions). Aerosol treatment was saline or N-cromolyn and an appropriate volume of albuterol via standard aerosolisation.
Outcomes	FVC, FEV ₁ and FEF ₂₅₋₇₅ measured at baseline, 30 days and at 180 days. Mean days of antibiotic use were documented both for oral and IV antibiotics as needed for hospitalisations.
Notes	Aerosolisation of saline or N-cromolyn and an appropriate volume of albuterol was used via standard aerosolisation in the CPT group. This was the same volume of saline and albuterol as was used in the IPV group. IPV is thought to aid secretion removal by introducing simultaneous application of aerosolisation and intrathoracic percussion using mini-bursts of gases.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	20 participants stratified by Schwachmann score and randomised to standard treatment or IPV. No further details were reported.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	No reasons for drop out of 4 participants following randomisation were discussed.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare study protocol with final paper.
Other bias	Low risk	Adverse reaction noted and detailed in one participant who experienced minor haemoptysis.

Homnick 1998

Study characteristics

Methods	<p>Quasi-RCT (alternate allocation).</p> <p>Cross-over design.</p> <p>Location: single centre in USA.</p> <p>Duration: length of hospitalisation.</p>
Participants	<p>22 enrolled into study, the data for 33 hospitalisations (20 males, 13 females) presented.</p> <p>Mean (range) age: 12 (7- 44) years.</p> <p>CF confirmed by sweat test and/or genetic testing.</p>
Interventions	<p>4x daily flutter (each treatment was 15 min) versus 4x daily CPT (each treatment was 30 min).</p>
Outcomes	<p>Change from baseline FVC, FEV₁, FEF₂₅₋₇₅, FEV₁/FVC, TLC, RV, RV/TLC. Measured at admission and discharge which was mean (SD) 8.9 (2.5) days of treatment in the flutter arm and 8.8 (2.4) days in the CPT arm.</p>
Notes	<p>Although 22 participants enrolled into the study, data were collected for 33 hospitalisations over the study period therefore baseline demographics may include some duplication of data.</p> <p>Subgroup analyses of 15 participants with only one admission and the initial admission of 7 were done with no change from overall outcome of the total 33 data sets analysed.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Initial participant randomised, but not stated how. Others followed alternating schedule.
Allocation concealment (selection bias)	High risk	Alternate assignment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs reported.
Selective reporting (reporting bias)	High risk	Although 22 participants enrolled into the study the data were collected for 33 hospitalisations over the study period therefore baseline demographics may include some duplication of data. Subgroup analyses of 15 participants with only one admission and the initial admission of 7 were done with no change from overall outcome of the total 33 data sets analysed.
Other bias	Low risk	Participants were monitored for side effects including haemoptysis, hypoxia and pneumothorax but none were identified.

Khan 2014

Study characteristics

Khan 2014 (Continued)

Methods	<p>RCT.</p> <p>Parallel design.</p> <p>Location: single centre in Russia.</p> <p>Duration: 10 'procedures' (not clear how many procedures per day).</p>
Participants	30 children aged 5 - 17 years.
Interventions	HFCWO versus control (control not mentioned so alternative ACT unknown, assumed that 15 participants were randomised to each treatment group).
Outcomes	<p>FEV₁, FVC, exercise tolerance, sputum volume and SpO₂</p> <p>But as we are unaware of the alternative "control" ACT we cannot include the data in the meta-analysis.</p>
Notes	Only abstract in English, therefore translation required but even following translation the paper had limited quality and limited information as to the actual interventions and their frequency.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation declared, not described.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs. All 30 data sets included in their analysis
Selective reporting (reporting bias)	Unclear risk	No objective data on sputum volume, although it was stated there was an improvement following the intervention.
Other bias	Unclear risk	Not clear as abstract only in English and no clear evidence of excluded bias in translated paper.

Kluft 1996
Study characteristics

Methods	<p>Quasi-RCT (alternate allocation).</p> <p>Cross-over design.</p> <p>Location: single centre in USA.</p> <p>Duration: 8 days (treatments alternating daily for 4 days).</p>
Participants	29 participants (15 males, 14 females).

Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Kluft 1996 (Continued)

Age range 7 - 47 years.
 Diagnosis of CF and clinical evidence of chronic disease.

Interventions	3x daily 30 min CPT/PD versus 3x daily 30 min HFCWO. Participants continued to receive their standard bronchodilators prior to therapies.
Outcomes	Sputum weight (wet and dry). Each participant provided 3 samples per day for 4 days and all 12 samples were used to calculate the means and standard deviations.
Notes	1 individual not enrolled due to intolerance of HFCWO, although had met the inclusion criteria - never really entered the study therefore not really a drop out.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Initially randomly assigned, but method not stated then treatment assignments alternating daily.
Allocation concealment (selection bias)	High risk	Alternate.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 individual not enrolled due to intolerance of HFCWO, although had met the inclusion criteria - never really entered the trial therefore not really a drop out.
Selective reporting (reporting bias)	Low risk	Potential adverse effects were identified but none occurred.
Other bias	Unclear risk	Not discussed.

Lyons 1992
Study characteristics

Methods	RCT. Cross-over design (4 treatment arms, no washout). Location: single centre in UK. Duration: 4 successive days (1 day per treatment arm).
Participants	12 participants (5 males, 7 females). Mean age 21 years (range 16 - 28).
Interventions	PD&P versus Flutter alone versus Flutter with PD&P versus sham flutter with PD&P. 3x a day for each treatment.
Outcomes	Used sputum volume and peak flows only. Measured after 24-hour period for 4 days.
Notes	

Risk of bias
Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Lyons 1992 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed.
Selective reporting (reporting bias)	Unclear risk	Not discussed.
Other bias	Unclear risk	Abstract only.

Marks 2001
Study characteristics

Methods	RCT. Parallel design. Location: single centre in USA. Duration: 24 weeks with 7-day run in period.
Participants	16 participants (9 males, 7 females). Only results from 15 participants (8 flutter and 7 IPV) analysed. 1 participant became pregnant and she was withdrawn from the study. Age not specified, but similar mean age was expressed.
Interventions	2x daily flutter versus 2x daily IPV; 8 randomised to each treatment group
Outcomes	Frequency of exacerbation, participant reported satisfaction, FEV ₁ , FVC, FEF ₂₅₋₇₅ , Schwachmann scores. Spirometry and Schwachmann scores were measured at enrolment and at baseline following the 7-day run in period, every 4 weeks during the study and at 24 weeks (the end of the study).
Notes	Unsure regarding the need to have all participants do the week run in with flutter, was this to eliminate bias for the flutter or to ensure all had similar experience before randomisation? Had they used either of the devices before? Abstracts only. There does not appear to have been a full paper published yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not stated.

Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Marks 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	One participant was excluded due to pregnancy; we are not made aware of when she was withdrawn and her data were not reported.
Selective reporting (reporting bias)	High risk	Days lost from work or school although identified as being an outcome variable have not been reported in the results.
Other bias	Unclear risk	Abstract only.

Mcllwaine 2001
Study characteristics

Methods	RCT. Parallel design. Location; single centre in Canada. Duration: 12 months.
Participants	40 participants (24 males, 16 females) were randomised. Age range 7 - 17 years. Participants had stable CF (judged by clinical evaluation, chest radiograph and pulmonary function) with FEV ₁ 47 - 107% and attended British Columbia's Children's Hospital CF Clinic. No participant entered the study within 1 month of hospitalisation for a pulmonary exacerbation.
Interventions	2x daily flutter versus 2x daily PEP (20 randomised to each treatment group).
Outcomes	Mean annual rate of decline in % predicted of FEV ₁ , FVC and FEF 25-75, number of exacerbations (hospitalisations), adherence or compliance with therapy. Measured at beginning of study, at 3-monthly intervals and at 12 months.
Notes	Most of the hospitalisations did not occur until months 7 - 9 of the study. People who did not adhere to treatment to a level of 85% adherence to 2x daily ACT as depicted in diaries were withdrawn by the researchers; but those who dropped out did so because they felt flutter to be ineffective.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised to either one group or another but generation of sequence not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.

Mcllwaine 2001 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Physicians were blinded to the method of physiotherapy received. Pulmonary function technician and radiographer were also blinded as to the airway clearance method.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs were reported and subgroup analysis carried out.
Selective reporting (reporting bias)	High risk	Less than 85% adherence over 1 month of treatment was considered not adherent to therapies and those participants were withdrawn.
Other bias	Unclear risk	There was a discrepancy between those withdrawn for non-compliance between the final paper which reported 2 from the PEP group and the 1998 abstract which reported 3 withdrawals. The author was contacted and advised that the final paper contained the correct information.

Mcllwaine 2013
Study characteristics

Methods	<p>RCT.</p> <p>Parallel design with 2-month washout period post randomisation and prior to start of trial.</p> <p>Location: multicentre (12 centres) in Canada.</p> <p>Duration 12 months.</p>
Participants	<p>107 participants (children and adults aged 6 - 47 years) enrolled in the study and randomised.</p> <p>PEP Group: 51 participants (mean age 13.5 years). 25 female, 26 male.</p> <p>HFCWO Group: 56 participants (mean age 14.3 years). 25 female, 31 male.</p> <p>19 dropouts within the study - 16 occurred prior to or at the time of randomisation (8 from each group - reasons given).</p> <p>At visit 2 (start of treatment arm) 43 were included in the PEP arm and 48 in the HFCWO arm.</p> <p>The study results were analysed on an ITT premise based on these participant numbers.</p> <p>Between visits 2 and 6 there was 1 further dropout from the PEP group and 2 from the HFCWO group.</p> <p>88 were analysed following completion of the study.</p>
Interventions	<p>1 - 2 sessions/day - participants to remain on individual regimen prescribed prior to study</p> <p>30 min of HFCWO (6x 5 min cycles) versus PEP (6 cycles of 15 PEP breaths followed by 2 - 3 huffs).</p>
Outcomes	<p>Time to exacerbation and frequency of exacerbation, health-related quality of life measurements, change in respiratory function parameters, participant preference.</p>
Notes	<p>Only randomised participants were included in the ITT analysis.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Mcllwaine 2013 (Continued)

Random sequence generation (selection bias)	Low risk	Randomised by an independent statistician using a computer-generated randomisation table.
Allocation concealment (selection bias)	Low risk	Central allocation - computer-generated by independent statistician.
Blinding (performance bias and detection bias) All outcomes	Low risk	Although participants could not be blinded to treatment, physicians and respiratory therapists performing the respiratory assessments and lung function tests were unaware of the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs were reported and data sets for all included were complete. ITT identified. At visit 2 when participants were to begin prescribed arm of treatment, there were 8 dropouts in each arm with similar reasons given. By the end of the study, there was 1 further dropout from the PEP group (diagnosed with CFRD) and 2 treatment-related from the HFCWO group (1 due to reflux and vomiting associated with treatment; 1 did not like HFCWO).
Selective reporting (reporting bias)	Low risk	On comparison with the protocol published on the clinical trials register, all outcomes identified are reported within the final paper. However, the data are presented as medians and percentiles which makes analysis problematic.
Other bias	Low risk	Both types of device (HFCWO and PEP) were loaned by their respective companies. It is considered therefore that this would not constitute bias as both groups were potentially equally influenced. The study was limited by the fact that the majority of participants were on PEP prior to the study, although attempts were made to limit any potential bias from this by having a washout period.

Milne 2004
Study characteristics

Methods	RCT (pilot study). Cross-over design (1 day washout between 2 treatment arms). Location; single-centre in South Africa. Duration: 5 days (2 days per treatment with 1 day washout in between).
Participants	7 participants with CF; mean age 28 years (range 16 - 42 years).
Interventions	Flutter versus ACBT. Group A: flutter, then washout, then ACBT. Group B: ACBT, then washout, then flutter.
Outcomes	Daily 24-hour sputum samples and lung function tests (FEV ₁ , FVC, PEF, FEF ₂₅ , FEF ₅₀ , FEF ₇₅), questionnaire at end of study.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised to either one group or another but generation of sequence not discussed.

Milne 2004 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Additional person was used to perform the lung function tests and is included in the acknowledgements it is not clear if this person was blinded to the treatments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data sets were complete for all those participants included in the study.
Selective reporting (reporting bias)	Unclear risk	No major side effects were experienced with either technique.
Other bias	Low risk	Possible limitations of the study were discussed and the author suggested various means to improve the findings of the study.

Modi 2010a

Study characteristics

Methods	<p>RCT.</p> <p>Parallel design (3 arms).</p> <p>Location: multicentre (20 centres) in USA.</p> <p>Duration: 3 years, but terminated early, duration of study participation ranged from 1.3 to 2.8 years.</p>
Participants	<p>166 participants with CF enrolled initially. 15 dropped out (11 from the CPT group and 4 from the flutter group) in the initial 60 days of the study with a further 41 withdrawing due to lost to follow up; lack of time; treatment preference and decrease in health. Data missing from 5 participants.</p> <p>Randomised 58 (31%) to PD&P, 51 (30%) to flutter and 57 (39%) to HFCWO.</p> <p>Gender split: 54% male.</p> <p>Mean (range) age: 14.2 (7 - 44) years. Participants split into 86 children (7 - 12 years), 44 adolescents (13 - 17 years) and 36 adults (over 18 years).</p> <p>Mean FEV₁ 88.2%.</p>
Interventions	<p>Flutter versus HFCWO versus PD&P.</p> <p>Flutter: self-administered in 3 stages - (1) loosening and mobilisation breaths (2) mucus mobilisation and (3) expectoration.</p> <p>PD&P: treatment administered by caregiver using a wedge and consisted of positioning, percussion (vibration) and forced expiratory technique with coughing between 6 positions; after each position participants instructed to do 3 forced expiratory technique and cough.</p> <p>Each treatment was 2x daily</p>
Outcomes	<p>Rate of decline in FEV₁, time to need for antibiotics for pulmonary exacerbations, use of other pulmonary therapies, participant satisfaction, adherence, quality of life.</p> <p>Measurements of satisfaction were recorded before and after study and every 4 months with phone diary, but no identification of type of activities outlined in this abstract. - details in online supplement</p>
Notes	<p>This study ID refers to the flutter versus PD&P section of the study.</p> <p>166 participants enrolled and a total of 56 withdrew (15 before Day 60, 41 after Day 60). 110 left in at early study termination and those who withdrew after Day 60 included in ITT analysis (n = 151).</p>

Modi 2010a (Continued)

Funded by Hill-Rom.

 Sample size calculation undertaken (60 participants per group) to detect a difference between annual rates of decline in FEV₁ of 2% predicted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Electronic randomisation stratified by age.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop outs apparent over the 3 abstracts but reasons not discussed. 15 dropped out and data missing from 5 participants. 130 provided adherence data in the 2006 abstract, but other abstracts and main papers describe 166 participants. Uneven drop outs across treatment arms and age groups led to early termination.
Selective reporting (reporting bias)	Low risk	Measurements of satisfaction were recorded before and after study and every 4 months with phone diary, these were identified as effectiveness, convenience, comfort, and overall satisfaction. Satisfaction with the therapy was an independent predictor of withdrawing.
Other bias	High risk	Study supported by Hill-Rom, Inc and the CF Foundation.

Modi 2010b
Study characteristics

Methods	RCT. Parallel design (3 arms). Location: multicentre (20 centres) in USA. Duration: 3 years, but terminated early, duration of study participation ranged from 1.3 to 2.8 years.
Participants	166 participants with CF enrolled initially. 15 dropped out (11 from the CPT group and 4 from the flutter group) in the initial 60 days of the study with a further 41 withdrawing due to lost to follow up; lack of time; treatment preference and decrease in health. Data missing from 5 participants. Randomised 58 (31%) to PD&P, 51 (30%) to flutter and 57 (39%) to HFCWO. Gender split: 54% male. Mean (range) age: 14.2 (7 - 44) years. Participants split into 86 children (7 - 12 years), 44 adolescents (13 - 17 years) and 36 adults (over 18 years). Mean FEV ₁ 88.2%.
Interventions	Flutter versus HFCWO versus PD&P. Each treatment was 2x daily

Modi 2010b (Continued)

HFCWO: self-administered using the Vest[®] using HFCWO, deep breathing and forced expiratory technique with coughing between each frequency. Each frequency to be done for 5 minutes with deep breathing to total lung capacity every 2 minutes and each cycle followed by 3 forced expiratory techniques.

PD&P: treatment administered by caregiver using a wedge and consisted of positioning, percussion (vibration) and forced expiratory technique with coughing between 6 positions; after each position participants instructed to do 3 forced expiratory technique and cough.

Outcomes	Rate of decline in FEV ₁ , time to need for antibiotics for pulmonary exacerbations, use of other pulmonary therapies, participant satisfaction, adherence, quality of life. Measurements of satisfaction were recorded before and after study and every 4 months with phone diary, but no identification of type of activities outlined in this abstract. - details in online supplement
Notes	<p>THIS DUPLICATE REFERENCE HAS BEEN CREATED TO ALLOW DATA FOR BOTH TYPES OF OSCILLATING DEVICE TO BE ENTERED IN THE ANALYSIS.</p> <p>This study ID refers to the HFCWO versus PD&P section of the study.</p> <p>166 participants enrolled and a total of 56 withdrew (15 before Day 60, 41 after Day 60). 110 left in at early study termination and those who withdrew after Day 60 included in ITT analysis (n = 151).</p> <p>Funded by Hill-Rom.</p> <p>Sample size calculation undertaken (60 participants per group) to detect a difference between annual rates of decline in FEV₁ of 2% predicted.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Electronic randomisation stratified by age.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Drop outs apparent over the 3 abstracts but reasons not discussed. 15 dropped out and data missing from 5 participants.</p> <p>130 provided adherence data in the 2006 abstract, but other abstracts and main papers describe 166 participants.</p> <p>Uneven drop outs across treatment arms and age groups led to early termination.</p>
Selective reporting (reporting bias)	Low risk	Measurements of satisfaction were recorded before and after study and every 4 months with phone diary, these were identified as effectiveness, convenience, comfort, and overall satisfaction. Satisfaction with the therapy was an independent predictor of withdrawing.
Other bias	High risk	Study supported by Hill-Rom, Inc and the CF Foundation.

Newbold 2005
Study characteristics

Methods	<p>RCT.</p> <p>Parallel design.</p> <p>Location: single centre in Canada.</p> <p>Duration: 13 months.</p>
Participants	<p>43 adults (25 males) with CF.</p> <p>FEV₁ > 40% predicted.</p> <p>No hospitalisations within 1 month of study entry, no change in medications within 1 month of study entry and willingness to attend 5 follow-up appointments.</p> <p>Exclusion criteria - absence of daily cough or daily production of sputum.</p> <p>Flutter group: mean (SD) age 31 (8.5) years.</p> <p>PEP group: mean (SD) age 28 (8.1) years.</p>
Interventions	<p>Flutter versus PEP mask (21 randomised to each treatment group out of 42 participants included in analysis)</p> <p>5 - 10 exhalations through the flutter with the degree of tilt adjusted to optimise the vibrations. Cycle is repeated until the individual felt "clear" or for approximately 20 minutes.</p> <p>10 - 15 breaths through the PEP followed by a huff or cough, followed by period of relaxed breathing. Cycle repeated 5 - 6 times taking approximately 20 minutes to complete.</p> <p>Participants were advised to perform their therapy 2x per day following any bronchodilator therapy. They were instructed to only use their Fflutter or PEP mask for the duration of the study. Followed every 3 months for 13 months. First month was the "training" month.</p>
Outcomes	<p>Lung function tests (FEV₁, FVC, FEF_{25-75%}), Quality of Well-being Scale, Chronic Respiratory Disease Index Questionnaire, daily diary record.</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table and block randomisation.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelope. Envelopes opened in sequence, and this may itself be a risk of allocation bias.
Blinding (performance bias and detection bias) All outcomes	Low risk	Lung function assessor was blinded to the device used by the participant and also to what stage they were at in the study period. It was not possible to blind the physiotherapist teaching the participant how to use the device nor indeed the participant themselves.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One drop out due to not attending at clinic appointments. Paper states that although not all participants attended every follow up assessment, baseline and final measures were obtained for all 42. All but 3 (1 flutter; 2 PEP) attended at least 4 follow-up visits in the 13-month period.

Newbold 2005 (Continued)

Selective reporting (reporting bias)	Low risk	Information available for all outcome variables measured.
Other bias	High risk	Flutter group and PEP group had different mean pulmonary function values at recruitment (flutter group higher). This led to divergence between groups in mean pulmonary function values at 1st and 2nd follow-up visits. Study fatigue is always a consideration when using small populations such as those with CF; and this study this as a reason why some participants declined inclusion into the study

Oermann 2001
Study characteristics

Methods	RCT. Cross-over design (2-week washout period). Location: multicentre (3 centres) in USA. Duration: 12 weeks (2-week run in period followed by 4-week treatment and 2-week washout with alternative 4-week treatment).
Participants	29 participants enrolled (14 males). Aged 6 years or greater. Mean (range) age - 23 (9 to 39) years. Diagnosis of CF confirmed by sweat test. Required ability to reliably perform spirometry and lung volume measurements, to have baseline FVC of 50 - 80 % predicted and be clinically stable for 1 month prior to enrolment. Excluded if in concurrent study or history of massive haemoptysis within 1 month or pneumothorax within 6 months of entrance. 5 participants withdrew (4 exited due to illness and 1 due to non-compliance with clinic visits).
Interventions	HFCWO versus oscillating PEP (flutter). As prescribed previous to study - no mention whether this was 2x daily etc. 4 weeks in each arm, 2-week lead-in and wash out periods during which time they resumed their normal routine therapies which were not outlined.
Outcomes	FEV ₁ , FVC, FEF _{25-75%} , participant satisfaction scores in domains of efficacy, convenience and comfort. Participant preference was measured as baseline and pre/post each intervention (5 data points).
Notes	5 withdrawals, ITT was identified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective randomisation, further details not given on method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.

Oermann 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants withdrew (4 exited due to illness and 1 due to non-compliance with clinic visits). ITT identified.
Selective reporting (reporting bias)	High risk	Only participants who completed both therapies were included in the final analysis. As we do not know what their normal therapy was perhaps they had already done a comparison?
Other bias	Unclear risk	None identified.

Osman 2010
Study characteristics

Methods	RCT. Cross-over design (no washout). Location: single centre in UK. Duration: 4 days.
Participants	30 participants recruited (22 males). Mean age: 29.7 years. Mean FEV ₁ : 37.7 %
Interventions	HFCWO versus "usual" ACT (83% of "usual" therapy was described as ACBT, AD, flutter or PEP). Participants received either HFCWO on days 1 and 3 and the "usual" ACT on days 2 and 4 or vice versa. Sessions were 2x daily for 30 min.
Outcomes	Wet weight of expectorated sputum, respiratory function, oxygen saturation monitoring, perceived efficacy and preference were measured.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to HFCWO or usual ACT on Day 1 was determined using a computer-generated randomisation table.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Not possible to blind participants or clinicians, but paper states: "An independent observer, blind to the daily method of airway clearance used, performed the spirometry, weighed the sputum samples and collected the 10 cm VAS throughout the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 sputum samples were removed from total of 116 collected as they were incomplete.

Osman 2010 (Continued)

Selective reporting (reporting bias)	Unclear risk	Powered to detect a 4 g difference in expectorated sputum.
Other bias	High risk	Supported by Robery Luff Foundation and Hill-Rom Ltd. Levels of oxygen saturation measured were higher at baseline in the HFCWO group which potentially could influence outcome as groups were not balanced at the beginning of the intervention.

Padman 1999a
Study characteristics

Methods	RCT. Cross-over design (used CPT between therapies as a washout period length of which was not defined). Location: single centre in USA. Duration: each therapy lasted 1 month.
Participants	15 participants aged 5 - 17 years with CF. Not stated how many were males and how many females. Participants were clinically stable and able to perform RFT's, no hospitalisations in the month prior to study. 5 excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given). 6 participants completed the study.
Interventions	Flutter versus PEP versus CPT/PD. Each therapy was performed for 15 min 3x daily for 1 month. No changes in established medication regimen.
Outcomes	RFTs (FEV ₁ , FEF ₂₅₋₇₅) performed at beginning and end of each new therapy, SaO ₂ , participant satisfaction.
Notes	This study ID refers to the flutter versus PEP section of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each participant was arbitrarily assigned to 1 of 3 groups of randomly sequenced therapies, no further details of method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 withdrawals after randomisation took place, 5 excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given).

Padman 1999a (Continued)

Selective reporting (reporting bias)	High risk	Gender split was not stated. Participants stated they felt better but there were no criteria given from which to establish this.
Other bias	Unclear risk	Scandipharm provided the flutter devices for the trial.

Padman 1999b
Study characteristics

Methods	RCT. Cross-over design (used CPT between therapies as a washout period length of which was not defined). Location: single centre in USA. Duration: each therapy lasted 1 month.
Participants	15 participants aged 5 - 17 years with CF. Not stated how many were males and how many females. Participants were clinically stable and able to perform RFT's, no hospitalisations in the month prior to study. 5 excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given). 6 participants completed the study.
Interventions	Flutter versus PEP versus CPT/PD. Each therapy was performed for 15 min 3x daily for 1 month. No changes in established medication regimen.
Outcomes	RFTs (FEV ₁ , FEF ₂₅₋₇₅) performed at beginning and end of each new therapy, SaO ₂ , participant satisfaction.
Notes	THIS DUPLICATE REFERENCE HAS BEEN CREATED TO ALLOW DATA FOR BOTH TYPES OF OSCILLATING DEVICE TO BE ENTERED IN THE ANALYSIS. This study ID refers to the Flutter versus CPT section of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each participant was arbitrarily assigned to 1 of 3 groups of randomly sequenced therapies, no further details of method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 withdrawals after randomisation took place, 5 excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given).
Selective reporting (reporting bias)	High risk	Gender split was not stated. Participants stated they felt better but there were no criteria given from which to establish this.

Padman 1999b (Continued)

Other bias	Unclear risk	Scandipharm provided the flutter devices for the study.
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Patel 2013
Study characteristics

Methods	RCT. Parallel design.
Participants	18 participants randomised to Metaneb [®] , 14 participants randomised to HFCWO. All admitted to hospital for management of a severe pulmonary exacerbation. Age, median (range): 29 (19 - 48) years. BMI, mean: 22.3 kg/m ² . FEV ₁ % predicted, mean: 41.4%.
Interventions	Intervention 1: Metaneb [®] over a 14-day period of hospitalisation. Intervention 2: HFCWO over a 14-day period of hospitalisation. Frequency and duration of each treatment not identified.
Outcomes	Participant satisfaction, sputum expectorated, spirometry and CFQ-R.
Notes	Await publication of full paper and authors contacted for further data for inclusion in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but generation of sequence not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	13 drop outs identified with reason of haemoptysis given for 3 participants. Haemoptysis necessitating cessation of ACT occurred in 1 (12.5%) Metaneb participant and 2 (40%) HFCC participants. No information given on remaining 10 drop outs.
Selective reporting (reporting bias)	Unclear risk	Abstract only, not possible to compare protocol with full paper.
Other bias	Unclear risk	Abstract only.

Phillips 2004
Study characteristics

Methods	<p>RCT.</p> <p>Cross-over design (no washout period). Location: single centre in UK.</p> <p>Duration: 2 days.</p>
Participants	<p>10 participants (7 males, 3 females). Median (range) age: 14 (9 - 16) years. CF diagnosed via sweat chloride testing or genetic testing. Participants admitted to the Brompton Hospital with an acute exacerbation as defined by conventional criteria and were adept at self-treatment of ACBT.</p>
Interventions	<p>ABCT versus HFCWO. 2 supervised treatments of either ACBT or HFCWO on 2 successive dates for 20 min.</p>
Outcomes	<p>FVC, FEV₁ (measured immediately before, immediately after and 10 min after each treatment), wet sputum weight (measured over 24-hour period, during treatment and 15 minutes after treatment), participant preference (measured at the end of the study).</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but generation of sequence not identified.
Allocation concealment (selection bias)	Low risk	Via sealed envelope.
Blinding (performance bias and detection bias) All outcomes	Low risk	Individual who collected sputum weight was blinded to therapy type.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data set complete, no drop outs identified.
Selective reporting (reporting bias)	Unclear risk	Not possible to compare study protocol with final paper.
Other bias	High risk	Paper identifies potential weakness of the study in that is short term and concludes that potentially a longer term study may have demonstrated improved adherence.

Pike 1999
Study characteristics

Methods	<p>RCT.</p> <p>Cross-over design (no washout period).</p>
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Pike 1999 (Continued)

Location: single centre in UK.
 Duration: 2 days of treatment and measurements taken at end.

Participants	21 participants (12 males, 9 females). Median age 26 years.
Interventions	Flutter and forced expiration versus ACBT. First treatment was performed 2x on Day 1 and then the other treatment 2x the following day.
Outcomes	RFTs, sputum weight, oxygen saturations and participant satisfaction were the outcome measures.
Notes	Abstract only, no full paper as yet published. Cross-over paired T-test and McNemars Chi ² tests were used for statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Independent observer measured pulmonary function and oxygen saturations.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts identified or discussed.
Selective reporting (reporting bias)	Unclear risk	Not discussed.
Other bias	Unclear risk	Abstract only.

Prasad 2005
Study characteristics

Methods	RCT. Parallel design. Location: single centre in UK. Duration: 12 months.
Participants	30 participants (20 girls, 10 boys matched). Age range 6 - 15 years; mean age 11.5 years. 15 to each treatment arm. BMI, LCI and FEV ₁ were well matched. One from each group withdrew because either they preferred their previous device, or they found it too fiddly to clean.

Prasad 2005 (Continued)

Interventions	PEP versus cornet. The treatment was used as their main ACT for 12 months.
Outcomes	FEV ₁ ; LCI; pulmonary exacerbations; health perception; quality of life. FEV ₁ and LCI were measured at start 6 months and 12 months. Quality of Well-Being Scale, health perception and frequency of exacerbations measured at beginning and end.
Notes	Abstracts only, no full paper published as yet. Blinding not possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified for age, sex and FEV ₁ , further details not given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One child from each group dropped out after randomisation, reason given.
Selective reporting (reporting bias)	High risk	Ongoing study which spanned 3 abstracts, but no full paper as yet identified.
Other bias	High risk	The authors themselves questioned whether quality of life measures were reliable in children as they may be unable to accurately compare current health to that experienced the previous year.

Pryor 1994
Study characteristics

Methods	RCT. Cross-over design (no washout period). Location: single centre in UK. Duration: 2 days.
Participants	24 participants (14 males, 10 females) with positive sweat test for CF were randomised, but only 20 included in the study. 4 participants withdrew (3 males, 1 female); 2 had to have drug regimens changed; 2 withdrew due to technical problems with oximeter and sputum collection. Age range 16 - 36 years; mean age 24.4 years. Stable as according to no clinical findings.
Interventions	ACBT versus flutter and ACBT. 2 supervised treatments per day then alternate treatment on following day.

Pryor 1994 (Continued)

In addition 2 different postural drainage positions were used, but no statistical difference noted between treatments.

Outcomes	RFTs, wet sputum weight and participant satisfaction.
Notes	No statistical data presented on RFTs apart from there being no statistical significance in the results. Most found both regimens easy to use, with majority finding ACBT easier to clear secretions. 17 out of 20 felt they would continue with ACBT. On follow-up the 3 participants who said they would continue with the flutter at home had discontinued it within the month and resumed ACBT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequentially admitted into the study, randomised to treatment regimens, but method not stated.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Independent observer used to measure lung function, sputum weight and oxygen saturations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 withdrawals after randomisation, (reasons given) analysis only on 20 remaining.
Selective reporting (reporting bias)	Unclear risk	Not discussed.
Other bias	Unclear risk	Not discussed.

Pryor 2010
Study characteristics

Methods	RCT. Parallel design. Location: single centre in UK. Duration: 12 months.
Participants	75 participants (47 males) enrolled. Aged over 16 years with positive diagnosis of CF. Median (SD) age: ACBT 31.1 (9.7) years, AD 25.9 (6.5) years, cornet 25.3 (8.3) years, flutter 32.1 (7.5) years, PEP 29.3 (12) years. Sex: ACBT - 11/15 male, AD 10/15 male, cornet 8/15 male, flutter 10/15 male, PEP 8/15 male. FEV ₁ >25% predicted. Exclusion criteria: respiratory exacerbation, recent acquisition of <i>Burkholderia cepacia</i> , previous history of pneumothorax, pregnancy, currently on transplantation waiting list and current haemoptysis.

Pryor 2010 (Continued)

Interventions	ACBT versus cornet versus AD versus flutter versus PEP (15 to each treatment group). Duration and frequency of treatments were individualised for each participant.
Outcomes	FEV ₁ , FVC, MEF, RV%/TLC, BMI, modified shuttle walk test, chronic respiratory disease questionnaire, Short form-36 and number of IV antibiotics required. Participants were observed for 1 year with outcomes measured every month.
Notes	Lung function data available on 65 participants only, as 10 lost to follow-up. Blinding of assessor but unclear as to whether person responsible for care was blinded to the randomisation. Used ITT. 53 completed study on technique to which they had been randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computerised and stratified according to FEV ₁ % predicted and sputum expectorated.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of assessor but unclear as to whether person responsible for care was blinded to the randomisation.
Incomplete outcome data (attrition bias) All outcomes	High risk	75 participants were randomised but data only available for 65 participants due to loss to follow-up. Used ITT. Withdrawals due to pleurodesis, listing for transplantation, one participant moved away, 3 withdrew with no reasons given, 1 did not want any more testing.
Selective reporting (reporting bias)	High risk	All outcomes were reported, although not all data provided.
Other bias	Unclear risk	None reported and no evidence of any other likely bias.

San Miguel Pagola 2016
Study characteristics

Methods	RCT. Cross-over design (2 arms, 1-week washout). Location: 7 Spanish Centres Duration: 17 days in total, each arm 5 days with a 1-week washout.
Participants	22 participants. Confirmed diagnosis of Cystic Fibrosis by sweat test or genetics. >16years of age . Able to expectorate >10mls of sputum per day on 2 different days. Clinically stable and able to nebulise independently.

San Miguel Pagola 2016 (Continued)

Interventions **Intervention:** participants inhaled 7% hypertonic saline + 0.1% hyaluronic acid (for 20 minutes) combined with an OPEP device (Acapella Duet) then following this performed their usual session of AD for 30 minutes.

Control: usual care, participants inhaled 7% hypertonic saline + 0.1% hyaluronic acid (for 10 minutes) then following this performed their usual session of AD for 20 minutes.

During the trial period the participants' pharmacological treatment remained unchanged.

Patients carried out the nebulisation and treatment at home for 5 consecutive days in each arm.

Outcomes

- Wet sputum production (mL) 2 hours after chest physiotherapy session.
- Wet sputum production (mL) 22 hours after chest physiotherapy session.
- Lung function at 5 days (FEV₁, FVC, FEF₂₅₋₇₅).
- Safety and tolerability of session (pulse-oximetry, heart rate, dyspnoea, haemoptysis, cough, throat irritability and saltiness, heart rate) after 45 minutes.
- Participant perception (Likert test) at 5 days.
- Leicester Cough Questionnaire and Cough and Sputum Questionnaire at 5 days.

Notes 32 participants were screened and 22 met the inclusion criteria for inclusion into the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Concealed allocation- opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Paper reports blinded assessors, however it is unclear who is assessing what result. Participants could not be blinded to the activity as they were using an additional device and the physiotherapists were assessing quality of treatment carried out based on video material therefore it would not be possible to blind them to the device use.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs identified
Selective reporting (reporting bias)	Unclear risk	Not discussed, although participants are self-administering and self-reporting and there is some concern that this could influence results and there appears to be no measures in place to limit this possibility.
Other bias	Unclear risk	Not identified

van Winden 1998
Study characteristics

Methods RCT.

Cross-over design (1-week washout period).
 Location: single centre in the Netherlands.

van Winden 1998 (Continued)

Duration: 6 weeks (each treatment 2 weeks and 1 week wash in/wash out period).

Participants	22 participants with CF confirmed by sweat test or DNA mutation analysis. Mean age 12 years; range 7 - 17 years. Sex: 12 males, 10 females. Clinically stable for 2 weeks before study.
Interventions	Flutter versus PEP mask. 2x daily, 2 weeks in each arm, 1 week wash-in and wash-out period.
Outcomes	FVC, FEV ₁ , RV/TLC, FEF ₂₅₋₇₅ % predicted, participant satisfaction. Outcomes were all measured before and after each treatment intervention.
Notes	Outcome assessor blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and clinicians could not be blinded, but outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study and their data were included.
Selective reporting (reporting bias)	Unclear risk	Not clear what happened in the run-in or wash out period between cross-over.
Other bias	Unclear risk	None identified.

Varekojis 2003a
Study characteristics

Methods	RCT. Cross-over design (no washout). Location: single centre in USA. Duration: 2 days in each arm which were consecutive so 6 days in total.
Participants	28 participants recruited, 24 (10 females, 14 males) analysed, reasons for withdrawals not reported. Mean age 24 years, range 14 - 34 years.
Interventions	PD&P versus IPV versus HFCWO. 3 treatments per day each lasting 30 min (24 min of therapy followed by 6 min of directed coughing). PD&P was delivered by pulmonary nurses; IPV and HFCWO delivered by respiratory therapists.

Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Varekojis 2003a (Continued)

This suggests inconsistency of personnel when delivering treatment modalities.

Outcomes	Wet and dry sputum weight collected over the 60-minute period, participant satisfaction questionnaire.
Notes	<p>This study ID refers to the IPV versus PD&P section of the study.</p> <p>It is not clear whether sputum was collected for each of the 6 treatment days or for first or last 60 min per treatment technique.</p> <p>Study reports that 4 participants received each of the 6 possible treatment sequences - this suggests that they had more than 1 admission during the study time which may lead to duplication of data.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 withdrawals following randomisation, but reasons for withdrawals not reported.
Selective reporting (reporting bias)	Low risk	Limitations of the study were outlined.
Other bias	High risk	<p>Study reports that 4 participants received each of the 6 possible treatment sequences - this suggests that they had more than 1 admission during the study time which may lead to duplication of data.</p> <p>Pulmonary nurses were used to perform physiotherapy techniques which may have had an impact on the accuracy and efficacy of treatments delivered.</p>

Varekojis 2003b
Study characteristics

Methods	<p>RCT.</p> <p>Cross-over design (no washout).</p> <p>Location: single centre in USA.</p> <p>Duration: 2 days in each arm which were consecutive so 6 days in total.</p>
Participants	28 participants recruited, 24 (10 females, 14 males) analysed, reasons for withdrawals not reported. Mean age 24 years, range 14 - 34 years.
Interventions	<p>PD&P versus IPV versus HFCWO.</p> <p>3 treatments per day each lasting 30 min (24 min of therapy followed by 6 min of directed coughing).</p>

Varekojis 2003b (Continued)

PD&P was delivered by pulmonary nurses; IPV and HFCWO delivered by respiratory therapists.
This suggests inconsistency of personnel when delivering treatment modalities.

Outcomes	Wet and dry sputum weight, participant satisfaction questionnaire.
Notes	THIS DUPLICATE REFERENCE HAS BEEN CREATED TO ALLOW DATA FOR BOTH TYPES OF OSCILLATING DEVICE TO BE ENTERED IN THE ANALYSIS. This study ID refers to the HFCWO vs PD&P section of the study. It is not clear whether sputum was collected for each of the 6 treatment days or for first or last 60 min per treatment technique. Study reports that 4 participants received each of the 6 possible treatment sequences - this suggests that they had more than 1 admission during the study time which may lead to duplication of data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 withdrawals following randomisation, but reasons for withdrawals not reported.
Selective reporting (reporting bias)	Low risk	Limitations of the study were outlined.
Other bias	High risk	Study reports that 4 participants received each of the 6 possible treatment sequences - this suggests that they had more than 1 admission during the study time which may lead to duplication of data. Pulmonary nurses were used to perform physiotherapy techniques which may have had an impact on the accuracy and efficacy of treatments delivered.

Warwick 1990

Study characteristics

Methods	RCT. Cross-over design. Location: single centre in USA. Duration: not clear.
Participants	Reported 13 pairs of samples but number of participants was not specified, therefore we can only assume there were 13 adolescents or adults.

Warwick 1990 (Continued)

Age and sex not specified.

Interventions	HFCWO versus CPT. Participants were randomised to 2 groups each with 4 sessions. 1st group: CPT, HFCWO, HFCWO, CPT. 2nd group: HFCWO, CPT, CPT, HFCWO.
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Outcomes	Wet and dry sputum weight.
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Notes	Interventions looks like 2 sessions just one the reverse of the other.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants or clinicians.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported 13 pairs of samples but number of participants was not specified, therefore we can only assume there were 13 adolescents or adults.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Age and sex of participants not stated.

Warwick 2004
Study characteristics

Methods	RCT. Cross-over design Location: single centre in USA. Duration: 2 weeks (2 study days in each week).
Participants	12 participants (all males) with CF. Mean (range) age 29.2 (19 - 50) years. Consistent sputum producers; all volunteers with no illness within 6 weeks of study.
Interventions	HFCWO versus CPT. HFCWO: 5 minutes at 6 frequencies, followed by 3 huffs and directed coughs at the end of each cycle; treatment time 36 - 40 min. CPT: 10 hand positions, 3 huffs and directed cough after each position treatment lasting about 45 - 50 min. All treatments preceded by nebulisers.

Warwick 2004 (Continued)

Outcomes	Wet and dry sputum weight measured at end of each session, data reported at end of week 1 and end of week 2.	
Notes	<p>As this study also appeared to compare the efficacy of 2 different therapists therefore we cannot be absolutely clear that the HFCWO was solely responsible for any and all improvements in sputum weight.</p> <p>In addition the hand positions used by the therapist were not defined and commonly we would use a variety of 13 postural drainage positions if this was the technique being evaluated.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants or clinicians, but paper states "all the subjects were analysed as soon as possible by a single scientist (LGH) with no knowledge of subject source or therapy given"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Complete data sets for all participants.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. All parameters measured were discussed.
Other bias	High risk	Paper also reports that a natural competition between two different therapists was created. In addition the hand positions used by the therapist were not defined.

West 2010

Study characteristics	
Methods	<p>RCT.</p> <p>Parallel design.</p> <p>Location: single centre in Australia.</p> <p>Duration: at least 10 days.</p>
Participants	<p>23 children and adolescents with CF admitted to hospital for IV antibiotics for a respiratory exacerbation (as defined by Wood 2002). Needed previous experience at home with any PEP device. 1 from acapella group was discharged early on Day 6, so only 10 analysed in that group.</p> <p>Age mean (SD) range: PEP 13.5 (3.3) 7 - 18 years; acapella 10.4 (2.2) 7 - 13 years.</p> <p>Sex: PEP 9 females, 3 males; acapella 8 females, 2 males, the gender of the one participant from the acapella group who was discharged early was not identified in the paper.</p> <p>FEV₁ % predicted mean (SD) range: PEP 74.67 (19.8)%, 56% - 114%; acapella 58.9 (23)%, 29% - 95%.</p>

West 2010 (Continued)

Exercise performance (m) mean (SD) range; PEP 798.3 (233.6), 390 - 1100 m; acapella 576 (293.7), 290 - 1200 m.

Interventions	PEP mask (n = 12) versus acapella (n = 11). 2 supervised treatment sessions each day for a 10-day period. Treatment was standardised to consist of 10 sets with the allocated device in a sitting position. Each set consisted of 10 breaths through the device followed by one or two huffs and cough. The pressure settings for the device were standardised for the study to provide between 15 and 20 cm H ₂ O of positive pressure. All participants received concurrent IV antibiotics; any other treatment was in accordance with direction from a respiratory physician who was not aware of the treatment allocation of participants.	
Outcomes	Lung function, exercise performance (modified shuttle walk test), wet weight of sputum and satisfaction questionnaire. Outcomes measured prior to randomisation and after 10 days.	
Notes	Sample size calculation undertaken (18 participants per treatment arm needed to detect a 10% change in FEV ₁).	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	36 pieces of paper (18 PEP and 18 acapella) were put in double-sealed envelopes and a research assistant (who was not involved with recruitment, assessment, or treatment) withdrew 1 envelope, determined group allocation, and then discarded the envelope.
Allocation concealment (selection bias)	Low risk	36 pieces of paper (18 PEP mask and 18 acapella) were placed in double-sealed envelopes and for each participant a research assistant (who was not involved with recruitment, assessment, or treatment) withdrew one envelope to determine group allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were blinded for lung function and modified 10-metre shuttle test.
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 out of 23 participants completed the study; 1 participant was discharged home on day 6 for home IV treatment and was not available to complete the 10 days of treatment.
Selective reporting (reporting bias)	Low risk	Limitations of the study were identified - specifically smaller than planned sample size due to changes in clinical practice. This impacts the power of the study to detect an effect if one exists and may have contributed to lack of statistical differences between the intervention groups.
Other bias	Unclear risk	There appeared to be differences at baseline for age, FEV ₁ , and exercise performance. The PEP mask group was older, had a higher FEV ₁ , and could cover more distance in the 10-metre shuttle test. It was noted that parents were allowed to assist their child in completing the satisfaction questionnaire.

Wheatley 2018
Study characteristics

Methods	<p>Phase I: cross-over RCT, but not randomised and only single intervention in each arm, therefore this part was ineligible for inclusion in the review.</p> <p>Phase II: parallel RCT.</p>
Participants	<p>Phase II</p> <p>12 hospitalised participants (VibraLung[®] group n = 3; Vest[®] group n = 9).</p> <p>Mean (SD) age: 23 (6) years.</p> <p>Mean (SD) height: 165 (6) cm.</p> <p>Mean (SD) weight: 60 (10) kg.</p> <p>Mean (SD) BMI: 22 (3) kg/m².</p> <p>Mean (SD) BSA: 1.7 (0.2) m².</p> <p>Mean (SD) FEV₁ % predicted: 60 (20) %.</p> <p>Mean (SD) FVC % predicted: 76 (18) %.</p>
Interventions	<p>Phase II: 5 days of in-hospital therapy for 2 sessions/day with either VibraLung[®] and the Vest or the Vest[®] independently.</p>
Outcomes	<p>Phase II: sputum collected for 20 minutes post-treatment.</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a random number generator to assign to 1 of the 3 treatment arms.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not possible to blind participants or clinicians due to the addition of one or other device. The paper did not allude to blinding of any of the assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Appears to be at least 1 drop out due to admission being shorter than total study time. However paper reports 2 people discharged.</p> <p>Difficulty identifying exactly how many completed the relevant conditions A,B and C and how many did in fact cross over or how many complete data sets there were.</p>
Selective reporting (reporting bias)	High risk	Measurement of diffusing capacity of the lungs for Carbon monoxide and nitric oxide, alveolar-capillary membrane conductance and pulmonary capillary blood volume and cardiac output was noted as being recorded but this was only described in the results of Phase I. It is not clear if it was measured in Phase II and omitted from results description.

Wheatley 2018 (Continued)

Other bias	Unclear risk	As this was essentially a study to evaluate the safety of the Vibralung, the VEST was used as an additional treatment even through the Vibralung arm of the study. This may have influenced the outcome of the study.
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6MWD: six minute walk distance
 ACBT: active cycle of breathing
 ACT: airway clearance technique
 AD: autogenic drainage
 BMI: body mass index
 bpm: bursts per minute
 CF: cystic fibrosis
 CFRD: cystic fibrosis-related diabetes
 CPT: chest physiotherapy
 FEF: forced expiratory flow
 FEV₁: forced expiratory volume at one second
 FVC: forced vital capacity
 HFCC: high frequency chest compression
 HFCWO: high force chest wall oscillation
 IPV: intrapulmonary percussive ventilator
 ITT: intention to treat
 IV: intravenous
 LCI: lung clearance index
 MEF: mid-expiratory flow
 PD: postural drainage
 PD&C: postural drainage and clapping
 PD&P: postural drainage and percussion
 PEF: peak expiratory flow
 PEP: positive expiratory pressure
 PO₂: partial pressure of oxygen
 RCT: randomised controlled trial
 RFT: respiratory function test
 RV: residual volume
 SaO₂: pulse oximetry
 SD: standard deviation
 SpO₂: peripheral capillary oxygen saturation, an estimate of the amount of oxygen in the blood
 TLC: total lung capacity
 VC: vital capacity

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amelina 2014	No randomisation. Despite what is inferred by abstract, after translation of the full paper there is no evidence or comment made as regards randomisation.
Borka 2012	Study considers comparing treatment sequence, when broken down into individual treatment options it is a single intervention study.
Cantin 2005	Use of the frequencer which is not a therapy modality for comparison.
Cegla 1993	Only one participant with CF involved in the study, therefore no comparable participants relevant to this review.
Clinkscale 2012	No comparable participants identified.
Dosman 2003	Single-intervention study.

Study	Reason for exclusion
Dunn 2013	Single-intervention study.
Dwyer 2017	Single-intervention study.
Elkins 2004	Single-intervention study. In addition uses non-invasive ventilation which was not in our inclusion characteristics as a therapy modality for comparison.
Elkins 2005	Single-dose comparison study.
Fainardi 2011	Single-intervention study.
Grosse-Onnebrink 2017	Single-intervention study.
Hartsell 1978	Single-dose comparison study. Uses a mechanical percussor which we have not formally included. Some of the study participants did not have CF.
Jarad 2010	HAT is not a recognised airway clearance technique and therefore not in our inclusion criteria. In particular we stated that external oscillation applied to the chest wall should have an effect on expiratory airflow. This is not the case with HAT and consequently should not be judged as an airway clearance adjunct.
Kempainen 2007	Single intervention and comparison made with HFCWO and different pressures and variable frequencies.
Kirkpatrick 1995	Use of acoustic percussion, not a therapy we have chosen to compare as not inclusive of oscillation therapy as a comparator.
Konstan 1994	After careful consideration of the methodology of the paper it was considered to be comparing single interventions only.
Kraemer 1996	Evaluating a bronchodilator (beta2-inhalation therapy) in sequence with flutter. This did not evaluate an oscillatory device with another form of ACT.
Lagerkvist 2006	Single-dose comparative study. Also principally looking at blood gases, tensions and RFTs were an aside.
Leemans 2018	Evaluated the mobile vest compared to the standard vest. There were no other differences therefore it was felt that the comparators were not something we intended to evaluate.
Lindemann 1992	Single-dose comparison study.
Majaesic 1996	Outcome measure is sputum viscosity, which is not one of our outcome measures.
Marks 1998	Single-dose comparison study.
Marks 2004	Single-dose comparison study.
McCarren 2006	Single-dose comparison study. Physiological effects of vibration is not an outcome measure of the review.
Morris 1982	Use of mechanical percussor, which is not in the inclusion criteria for therapies to be compared.
Natale 1994	Comparison of 3 treatment techniques, but only single doses of each.
NCT01923753	Not using a treatment modality that we are currently evaluating.

Study	Reason for exclusion
NCT02600039	Not using a treatment modality that we are currently evaluating, also outcomes are not eligible for our inclusion.
NCT03261219	Study was withdrawn without any recruitment.
Newhouse 1998	Single-dose study.
O'Neil 2017	Both groups received same oscillating device regimen, difference between groups was the timing of administration of hypertonic saline.
Orlik 2000a	CCT not RCT or quasi-RCT.
Orlik 2000b	CCT not RCT or quasi-RCT.
Orlik 2001	CCT not RCT or quasi-RCT.
Radtke 2018	Single intervention.
Roos 1987	Study was not completed when abstract was published. Authors were contacted but they were unable to provide us with any data to support this or any subsequently related study.
Salh 1989	Assessing exercise for sputum clearance but not compared with oscillatory therapies.
Scherer 1998	Single-dose study.
Skopnik 1986	Use of 'Knock and Vibration' therapy, which is not part of our review inclusion criteria.
Stites 2006	Single-dose comparison and outcome measure of drug deposition whilst using the device rather than evaluating it as an airway clearance system.
Van Ginderdeuren 2008	Single-dose study.
Webber 1984	Self-percussor, not in criteria for comparison as not oscillatory.

ACT: airway clearance technique

CF: cystic fibrosis

HAT: hydro-acoustic therapy

RFT: respiratory function test

DATA AND ANALYSES

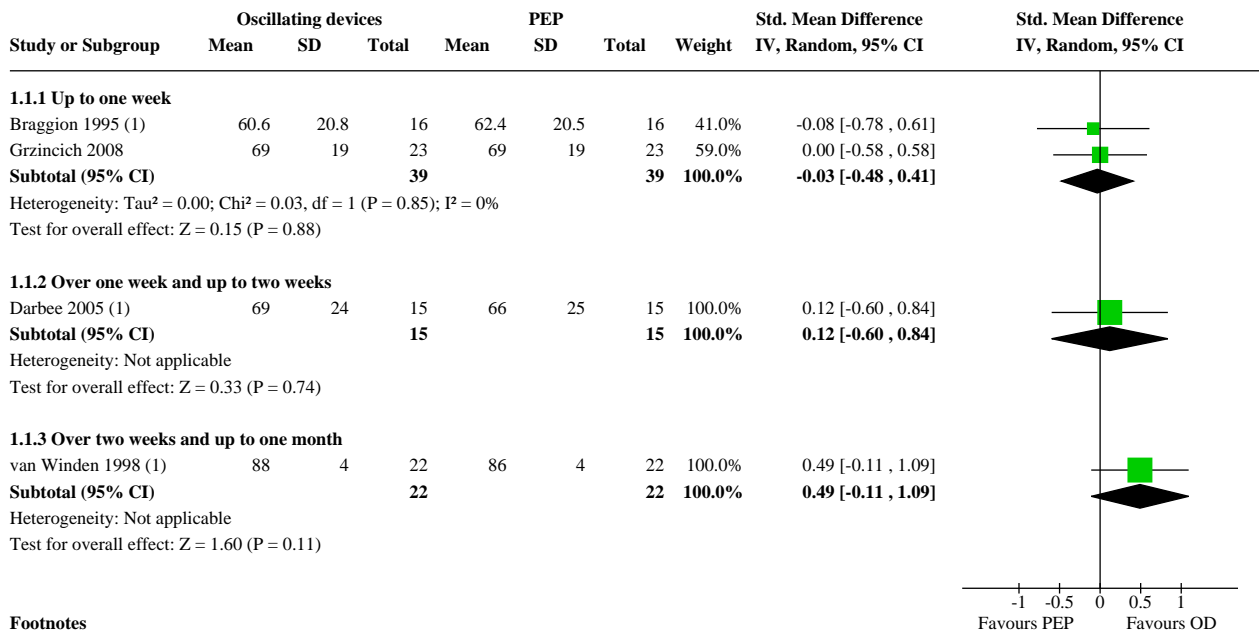
Comparison 1. Oscillating devices (OD) versus positive expiratory pressure (PEP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 FEV ₁ post-intervention [% predicted]	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 Up to one week	2	78	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.48, 0.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.2 Over one week and up to two weeks	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.60, 0.84]
1.1.3 Over two weeks and up to one month	1	44	Std. Mean Difference (IV, Random, 95% CI)	0.49 [-0.11, 1.09]
1.2 FEV₁ change from baseline [% predicted]	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Over one week and up to two weeks	1	22	Mean Difference (IV, Fixed, 95% CI)	9.37 [-6.16, 24.90]
1.2.2 Over two weeks and up to one month	1	12	Mean Difference (IV, Fixed, 95% CI)	-4.08 [-12.82, 4.66]
1.2.3 At one year	3	162	Mean Difference (IV, Fixed, 95% CI)	1.54 [-1.97, 5.06]
1.3 FEF₂₅₋₇₅ post intervention [% predicted]	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Up to one week	2	78	Mean Difference (IV, Fixed, 95% CI)	0.09 [-9.33, 9.52]
1.3.2 Over one week and up to two weeks	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-27.84, 25.84]
1.3.3 Over two weeks and up to one month	1	44	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-3.95, 1.95]
1.4 FEF₂₅₋₇₅ change from baseline [% predicted]	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 Over one week and up to two weeks	1	22	Mean Difference (IV, Fixed, 95% CI)	15.26 [-10.12, 40.64]
1.4.2 Over two weeks and up to one month	1	12	Mean Difference (IV, Fixed, 95% CI)	-20.07 [-45.00, 4.86]
1.4.3 At one year	3	162	Mean Difference (IV, Fixed, 95% CI)	0.13 [-4.46, 4.72]
1.5 FVC post intervention [% predicted]	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 Up to one week	2	78	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-8.71, 7.40]
1.5.2 Over one week and up to two weeks	1	30	Mean Difference (IV, Fixed, 95% CI)	3.00 [-10.60, 16.60]
1.5.3 Over two weeks and up to one month	1	44	Mean Difference (IV, Fixed, 95% CI)	2.00 [-0.09, 4.09]
1.6 FVC change from baseline [% predicted]	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.1 Over one week and up to two weeks	1	22	Mean Difference (IV, Random, 95% CI)	5.40 [-9.21, 20.01]
1.6.2 At one year	3	162	Mean Difference (IV, Random, 95% CI)	0.25 [-6.14, 6.65]
1.7 Sputum volume [ml]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 Up to 1 week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Sputum weight [g]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Quality of life indices	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 Quality of well being score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.2 CRQ Disease specific interviewer administered questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.3 CFQ: physical domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.4 CFQ: emotional domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.5 CFQ: treatment burden domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.6 CFQ: respiratory domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.7 CFQ: digestion/weight domain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 Number of hospitalizations	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10.1 At one year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 Pulmonary exacerbations (at 1 year)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.1 Total number of patient requiring antibiotics for exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.2 Number of patients requiring IV antibiotics for exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12 Exercise performance % change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12.1 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13 Participant satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

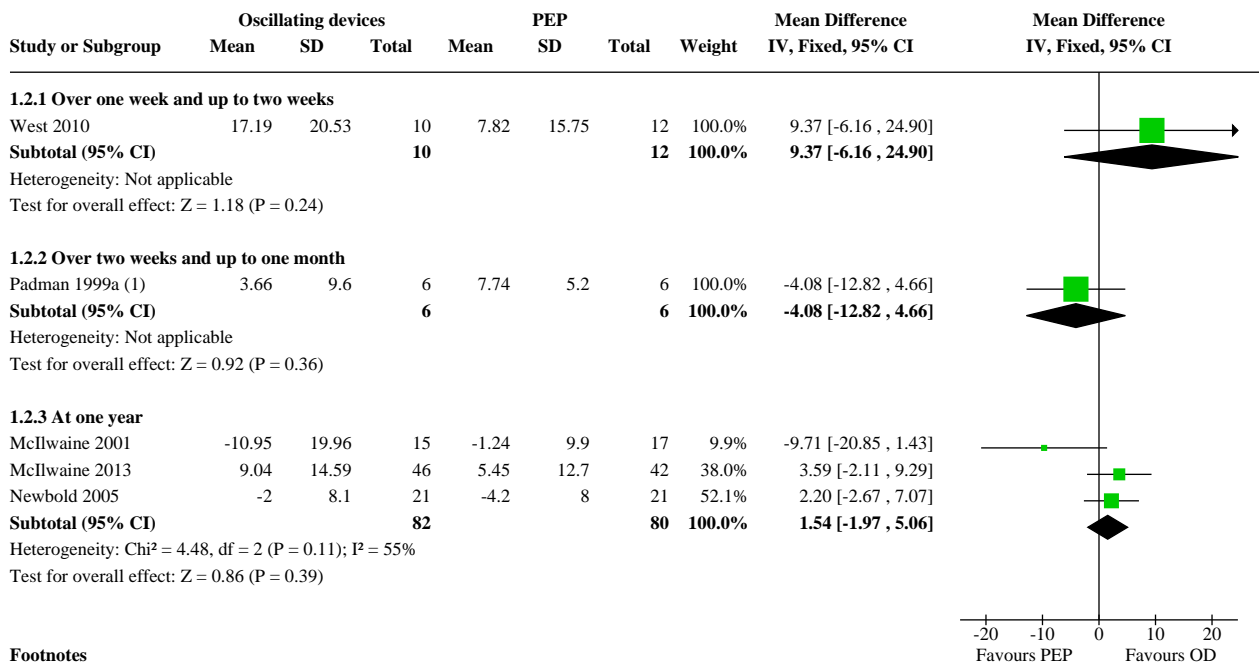
Analysis 1.1. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 1: FEV₁ post-intervention [% predicted]



Footnotes

(1) This study is of a cross-over design

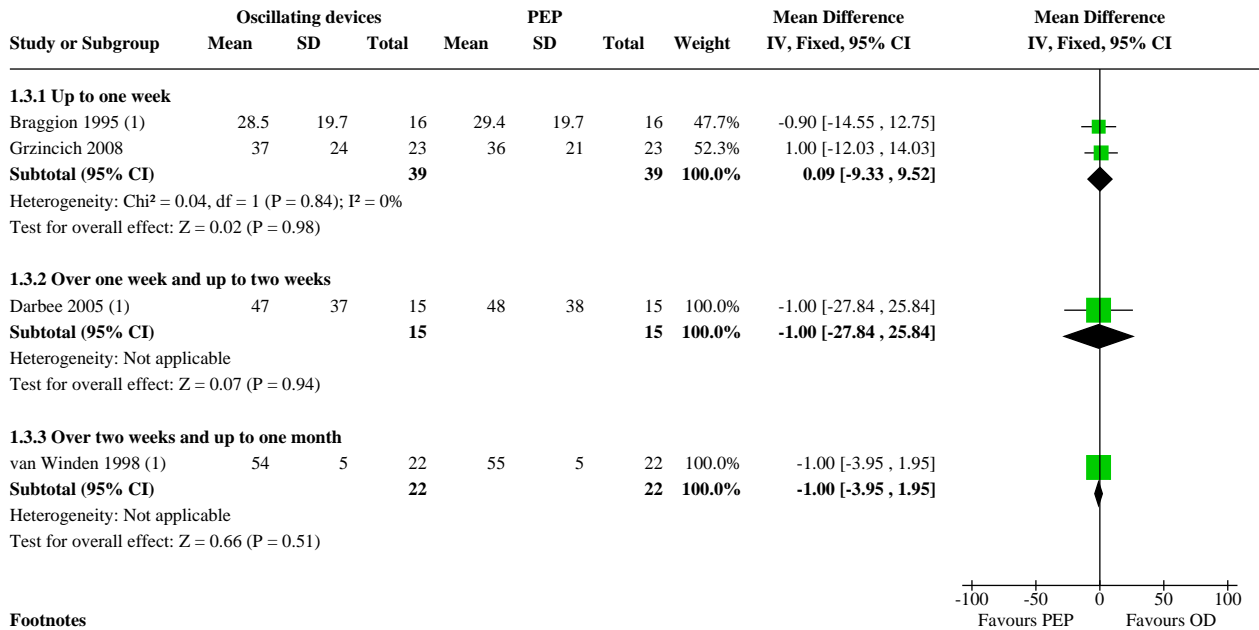
Analysis 1.2. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 2: FEV₁ change from baseline [% predicted]



Footnotes

(1) This study is of a cross-over design

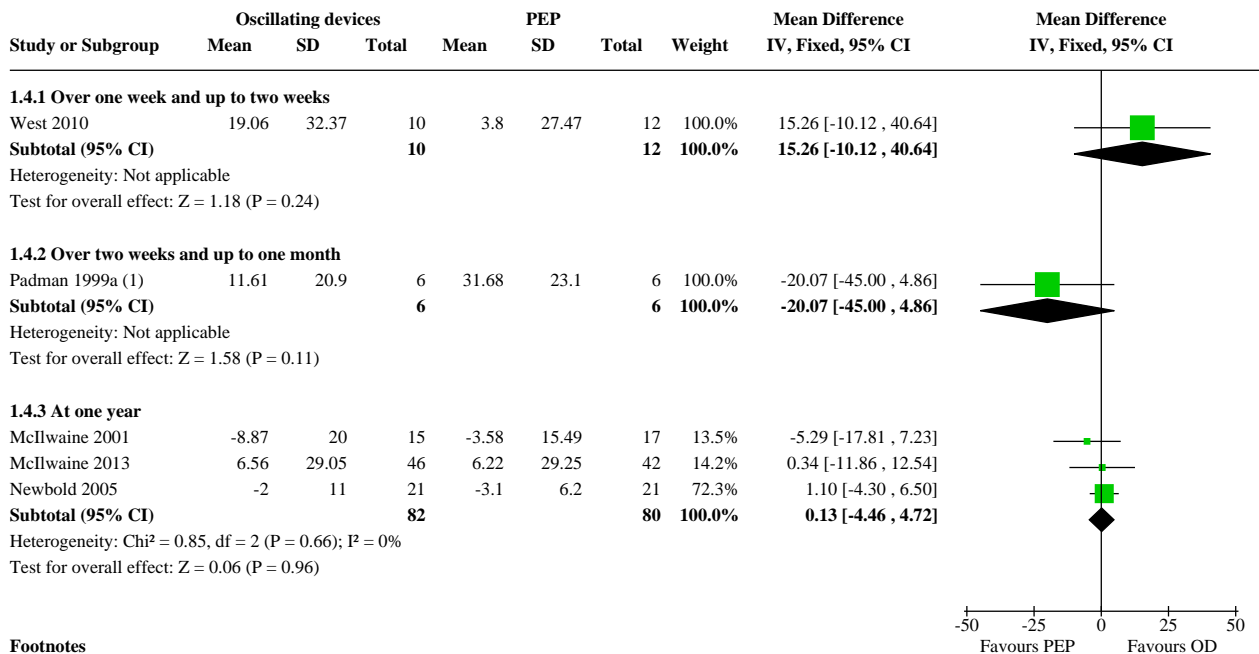
Analysis 1.3. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 3: FEF₂₅₋₇₅ post intervention [% predicted]



Footnotes

(1) This study is of a cross-over design

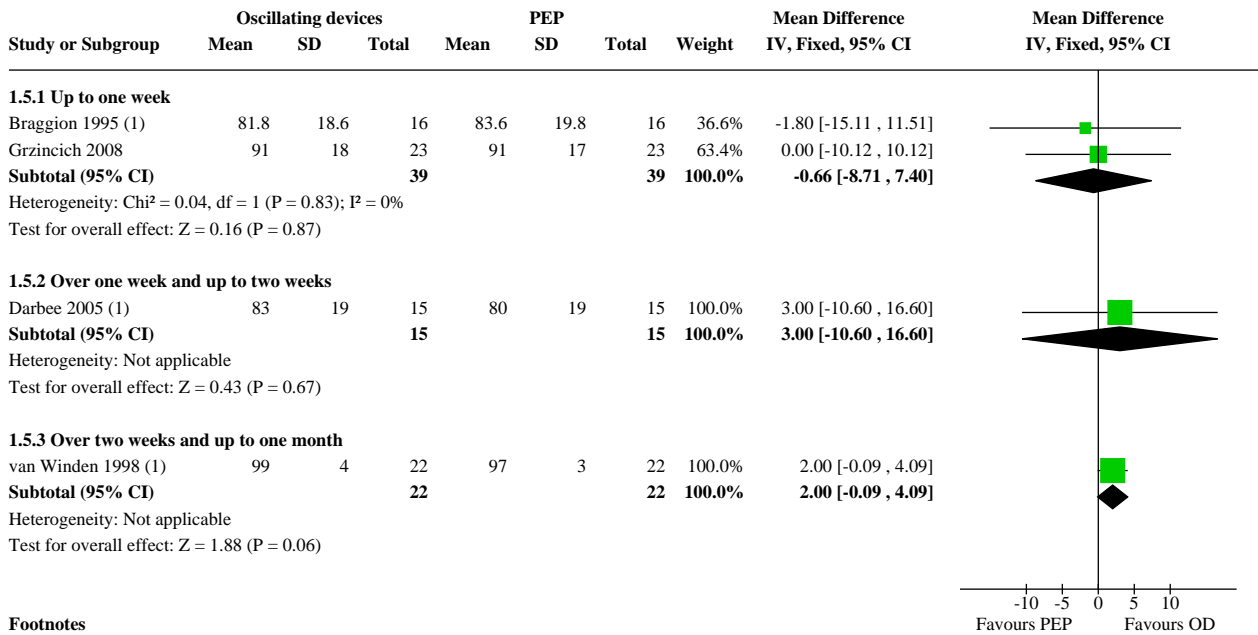
Analysis 1.4. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 4: FEF₂₅₋₇₅ change from baseline [% predicted]



Footnotes

(1) This study is of a cross-over design

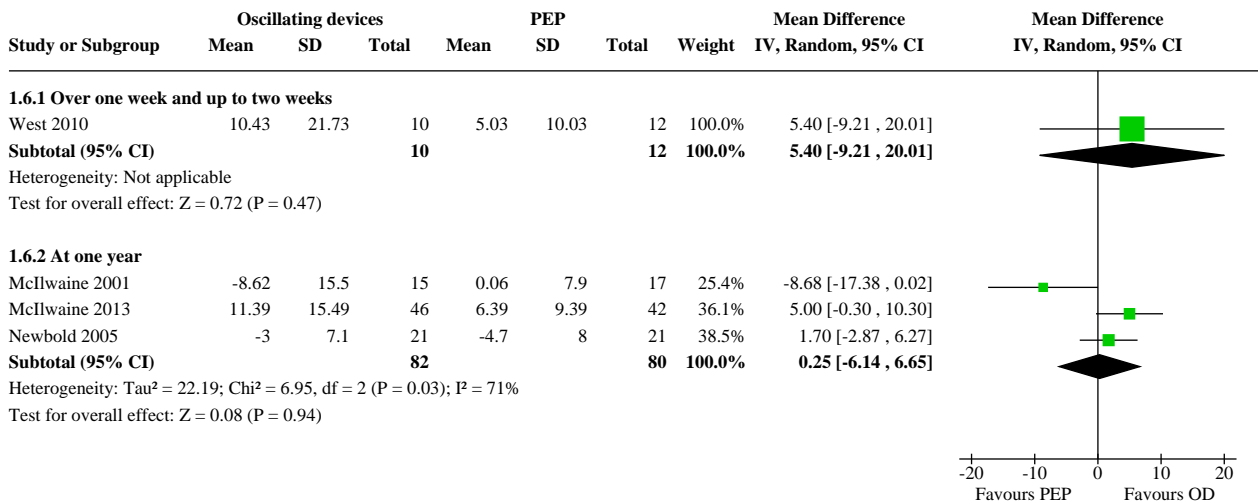
Analysis 1.5. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 5: FVC post intervention [% predicted]



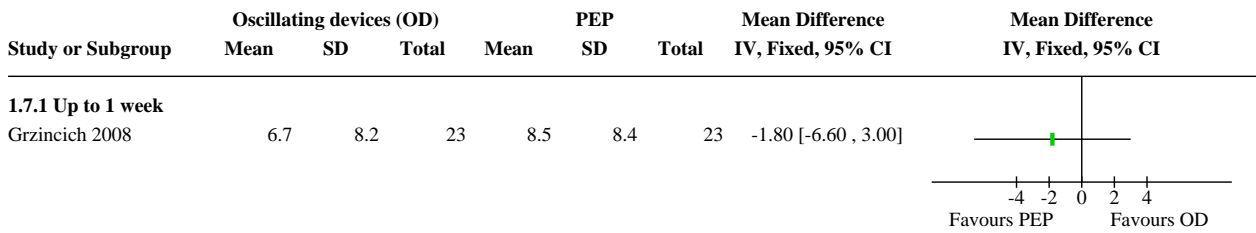
Footnotes

(1) This study is of a cross-over design

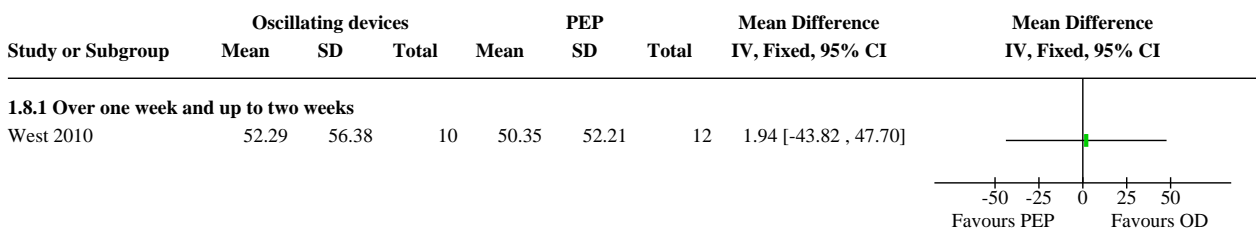
Analysis 1.6. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 6: FVC change from baseline [% predicted]



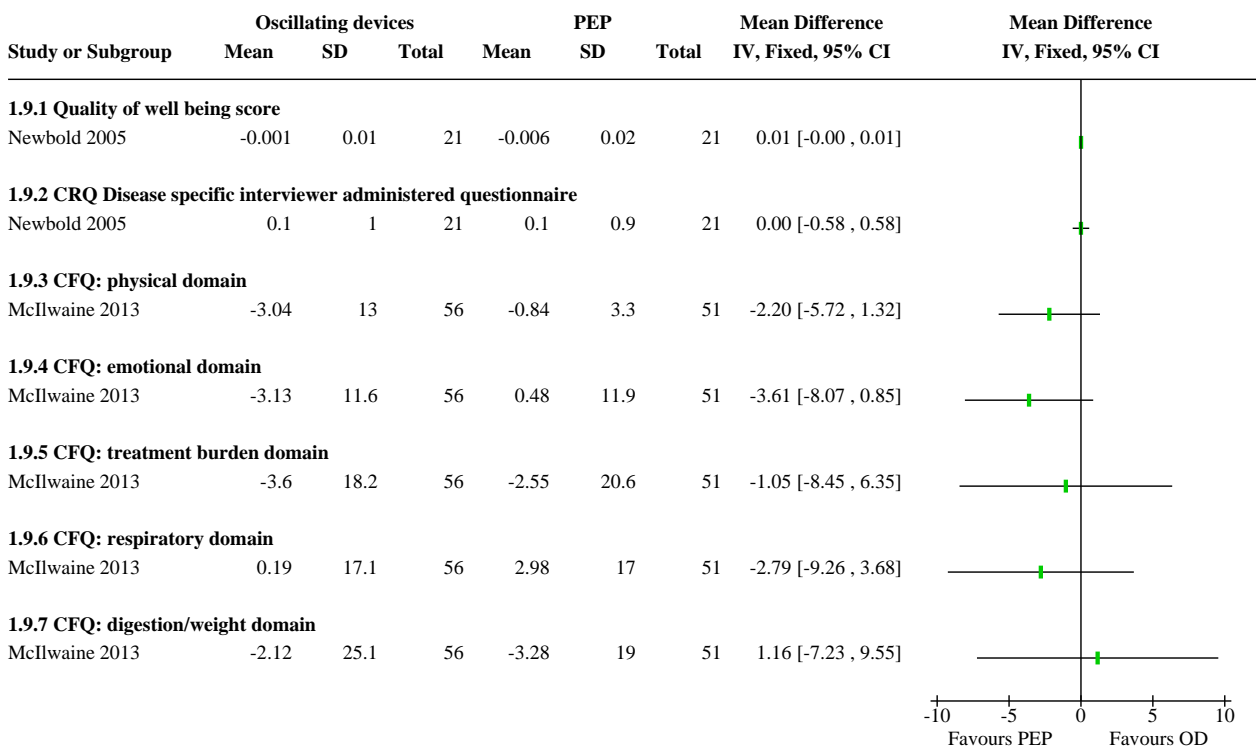
Analysis 1.7. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 7: Sputum volume [ml]



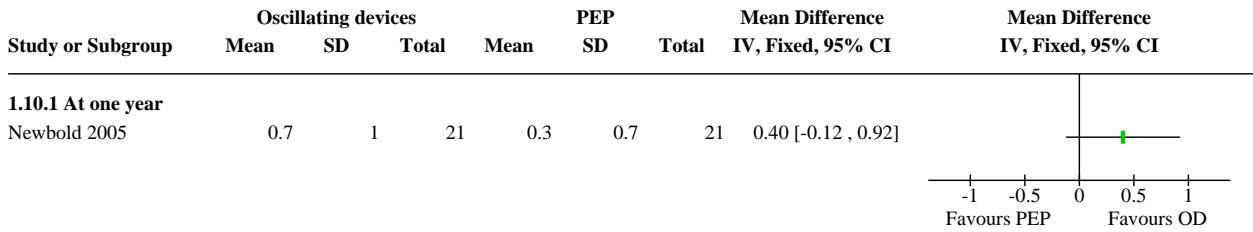
Analysis 1.8. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 8: Sputum weight [g]



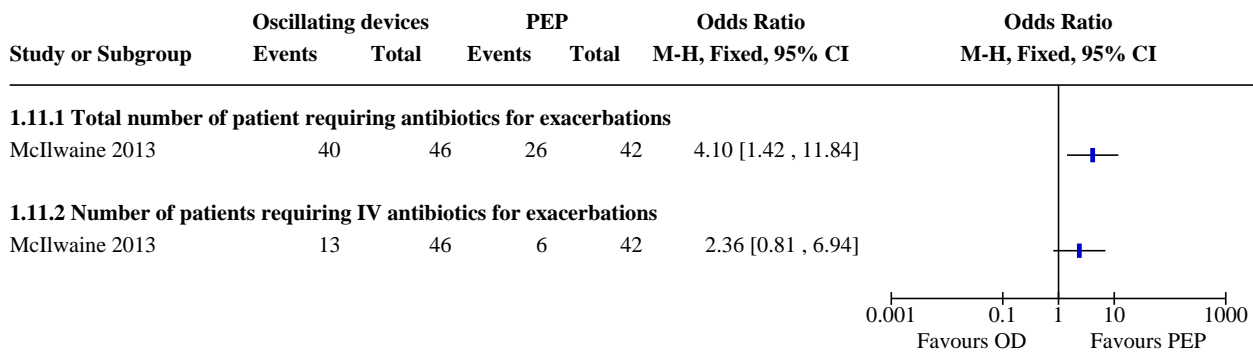
Analysis 1.9. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 9: Quality of life indices



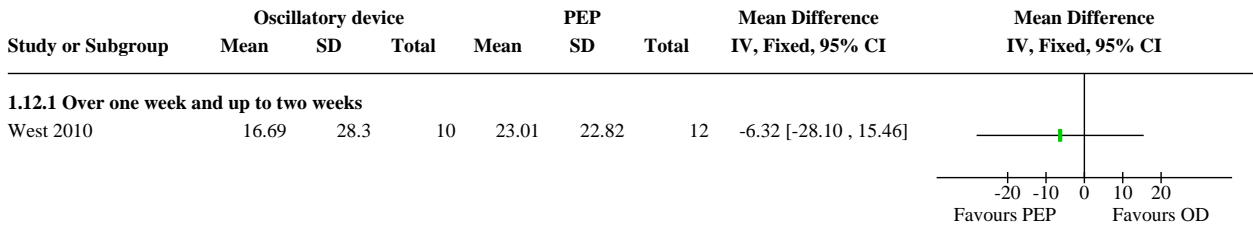
Analysis 1.10. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 10: Number of hospitalizations



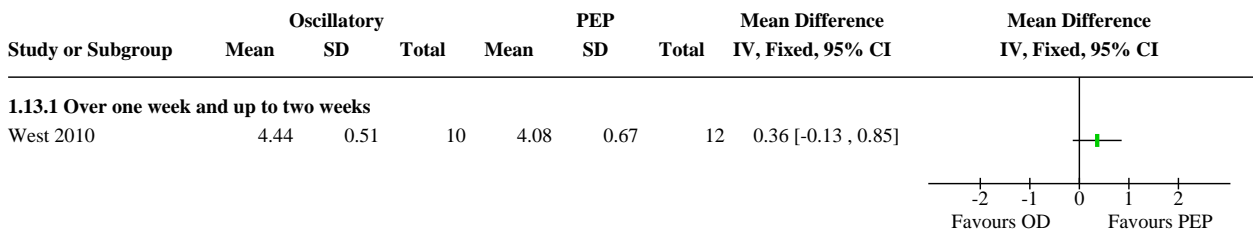
Analysis 1.11. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 11: Pulmonary exacerbations (at 1 year)



Analysis 1.12. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 12: Exercise performance % change from baseline



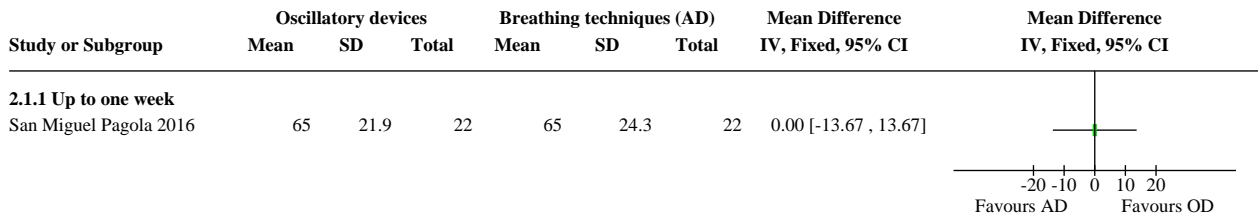
Analysis 1.13. Comparison 1: Oscillating devices (OD) versus positive expiratory pressure (PEP), Outcome 13: Participant satisfaction



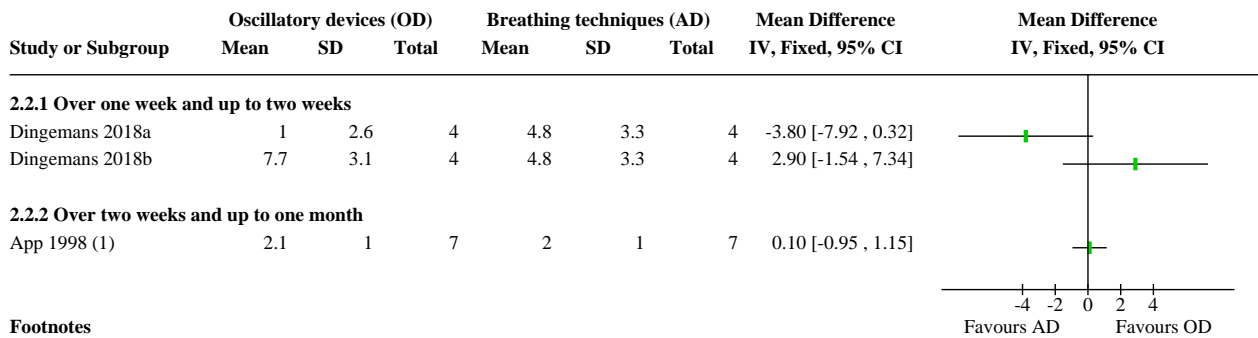
Comparison 2. Oscillating devices (OD) versus breathing techniques

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 FEV ₁ post-intervention [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1.1 Up to one week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 FEV ₁ change from baseline [% predicted]	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2.1 Over one week and up to two weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2.2 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.3 FEF ₂₅₋₇₅ absolute post-treatment values [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Up to one week	1	44	Mean Difference (IV, Fixed, 95% CI)	2.00 [-13.44, 17.44]
2.4 FVC post-intervention [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 up to one week	1	44	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-12.63, 7.63]
2.5 FVC change from baseline [% predicted]	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.5.1 Over one week and up to two weeks	2	16	Mean Difference (IV, Fixed, 95% CI)	0.19 [-2.31, 2.69]
2.5.2 Over two weeks and up to one month	1	14	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.83, 1.43]
2.6 Sputum volume [g]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.6.1 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7 Sputum weight (wet) [g]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7.1 Up to one week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 1: FEV₁ post-intervention [% predicted]



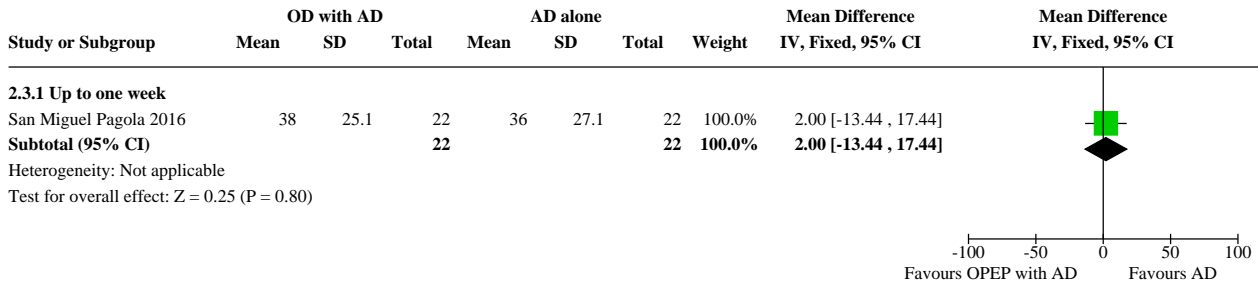
Analysis 2.2. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 2: FEV₁ change from baseline [% predicted]



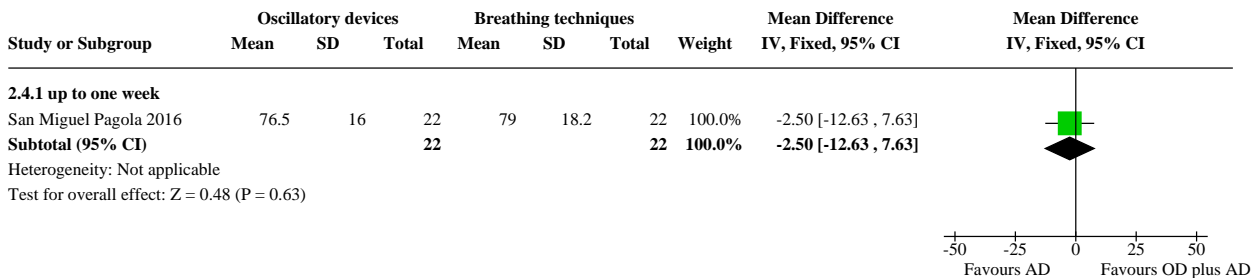
Footnotes

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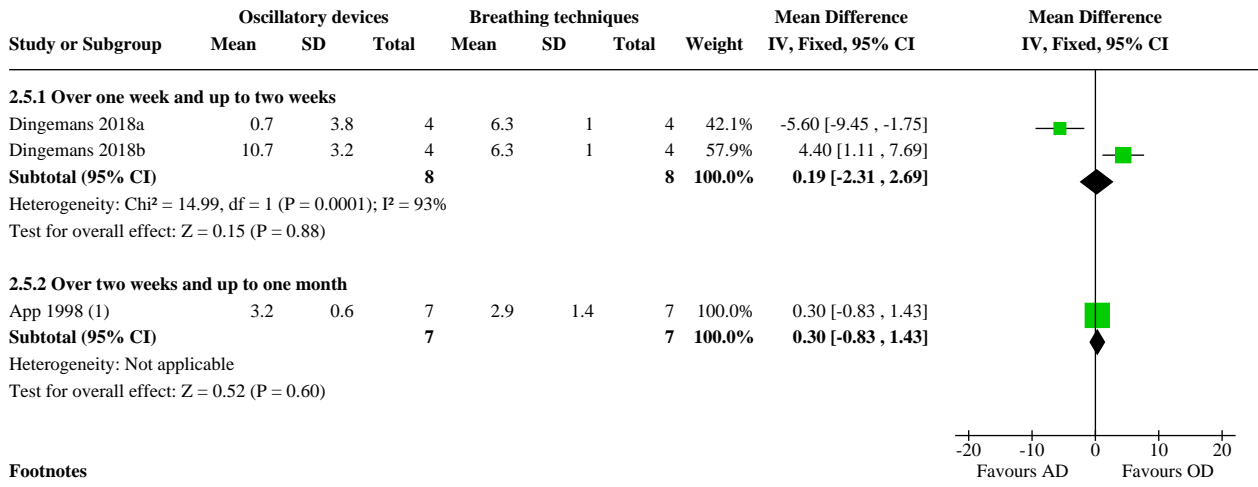
Analysis 2.3. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 3: FEF₂₅₋₇₅ absolute post-treatment values [% predicted]



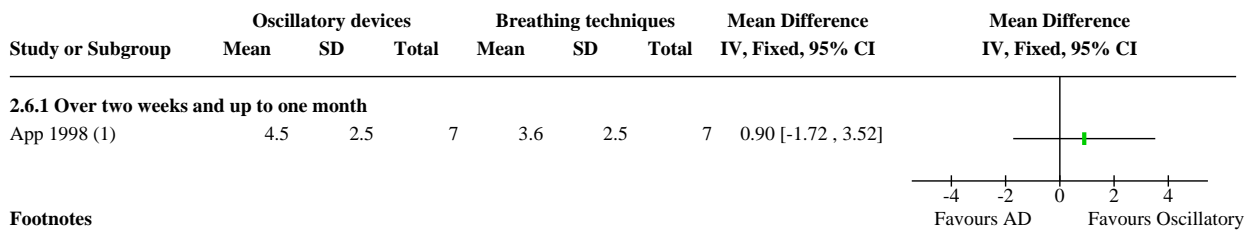
Analysis 2.4. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 4: FVC post-intervention [% predicted]



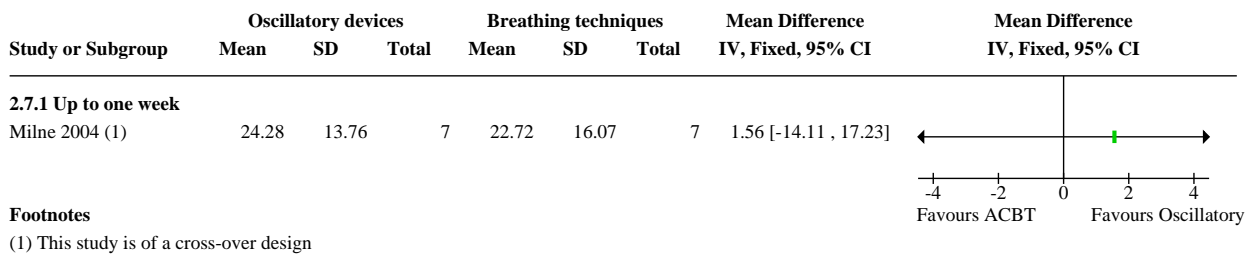
Analysis 2.5. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 5: FVC change from baseline [% predicted]



Analysis 2.6. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 6: Sputum volume [g]



Analysis 2.7. Comparison 2: Oscillating devices (OD) versus breathing techniques, Outcome 7: Sputum weight (wet) [g]



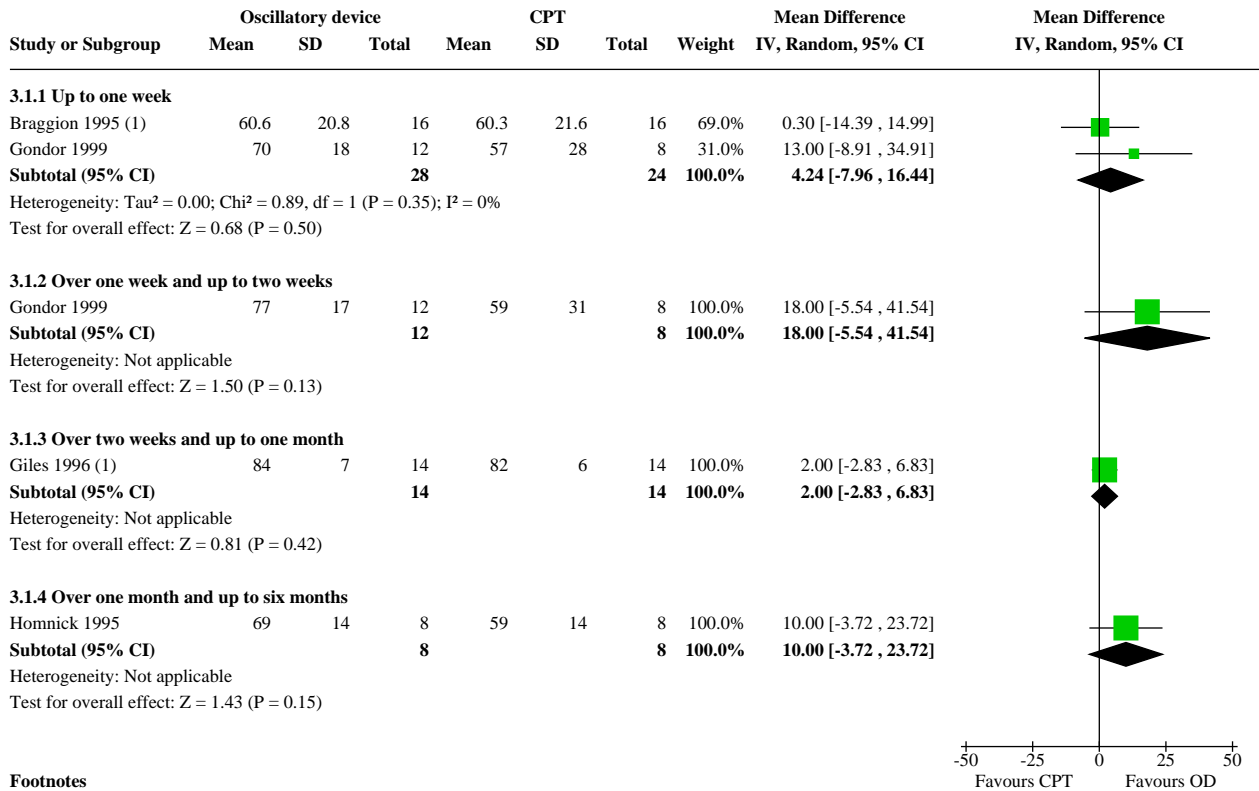
Comparison 3. Oscillating devices (OD) versus conventional physiotherapy (CPT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 FEV₁ post intervention [% predicted]	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 Up to one week	2	52	Mean Difference (IV, Random, 95% CI)	4.24 [-7.96, 16.44]
3.1.2 Over one week and up to two weeks	1	20	Mean Difference (IV, Random, 95% CI)	18.00 [-5.54, 41.54]
3.1.3 Over two weeks and up to one month	1	28	Mean Difference (IV, Random, 95% CI)	2.00 [-2.83, 6.83]
3.1.4 Over one month and up to six months	1	16	Mean Difference (IV, Random, 95% CI)	10.00 [-3.72, 23.72]
3.2 FEV₁ change from baseline [% predicted]	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2.1 Up to one week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2.2 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2.3 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3 FEF₂₅₋₇₅ post intervention [% predicted]	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3.1 Up to one week	2	52	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.35, 0.83]
3.3.2 Over one week and up to two weeks	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.65 [-0.27, 1.58]
3.3.3 Over one month and up to six months	1	16	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.70, 1.28]
3.4 FEF₂₅₋₇₅ change from baseline [% predicted]	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.1 Up to one week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.2 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.3 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 FVC [% predicted]	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

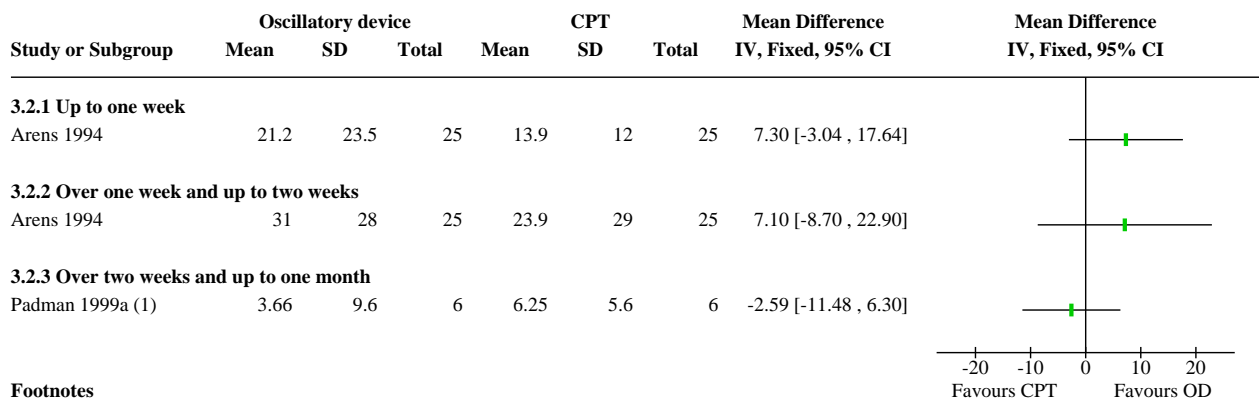
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.1 Up to one week	2	52	Mean Difference (IV, Fixed, 95% CI)	2.60 [-8.63, 13.84]
3.5.2 Over one week and up to two weeks	1	20	Mean Difference (IV, Fixed, 95% CI)	13.00 [-10.54, 36.54]
3.5.3 Over two weeks and up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	3.00 [-0.78, 6.78]
3.5.4 Over one month and up to six months	1	16	Mean Difference (IV, Fixed, 95% CI)	11.00 [-2.86, 24.86]
3.6 Residual volume [% change from baseline]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6.1 Up to one week	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6.2 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7 Sputum weight (dry) [g]	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7.1 Up to one week	5	228	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.13, 0.06]
3.7.2 Over one week and up to two weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.16, 0.42]
3.7.3 Over two weeks and up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.35, 0.55]
3.8 Sputum weight (wet) [g]	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.8.1 Up to one week	5	228	Mean Difference (IV, Fixed, 95% CI)	1.11 [-0.60, 2.83]
3.8.2 Over one week and up to two weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	4.04 [-2.69, 10.77]
3.8.3 Over two weeks and up to one month	1	28	Mean Difference (IV, Fixed, 95% CI)	1.00 [-2.56, 4.56]
3.9 Six minute walking distance [metres]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9.1 Over one week and up to two weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10 Oxygen saturation (SaO₂) [% change from baseline]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.10.1 Up to one week	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.51, 1.11]
3.10.2 Over one week and up to two weeks	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.51, 1.31]
3.11 Days of hospitalization	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.11.1 Over one week and up to two weeks	2	70	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.99, 1.97]
3.11.2 Over one month and up to six months	1	16	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-6.95, 3.55]
3.12 Patient satisfaction / overall preference (short term)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.12.1 up to one week	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13 Patient satisfaction / overall preference (long term)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.1 Effectiveness	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.2 Convenience	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.3 Discomfort	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.4 Overall satisfaction	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.13.5 Mean score	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

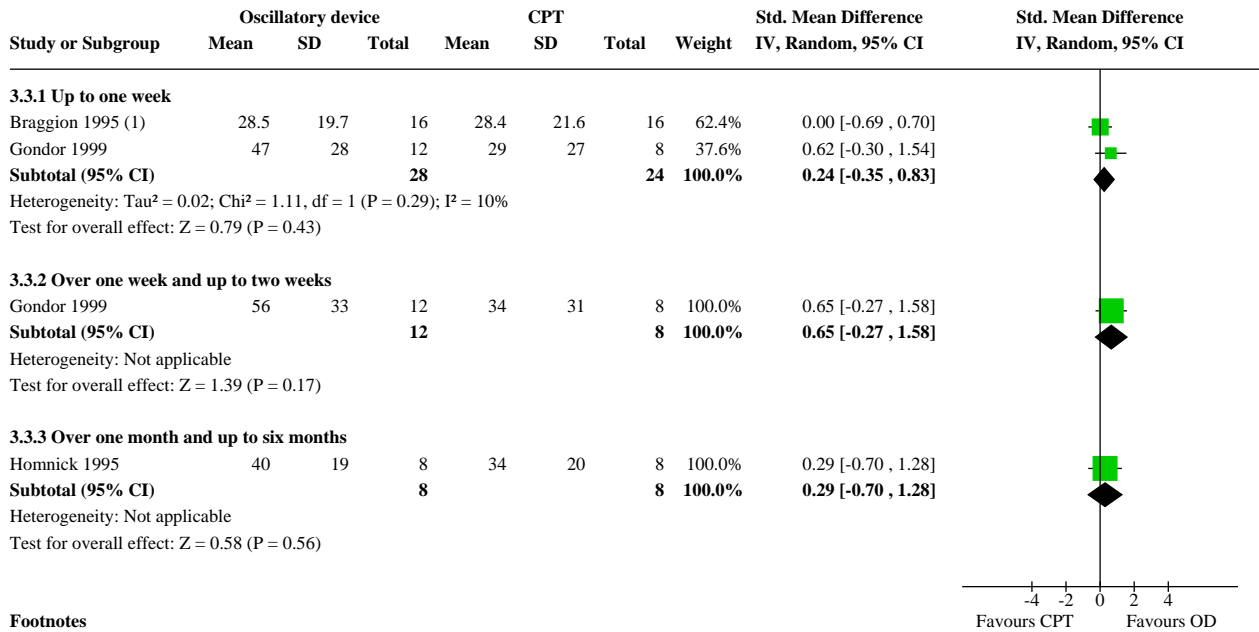
Analysis 3.1. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 1: FEV₁ post intervention [% predicted]



Analysis 3.2. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 2: FEV₁ change from baseline [% predicted]



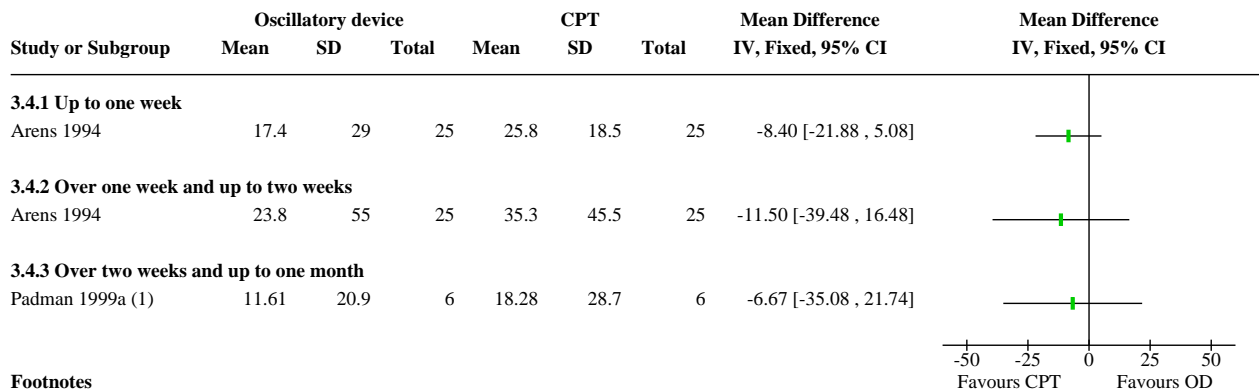
Analysis 3.3. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 3: FEF₂₅₋₇₅ post intervention [% predicted]



Footnotes

(1) This study is of a cross-over design

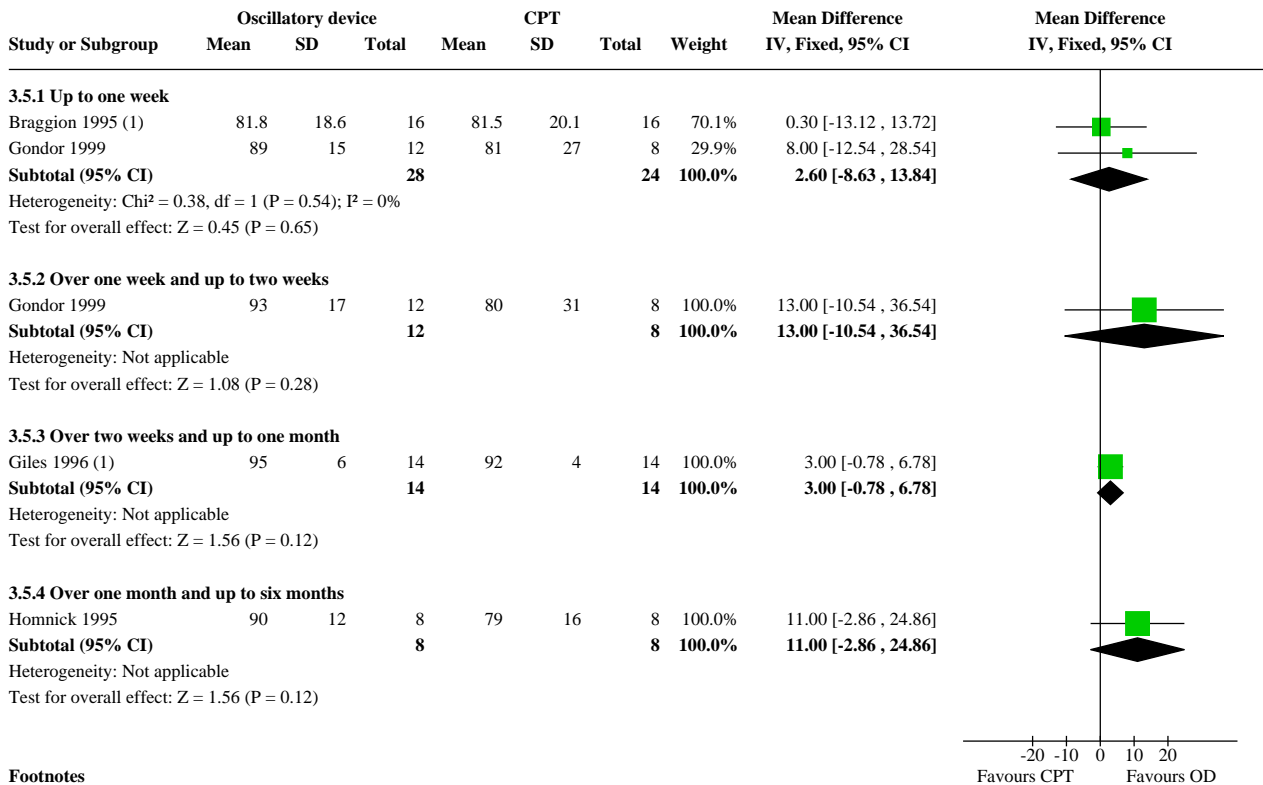
Analysis 3.4. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 4: FEF₂₅₋₇₅ change from baseline [% predicted]



Footnotes

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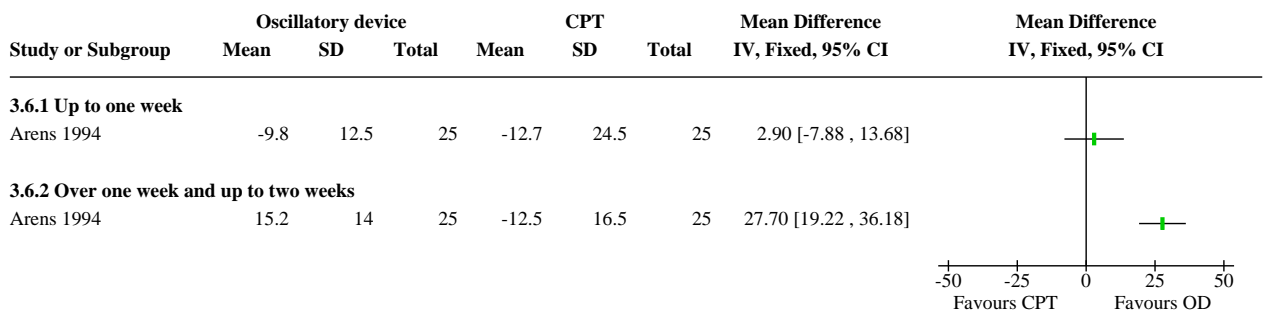
Analysis 3.5. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 5: FVC [% predicted]



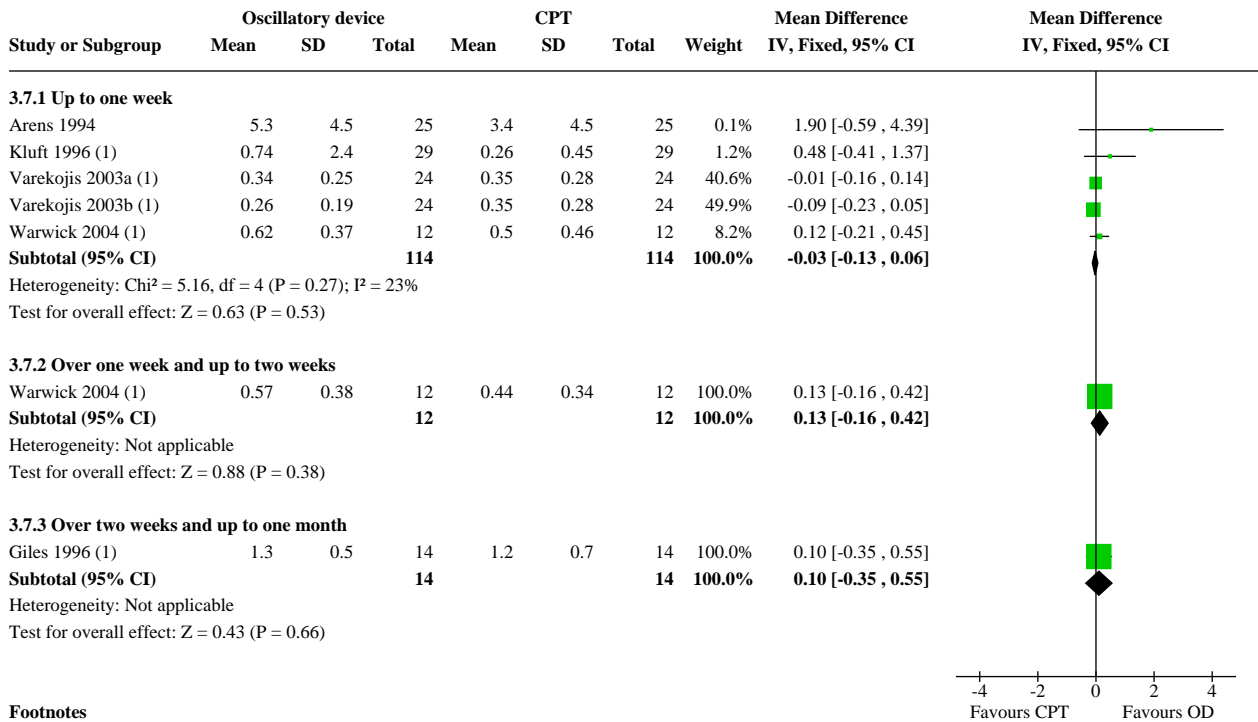
Footnotes

(1) This study is of a cross-over design

Analysis 3.6. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 6: Residual volume [% change from baseline]



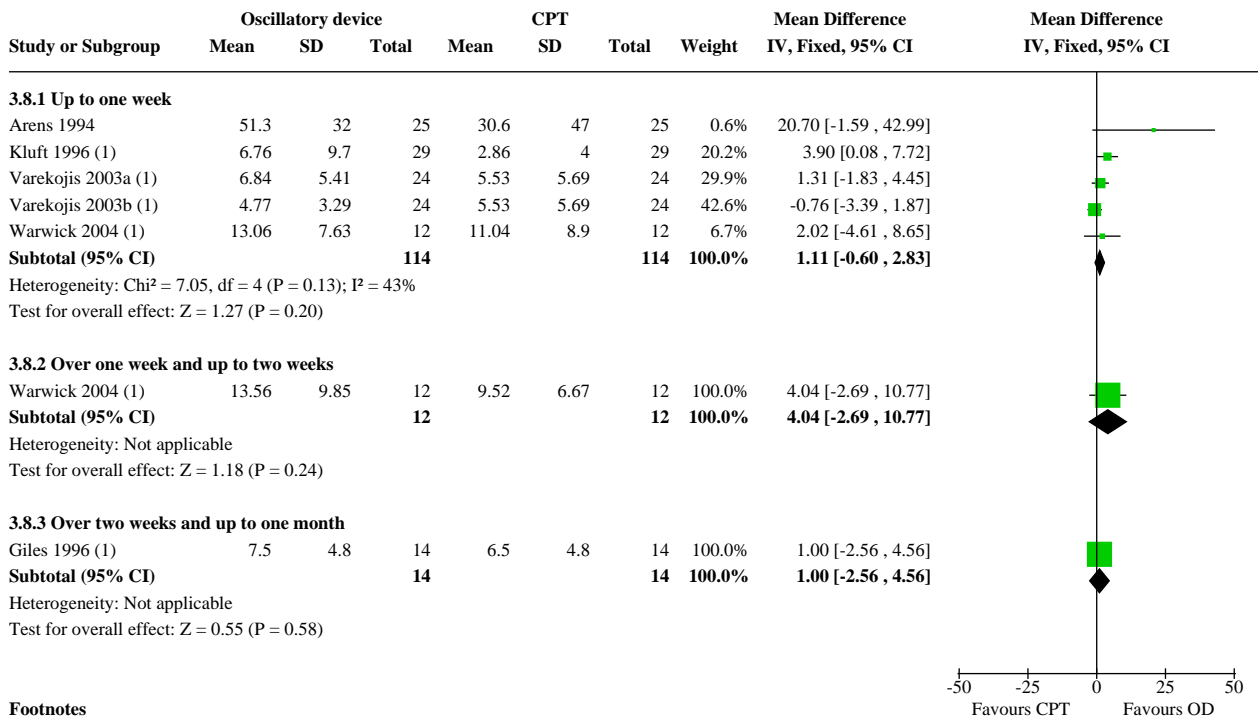
Analysis 3.7. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 7: Sputum weight (dry) [g]



Footnotes

(1) This study is of a cross-over design

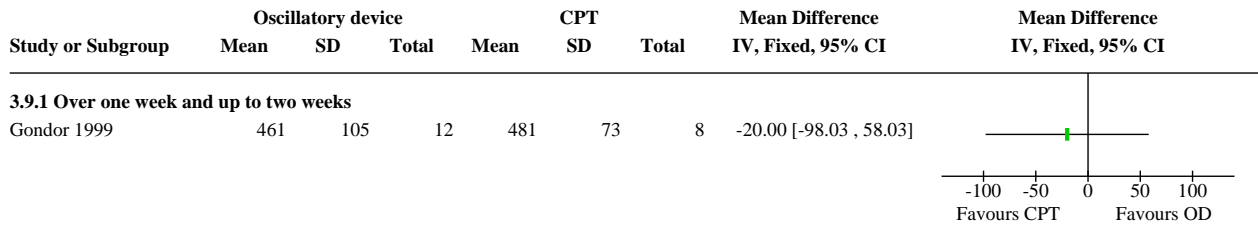
Analysis 3.8. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 8: Sputum weight (wet) [g]



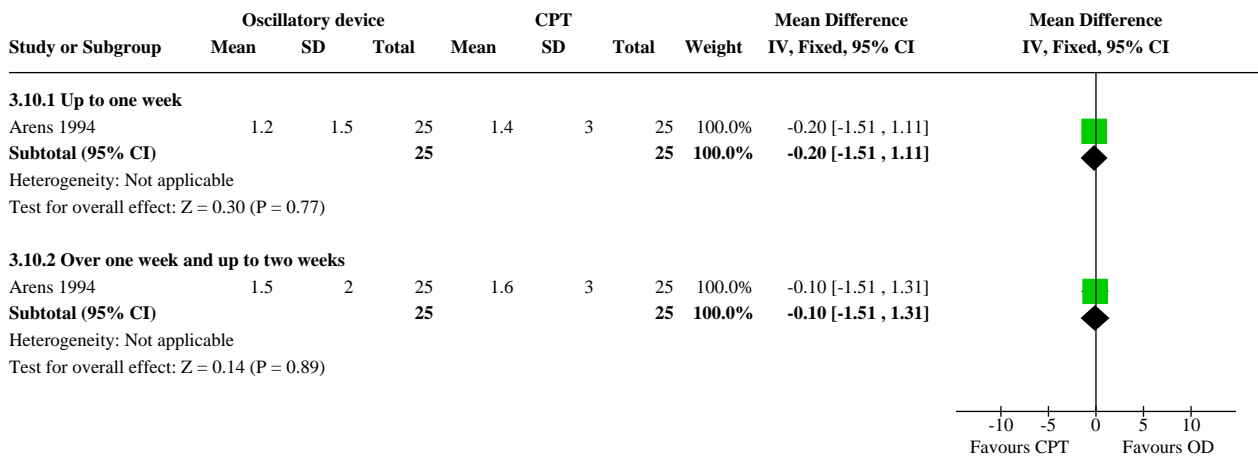
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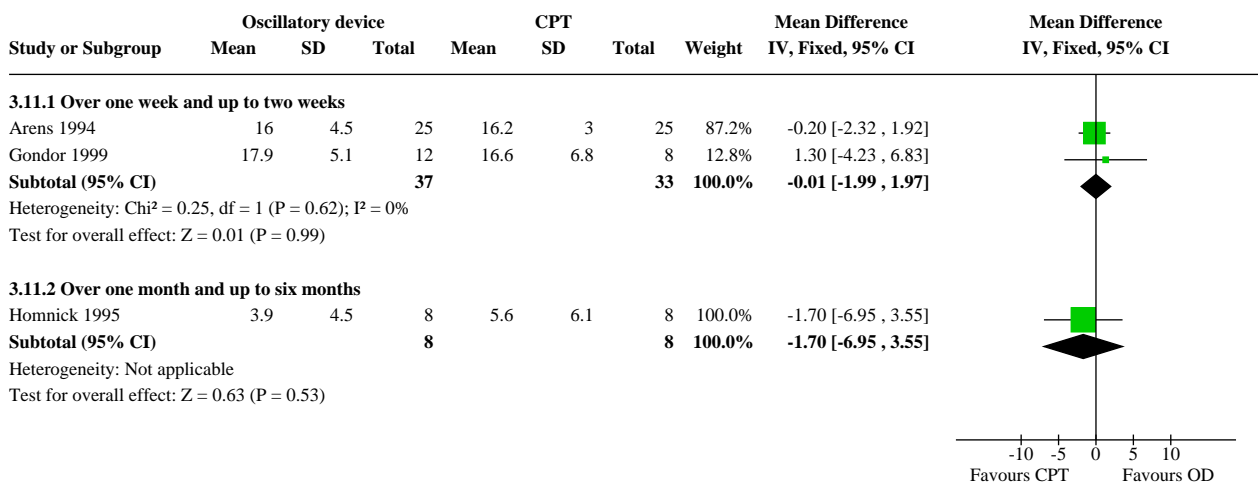
Analysis 3.9. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 9: Six minute walking distance [metres]



Analysis 3.10. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 10: Oxygen saturation (SaO₂) [% change from baseline]



Analysis 3.11. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 11: Days of hospitalization



Analysis 3.12. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 12: Patient satisfaction / overall preference (short term)

Study or Subgroup	Oscillatory device			CPT			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
3.12.1 up to one week								
Varekojjs 2003a (1)	1.96	0.77	24	2	0.74	24	-0.04 [-0.47 , 0.39]	
Varekojjs 2003b (1)	2.04	0.98	24	2	0.74	24	0.04 [-0.45 , 0.53]	

Footnotes

(1) This study is of a cross-over design

Analysis 3.13. Comparison 3: Oscillating devices (OD) versus conventional physiotherapy (CPT), Outcome 13: Patient satisfaction / overall preference (long term)

Study or Subgroup	Oscillatory device			CPT			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
3.13.1 Effectiveness								
Modi 2010a	17.9	4.73	35	16.3	0.38	23	1.60 [0.03 , 3.17]	
Modi 2010b	19.4	2.88	52	16.3	0.38	23	3.10 [2.30 , 3.90]	
3.13.2 Convenience								
Modi 2010a	22.5	2.37	35	12.1	0.43	23	10.40 [9.60 , 11.20]	
Modi 2010b	17.7	4.33	52	12.1	0.43	23	5.60 [4.41 , 6.79]	
3.13.3 Discomfort								
Modi 2010a	22.3	1.77	35	18.7	0.29	23	3.60 [3.00 , 4.20]	
Modi 2010b	21.2	3.61	52	18.7	0.29	23	2.50 [1.51 , 3.49]	
3.13.4 Overall satisfaction								
Modi 2010a	7.9	2.37	35	5.1	0.14	23	2.80 [2.01 , 3.59]	
Modi 2010b	8.5	2.16	52	5.1	0.14	23	3.40 [2.81 , 3.99]	
3.13.5 Mean score								
Modi 2010a	4.2	0.47	35	3.1	0.05	23	1.10 [0.94 , 1.26]	
Modi 2010b	3.9	0.65	52	3.1	0.05	23	0.80 [0.62 , 0.98]	

Comparison 4. Flutter versus HFCWO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 FEV ₁ [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1.1 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2 FEF ₂₅₋₇₅ [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.1 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3 FVC [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3.1 Over two weeks and up to one month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4 Treatment satisfaction (long term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.1 Effectiveness	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.2 Convenience	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.3 Discomfort	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.4 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.5 Mean score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Flutter versus HFCWO, Outcome 1: FEV₁ [% predicted]

Study or Subgroup	Favours Flutter			Favours Vest			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.1.1 Over two weeks and up to one month								
Oermann 2001 (1)	54.9	3	24	56.5	3.5	24	-1.60 [-3.44, 0.24]	

Footnotes

(1) This study is of a cross-over design

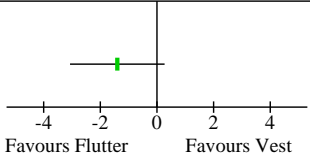
Analysis 4.2. Comparison 4: Flutter versus HFCWO, Outcome 2: FEF₂₅₋₇₅ [% predicted]

Study or Subgroup	Flutter			Vest			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.2.1 Over two weeks and up to one month								
Oermann 2001 (1)	31.5	4.3	24	33.3	4.6	24	-1.80 [-4.32, 0.72]	

Footnotes

(1) This study is of a cross-over design

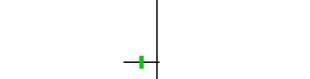



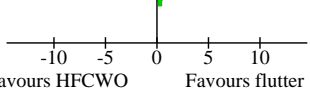
Analysis 4.3. Comparison 4: Flutter versus HFCWO, Outcome 3: FVC [% predicted]

Study or Subgroup	Flutter			Vest			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.3.1 Over two weeks and up to one month								
Oermann 2001 (1)	72.6	2.9	24	74	3	24	-1.40 [-3.07, 0.27]	

Footnotes

(1) This study is of a cross-over design

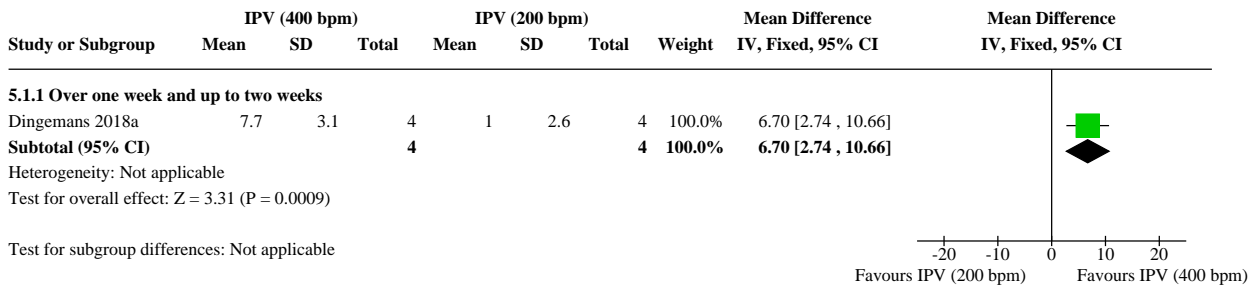
Analysis 4.4. Comparison 4: Flutter versus HFCWO, Outcome 4: Treatment satisfaction (long term)

Study or Subgroup	Flutter			HFCWO			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.4.1 Effectiveness								
Modi 2010a	17.9	4.73	35	19.4	2.88	52	-1.50 [-3.25, 0.25]	
4.4.2 Convenience								
Modi 2010a	22.5	2.37	35	17.7	4.33	52	4.80 [3.39, 6.21]	
4.4.3 Discomfort								
Modi 2010a	22.3	1.77	35	21.2	3.61	52	1.10 [-0.04, 2.24]	
4.4.4 Overall satisfaction								
Modi 2010a	7.9	2.37	35	8.5	2.16	52	-0.60 [-1.58, 0.38]	
4.4.5 Mean score								
Modi 2010a	4.2	0.47	35	3.9	0.65	52	0.30 [0.06, 0.54]	

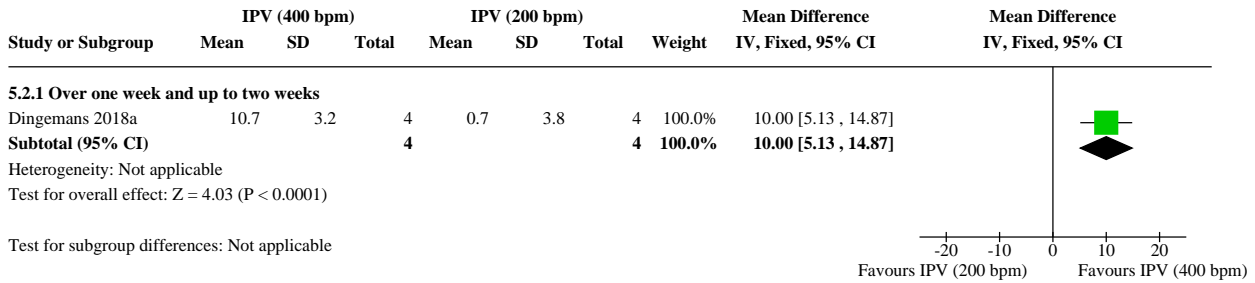
Comparison 5. IPV (400 bpm) versus IPV (200 bpm)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 FEV₁ change from baseline [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1.1 Over one week and up to two weeks	1	8	Mean Difference (IV, Fixed, 95% CI)	6.70 [2.74, 10.66]
5.2 FVC change from baseline [% predicted]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.2.1 Over one week and up to two weeks	1	8	Mean Difference (IV, Fixed, 95% CI)	10.00 [5.13, 14.87]

Analysis 5.1. Comparison 5: IPV (400 bpm) versus IPV (200 bpm), Outcome 1: FEV₁ change from baseline [% predicted]



Analysis 5.2. Comparison 5: IPV (400 bpm) versus IPV (200 bpm), Outcome 2: FVC change from baseline [% predicted]



WHAT'S NEW

Date	Event	Description
16 April 2020	New search has been performed	<p>A search of the Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Trials Register identified 28 references potentially eligible for inclusion in this review .</p> <p>Eight were additional references to already included studies (Braggion 1995; Davies 2012; Mcllwaine 2013; Modi 2010a; Osman 2010; Pryor 2010).</p> <p>Three were additional references to already excluded studies (Cantin 2005; O'Neil 2017; Webber 1984).</p> <p>Three were additional references to two studies previously identified as ongoing, but included in this update (San Miguel Pagola 2016; Wheatley 2018).</p> <p>Three references to two new studies have been included (Dingemans 2018a; Patel 2013).</p> <p>11 references to five newly excluded studies (Clinkscale 2012; Leemans 2018; NCT01923753; NCT03261219; Radtke 2018).</p> <p>We have added the Aerobika® (a hand-held oscillating positive expiratory pressure device) to the list of eligible interventions.</p>

Date	Event	Description
16 April 2020	New citation required but conclusions have not changed	Despite the inclusion of two new studies in this updated review, our conclusions have not changed.

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 1, 2009

Date	Event	Description
12 June 2017	Amended	Error in Abstract corrected - a sentence referring to a previously included study, which was excluded at the 2017 update (Orlik 2001), had been left in the Results section of the Abstract; this sentence has now been removed.
26 April 2017	New search has been performed	<p>A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 15 references to 10 studies for possible inclusion in this update of the review.</p> <p>A total of three new studies have been included at this update. Two were newly identified studies (one reference each) (Khan 2014; West 2010) and one further reference was an additional reference to a study previously listed as 'Awaiting classification' which is now also included (Davies 2012).</p> <p>One study was only available in abstract form (two references) and has been listed as 'Awaiting classification' until further details are available to allow a judgement on inclusion or exclusion (Herrero 2016a).</p> <p>10 references to six studies were excluded (Amelina 2014a; Dwyer 2017; Fainardi 2011; Grosse-Onnebrink 2017; Kempainen 2007; O'Neil 2017).</p> <p>Following communication with the authors of the previously included Orlik studies, we established that there were no random elements in the allocation procedure of these studies. These therefore do not meet the review's inclusion criteria and have been excluded at this 2017 update (Orlik 2000a; Orlik 2000b; Orlik 2001).</p>
26 April 2017	New citation required but conclusions have not changed	<p>Despite the inclusion of new studies, our conclusions remain the same.</p> <p>Jennifer Agnew has stepped down from the review team and a new author, Stephanie Innes, has joined.</p>
11 August 2014	Amended	An error in the text of the plain language summary has been corrected.
17 July 2014	New citation required but conclusions have not changed	Despite the inclusion of a new study with 92 participants, the conclusions of our review remain the same (McIlwaine 2013).
17 July 2014	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified 14 new references. A further study was identified through further hand searching (Borka 2012). Two of the new references were ad-

Date	Event	Description
		<p>ditional references to already included studies (Lyons 1992; Modi 2010a). One new study (five references) has been included (McIlwaine 2013). Five studies, with single references to each, were excluded (Borka 2012; Dosman 2003; Dunn 2013; Jarad 2010; Van Ginderdeuren 2008). Three new studies have been listed as 'Awaiting classification' (Davies 2012a; Patel 2013a; Wheatley 2018a).</p> <p>A reference previously listed under 'Studies awaiting classification' was an additional reference to an already included study (Modi 2010a).</p> <p>In the 'Types of interventions' we have included two new types of devices that have recently come onto the market, both of which have an oscillatory component to their function. The VibraLung (VL) is an acoustic percussor and incorporates positive expiratory pressure. The MetaNeb is a pneumatic compressor system delivering continuous high frequency oscillation and positive expiratory pressure.</p>
3 December 2010	New search has been performed	<p>A search of the Group's Cystic Fibrosis Trials Register identified three new references to two new studies (Grzincich 2008; Kraemer 1996). We included the Grzincich study as this compared HFCWO with PEP (Grzincich 2008). We excluded the two references to the Kraemer study as they did not compare oscillation with another form of physiotherapy treatment (Kraemer 1996).</p> <p>We identified the full paper to a previously identified abstract and this now supercedes all previous references and has been included in this review (Osman 2010). We also identified the full paper to another previously included study (Modi 2010a) and this is listed as 'Awaiting classification' until the next update when we will include any new data.</p> <p>Three studies which were listed as 'Awaiting classification' have now been translated and assessed for eligibility. These studies were included in this updated review (Orlik 2000c; Orlik 2000c; Orlik 2001a).</p>
10 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

LM conceived and drafted the protocol and the review. JA commented on the protocol and the review. Both authors independently selected studies for inclusion in the review and extracted data.

From the 2017 update, JA stepped down from the review team and SM took on the role of co-author.

LM acts as guarantor for this review.

DECLARATIONS OF INTEREST

Lisa Morrison declares that she has no interest in any of the papers or references within this document and has received no funding in whole or in part for any of this work.

Stephanie Milroy: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Update 2020

The Aerobika® Oscillating Positive Expiratory Pressure (OPEP) device has been added to the list of possible oscillatory devices in '[Types of interventions](#)', although there are no currently no relevant studies evaluating its use in CF when compared to other airway clearance systems.

Update 2017

We originally planned to group outcome data those measured at one, three, six, 12 months and annually thereafter. We subsequently considered these time points and felt that to combine data measured at two weeks with data measured at four weeks was inappropriate. Therefore we have split the original proposed time point of one month and separately reported data at up to two weeks and at over two weeks and up to one month.

We have also amended the wording of our eligibility criteria so it is clear we are only considering randomised or quasi-randomised studies and not all controlled clinical studies (which may not have any random element involved in allocation to treatment groups).

Update 2014

Two further devices (MetaNeb® and VibraLung®) have been added to the list of possible oscillatory devices in '[Types of interventions](#)'. The data for these devices are only included in abstract form and we await full publication or additional information. The references to the studies of these devices are included under '[Characteristics of studies awaiting classification](#)'.

Update 2010

Since the publication of the protocol there has been a new version of the RevMan software released. The full review has been developed using the RevMan 5 programme and consequently there are several sections now included which were previously not available.

A further device (Quake®) has been added to the list of possible oscillatory devices in '[Types of interventions](#)'. There are currently no trial data published for this device.

Original review

A new team of review authors have worked on the review and taken on the protocol from the previous review team. They have added a further planned subgroup analysis which they felt was clinically relevant. Furthermore in a second post hoc change, they decided to perform a sensitivity analysis including and excluding the studies with a cross-over design to assess whether the study design had an effect on the results.

INDEX TERMS

Medical Subject Headings (MeSH)

Breathing Exercises; Chest Wall Oscillation [*instrumentation]; Cystic Fibrosis [*complications] [physiopathology]; Disease Progression; Forced Expiratory Flow Rates; Forced Expiratory Volume; Lung Diseases, Obstructive [etiology] [*therapy]; *Mucociliary Clearance; Mucus [*metabolism]; Patient Satisfaction; Randomized Controlled Trials as Topic; Sputum [metabolism]; Vibration [*therapeutic use]

MeSH check words

Adolescent; Adult; Child; Humans; Middle Aged