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Airway Clearance Devices for Cystic Fibrosis

An Evidence-Based Analysis

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Table of Contents

List of Tables & Figures

List of Abbreviations

ACD	Airway clearance device
ADP	Assistive Devices Program
AOD	Airway oscillating device
AUC	Area under the curve
CCPT	Conventional chest physiotherapy
CF	Cystic fibrosis
CI	Confidence interval(s)
CINAHL	Cumulative Index to Nursing & Allied Health Literature
FEF25-75%	Forced midexpiratory flow rate
FEV-1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFCC	High frequency chest compression
INAHTA	International Agency for Health Technology Assessment
IPV	Intrapulmonary percussive ventilation
MAS	Medical Advisory Secretariat
MP	Mechanical percussion
NR	Not reported
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
PEP	Positive expiratory pressure
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SROC	Summary receiver operating characteristic

Executive Summary

Objective

The purpose of this evidence-based analysis is to examine the safety and efficacy of airway clearance devices (ACDs) for cystic fibrosis and attempt to differentiate between devices, where possible, on grounds of clinical efficacy, quality of life, safety and/or patient preference.

Background

Cystic fibrosis (CF) is a common, inherited, life-limiting disease that affects multiple systems of the human body. Respiratory dysfunction is the primary complication and leading cause of death due to CF. CF causes abnormal mucus secretion in the airways, leading to airway obstruction and mucus plugging, which in turn can lead to bacterial infection and further mucous production. Over time, this almost cyclical process contributes to severe airway damage and loss of respiratory function. Removal of airway secretions, termed airway clearance, is thus an integral component of the management of CF.

A variety of methods are available for airway clearance, some requiring mechanical devices, others physical manipulation of the body (e.g. physiotherapy). Conventional chest physiotherapy (CCPT), through the assistance of a caregiver, is the current standard of care for achieving airway clearance, particularly in young patients up to the ages of six or seven. CF patients are, however, living much longer now than in decades past. The median age of survival in Canada has risen to 37.0 years for the period of 1998–2002 (5-year window), up from 22.8 years for the 5-year window ending in 1977. The prevalence has also risen accordingly, last recorded as 3,453 in Canada in 2002, up from 1,630 in 1977. With individuals living longer, there is a greater need for independent methods of airway clearance.

Airway Clearance Devices

There are at least three classes of airway clearance devices: positive expiratory pressure devices (PEP), airway oscillating devices (AOD; either handheld or stationary) and high frequency chest compression (HFCC)/mechanical percussion (MP) devices. Within these classes are numerous different brands of devices from various manufacturers, each with subtle iterations. At least 10 devices are licensed by Health Canada (ranging from Class 1 to Class 3 devices).

Evidence-Based Analysis of Effectiveness

Research Questions

1. Does long-term use of ACDs improve outcomes of interest in comparison to CCPT in patients with CF?
2. Does long-term use of one class of ACD improve outcomes of interest in comparison to another class of ACD in CF patients?

Literature Search

A comprehensive literature search was performed on March 7, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 1950 to March 7, 2009.

Inclusion Criteria

- All randomized controlled trials including those of parallel and crossover design,
- Systematic reviews and/or meta-analyses. Randomized controlled trials (RCTs), systematic reviews and meta-analyses

Exclusion Criteria

- Abstracts were generally excluded because their methods could not be examined; however, abstract data was included in several Cochrane meta-analyses presented in this paper;
- Studies of less than seven days duration (including single treatment studies);
- Studies that did not report primary outcomes;
- Studies in which less than 10 patients completed the study.

Outcomes of Interest

Primary outcomes under review were percent-predicted forced expiratory volume (FEV-1), forced vital capacity (FVC), and forced expiratory flow between 25%-75% (FEF25-75).Secondary outcomes included number of hospitalizations, adherence, patient preference, quality of life and adverse events. All outcomes were decided a priori.

Summary of Findings

Literature searching and back-searching identified 13 RCTs meeting the inclusion criteria, along with three Cochrane systematic reviews. The Cochrane reviews were identified in preliminary searching and used as the basis for formulating this review. Results were subgrouped by comparison and according to the available literature. For example, results from Cochrane meta-analyses included abstract data and therefore, additional meta-analyses were also performed on trials reported as full publications only (MAS generally excludes abstracted data when full publications are available as the methodological quality of trials reported in abstract cannot be properly assessed).

Executive Summary Table 1 summarizes the results across all comparisons and subgroupings for primary outcomes of pulmonary function. Only two comparisons yielded evidence of moderate or high quality according to GRADE criteria – the comparisons of CCPT vs. PEP and handheld AOD vs. PEP – but only the comparison of CCPT vs. PEP noted a significant difference between treatment groups. In comparison to CCPT, there was a significant difference in favour of PEP for % predicted FEV-1 and FVC according to one long-term, parallel RCT. This trial was accepted as the best available evidence for the comparison. The body of evidence for the remaining comparisons was low to very low, according to GRADE criteria, being downgraded most often because of poor methodological quality and low generalizability. Specifically, trials were likely not adequately powered (low sample sizes), did not conduct intention-to-treat analyses, were conducted primarily in children and young adolescents, and outdated (conducted more than 10 years ago).

Secondary outcomes were poorly or inconsistently reported, and were generally not of value to decision-making. Of note, there were a significantly higher number of hospitalizations among participants undergoing AOD therapy in comparison to PEP therapy.

ES Table 1: Summarization of results for primary outcomes by comparison and subgroupings

Outcome or Subgroup	No. of Studies	Estimate of Effectiveness (95% CI)	P-value	Heterogeneity (I^2)	GRADE
CCPT vs. PEP					
Cochrane					
FEV-1	6	0.08 (-1.45 to 1.62)	0.91	46%	
FVC	6	0.38 (-1.56 to 2.23)	0.70	63%	N/A
$FEF_{25-75\%}$	4	-0.44 (-3.38 to 2.50)	0.77	36%	
Full publications only					
FEV-1	3	-0.50 (-3.93 to 2.92)	0.77	77%	
FVC	3	-0.86 (-4.66 to 2.95)	0.66	74%	
$FEF_{25-75\%}$	2	-0.12 (-6.22 to 5.98)	0.97	0%	N/A
Long-term, parallel RCTs only					
FEV-1	1	**-8.25 (-15.77 to -0.75)**	**0.03**	N/A	
FVC	1	**-8.74 (-16.03 to -1.45)**	**0.02**	N/A	1 Trial
$FEF_{25-75\%}$	1	-3.56 (-13.30 to 6.18)	0.47	N/A	MODERATE
CCPT vs. HFCC/MP					
Cochrane					
FEV-1	3	-1.76 (-4.67 to 1.16)	0.24	0%	
FVC	3	-1.42 (-5.17 to 2.33)	0.46	70%	
$FEF_{25-75\%}$	2	0.49 (-2.54 to 3.52)	0.75	0%	N/A
Full publications only					
FEV-1	3	-2.10 (-5.49 to 1.29)	0.23	0%	
FVC	3	-3.86 (-8.05 to 0.33)	0.07	0%	3 Trials
$FEF_{25-75\%}$	2	0.49 (-2.54 to 3.52)	0.75	0%	LOW
CCPT vs. AOD					
2 of 3 RCTs/Cochrane					
FEV-1	2	0.80 (-5.79 to 7.39)	0.81	0%	
FVC	2	6.06 (-2.42 to 14.55)	0.16	12%	3 Trials
$FEF_{25-75\%}$	2	1.26 (-7.56 to 10.09)	0.78	0%	LOW
AOD vs. PEP					
Long-term, parallel RCTs only/Cochrane					
FEV-1	2	0.29 (-4.17 to 4.75)	0.90	73%	
FVC	2	-0.55 (-4.60 to 3.50)	0.79	77%	2 Trials
$FEF_{25-75\%}$	2	0.10 (-4.86 to 5.06)	0.97	0%	MODERATE
AOD vs. HFCC/MP					
Long-term, parallel RCTs only/Cochrane					
FEV-1	1	-1.6 (-3.44 to 0.24)	0.09	N/A	
FVC	1	-1.80 (-4.32 to 0.72)	0.08	N/A	1 Trial
$FEF_{25-75\%}$	1	-1.40 (-3.07 to 0.27)	0.16	N/A	VERY LOW

Bolding indicates significant difference

Positive summary statistics favour the former intervention

Abbreviations: AOD, airway oscillating device; CCPT, conventional chest physiotherapy; CI, confidence interval; HFCC, high frequency chest compression; MP, mechanical percussion; N/A: not applicable; PEP, positive expiratory pressure

Economic Analysis

Devices ranged in cost from around $60 for PEP and handheld AODs to upwards of $18,000 for a HFCC vest device. Although the majority of device costs are paid out-of-pocket by the patients themselves, their parents, or covered by third-party medical insurance, Ontario did provide funding assistance through the Assistive Devices Program (ADP) for postural drainage boards and MP devices. These technologies, however, are either obsolete or their clinical efficacy is not supported by evidence. ADP provided roughly $16,000 in funding for the 2008/09 fiscal year. Using device costs and prevalent and incident cases of CF in Ontario, budget impact projections were generated for Ontario. Prevalence of CF in Ontario for patients from ages 6 to 71 was cited as 1,047 cases in 2002 while incidence was estimated at 46 new cases of CF diagnosed per year in 2002. Budget impact projections indicated that PEP and handheld AODs were highly economically feasible costing around $90,000 for the entire prevalent population and less than $3,000 per year to cover new incident cases. HFCC vest devices were by far the most expensive, costing in excess of $19 million to cover the prevalent population alone.

Conclusions

There is currently a lack of sufficiently powered, long-term, parallel randomized controlled trials investigating the use of ACDs in comparison to other airway clearance techniques. While much of the current evidence suggests no significant difference between various ACDs and alternative therapies/technologies, at least according to outcomes of pulmonary function, there is a strong possibility that past trials were not sufficiently powered to identify a difference. Unfortunately, it is unlikely that there will be any future trials comparing ACDs to CCPT as withholding therapy using an ACD may be seen as unethical at present.

Conclusions of clinical effectiveness are as follows:

1. Moderate quality evidence suggests that PEP is at least as effective as or more effective than CCPT, according to primary outcomes of pulmonary function.
2. Moderate quality evidence suggests that there is no significant difference between PEP and handheld AODs, according to primary outcomes of pulmonary function; however, secondary outcomes may favour PEP.
3. Low quality evidence suggests that there is no significant difference between AODs or HFCC/MP and CCPT, according to both primary and secondary outcomes.
4. Very low quality evidence suggests that there is no significant difference between handheld AOD and CCPT, according to primary outcomes of pulmonary function.
5. Budget impact projections show PEP and handheld AODs to be highly economically feasible.

Background

Objective

The purpose of this evidence-based analysis is to examine the safety and efficacy of airway clearance devices (ACDs) for cystic fibrosis and to attempt to differentiate between devices, where possible, on the grounds of clinical efficacy, quality of life, safety, and/or patient preference.

Clinical Need and Target Population

Cystic fibrosis (CF) is a common, inherited, life-limiting disease that affects multiple systems of the human body. Respiratory dysfunction is the primary complication and leading cause of death due to CF. (1) CF causes abnormal mucus secretion in the airways, leading to airway obstruction and mucus plugging, (2) which in turn predisposes the lungs to persistent infection by *Staphylococcus aureus* and *Haemophilus influenzae* in early life, and by *Pseudomonas aeruginosa* in later years. (3) Infection results in inflammation, which furthers mucus production in an almost cyclical process that can contribute to severe airway damage and loss of respiratory function over time. (4;5) Removal of airway secretions, termed airway clearance, is thus an integral component of the management of CF.

Individuals with CF are born with a mutation in the CF transmembrane conductance regulator (CFTR) gene, predisposing them to disease. (6;7) Although CFTR mutations are present at birth, delayed diagnosis or late onset of symptoms results in a number of patients being diagnosed well after birth. (8) Data from the Canadian Cystic Fibrosis Foundation's (CCFF) Patient Data Registry Report for 2002 (9) noted that 40% of patients alive in 2000 were diagnosed after the first year of age, 9.6% after age 10, and 2% after age 30. Of 3,453 people living with CF in Canada in 2002 (total prevalence), 47.6% of were older than 18 years and 54% were male. In the same year, 51 patients died of CF. For the period of 1998–2002 (5-year window), the median age of survival was 37.0 years, up from 22.8 years for the 5-year window ending in 1977.

The overall prevalence of CF in Canada has nearly doubled from 1977 to 2002 (from 1,630 to 3,453); however, this increase is almost entirely attributable to improved survival rates in older age groups as the incidence of CF has been steadily dropping over the past 3 decades. (9) The most recent epidemiologic data shows that the rate of individuals born with CF in Canada was 2.8 per 10,000 births in 2002, down from 3.7 per 10,000 births observed from 1971 to 1987. (8) This decrease is thought to be largely due to the discovery of the CFTR mutation in 1989 and genetic testing. Further reductions in overall incidence are envisioned with the implementation of carrier screening in the general population.

A variety of methods are available for airway clearance, some requiring mechanical devices, others requiring physical manipulation of the body (e.g. physiotherapy). The goal of all airway clearance therapies is to augment normal mucociliary clearance of the lungs and facilitate expectoration of sputum, in hopes of optimizing respiratory status and reducing the progress of respiratory disease and infection.

The face of CF in Canada is clearly changing as children born with CF are now living well into adulthood. On account of the diversity of this patient population, all ages and genders were examined in this review.

Airway Clearance Techniques

A variety of mechanical devices, physical, and breathing control therapies are available for achieving airway clearance in patients with CF. Because this review was designed as an update and summary of previous Cochrane systematic reviews (see Methods below), (10-12) all definitions of technologies and outcomes are consistent with these prior reports.

Conventional chest physiotherapy

Conventional chest physiotherapy (CCPT) techniques, considered by many as the current standard, involve the assistance of another person such as a physiotherapist, parent or caregiver. The techniques include postural drainage, percussion (or clapping), vibration, huffing and coughing. For this review, CCPT techniques did not include the use of exercise, forced expiration technique (FET), or other active cycle breathing techniques (ACBT) such as thoracic expansion.

Positive expiratory pressure (PEP) therapy

PEP is a technique in which individuals breathe through a face mask or mouthpiece attached to a mechanical resistor, causing pressure to build-up in the lungs to effectively open the airways for mucus expiration. It is defined as breathing with a PEP of 10–25 cm H_2O (with or without additional techniques). Hi-PEP, a modification of the above technique, which includes a full forced expiration against fixed mechanical resistance, generates PEP ranging from 40–100 cm H_2O. The PARI PEP, TheraPEP, and Resistex are examples of such devices.

Airway oscillating devices (AOD)

AODs are a class of devices that produce an oscillatory or vibratory pressure effect within the airways. Two subclasses of devices achieve this effect: a) handheld devices and b) stationary intrapulmonary percussion (IPV) devices. Handheld devices include the Flutter, RC-Cornet, Acapella and Quake. Stationary IPV devices provide high-frequency mini-bursts of air or oxygen into the lungs, while simultaneously delivering therapeutic aerosols. Examples of IPV devices include the IPV-1, TXP, Impulsator, Phasitron, Universal Ventilator, and Percussionator.

MP devices and external HFCC, HFCWC, and HFCWO devices

Mechanical percussive (MP) devices provide localized chest wall percussion to loosen mucous and include the Fluid Flo and the Frequencer (which combines mechanical and acoustical percussion). High frequency chest compression (HFCC) devices provide external chest wall compression (HFCWC) or oscillation (HFCWO) and include The Vest Airway Clearance System, the SmartVest, the Medpulse Respiratory Vest System and the ThAIRapy Vest.

Status in Ontario

Currently, 11 ACDs are licensed by Health Canada:

- The Vest by Hill-Rom Services, Inc.;
- the SmartVest by Electromed, Inc.;
- the PARI PEP by PARI Respiratory Equipment;
- the Frequencer by Dymedso, Inc.;
- the TheraPEP by Smiths Medical;
- the Flutter by Axcan Scandipharm, Inc. (Class 1 Medical Device Establishment License)
- the Acapella by Smiths Medical;

- the Impulsator by Percussionare;
- the Intrapulmonary Percussionator Ventilator (IPV-1) by Percussionare;
- the Resistex by Mercury Medical;
- and the Quake by Thayer Medical.

These devices range in classification number from device class 1 to class 3.

These devices are not currently funded by the Ontario government or any of its subsidiary agencies. The majority of expenses are covered out-of-pocket by patients or their parents. While private insurance plans may cover some of the less-expensive devices (e.g., PEP mask, the Flutter or the Acapella), other more expensive devices like the vests are rarely covered. Children are often covered under their parents' private insurance plans. Detailed economic discussions are provided further below.

Diffusion Pressure

As patients age, their ability to receive CCPT becomes increasingly difficult as this form of therapy requires the aid of a caregiver (usually a parent). Caregivers will often require extreme time commitment as CCPT therapy sessions can last upwards of 30 minutes per day and are usually undertaken two to three times per day or more. Furthermore, because the median age of survival is rising rapidly, CF patients are surviving to ages of independence at much greater rates than in decades past. The use of ACDs has thus risen greatly in the past few decades.

Data from the Cystic Fibrosis Foundation in the United States indicates that 59.4% of patients with cystic fibrosis now use HFCWO devices as their main method of airway clearance. Meanwhile, only 13.2% use CCPT and 12.3% use PEP (exact ages of reference population were not reported). (13)

In Canada, exact usage statistics differ. Expert consultants have indicated that at anywhere from one-third to two-thirds of patients ages six to seven years or older use PEP as their main method of airway clearance. AOD devices such as the Flutter and Acapella are by far the next most popular device in use in Canada. Unlike in the United States, HFCC devices such as The Vest are used much less frequently in Canada due to the exorbitant costs of these devices. Only a very small minority of patients will not use any ACD throughout their lifetime. In fact, ACDs have become an integral component of CF physiotherapy programs; so much so, that forcing patients to not use an ACD may be seen as unethical, thus affecting the possibility of there being future long-term, RCTs that include arms without some form of ACD.

Evidence-Based Analysis

Research Questions

1. Does long-term use of ACDs improve outcomes of interest in comparison to CCPT in patients with CF?
2. Does long-term use of one class of ACD improve outcomes of interest in comparison to another class of ACD in patients with CF?

Methods

Search Strategy

A comprehensive literature search was performed on March 7, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 1950 to March 7, 2009. The search strategy is detailed in Appendix 1. Abstracts were reviewed by a single reviewer and, and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist or more if necessary until consensus was established.

Inclusion Criteria

- All randomized controlled trials including those of parallel and crossover design,
- Systematic reviews and/or meta-analyses.

Exclusion Criteria

- Abstracts were generally excluded because their methods could not be examined; however, abstract data was included in several Cochrane meta-analyses that are presented in this paper;
- Studies of less than seven days duration (including single treatment studies);
- Studies which did not report primary outcomes;
- Studies in which less than 10 patients completed the study.

Outcomes of Interest

Primary Outcomes

Primary outcomes under review were forced expiratory volume (FEV-1), forced vital capacity (FVC), and forced expiratory flow between 25%-75% (FEF_{25-75}). These pulmonary function outcomes were consistently evaluated as primary outcomes of interest across the majority of trials under review. Values were obtained as percentage predicted (corrected for age and height) due to the potential for variation among participant age groups (trials were mostly conducted in young, growing children).

Secondary Outcomes

Secondary outcomes included number of hospitalizations, adherence, patient preference, quality of life and adverse events. All outcomes were decided *a priori*. Expectorated secretions such as mucus, sputum, phlegm, dry or wet weight, or volume were not assessed as these outcomes are usually only measured in

single treatment studies or trials of short duration (less than one week). Additional literature also fails to prove a strong association between expectorated sputum volume and pulmonary function or clinical status. (14-19)

Statistical Analysis

Data were summarized by meta-analysis when possible. All meta-analyses were calculated with data provided from three Cochrane reviews (11;12;20) using RevMan 5.0 software provided by the Cochrane Collaboration. Detailed methods used in data extraction and meta-analysis are reported in the review by Main (12). Briefly, all meta-analyses used a fixed-effects generic inverse variance model using mean differences for parallel trials or paired mean differences for crossover trials and their associated standard errors. For the comparison of AOD vs. PEP, however, data were summarized using a fixed-effects inverse variance model using mean differences and their associated standard deviations and sample sizes (due to reporting differences between Cochrane reviews). For all comparisons, mean differences for continuous outcomes were recorded either as change from baseline or post-treatment/post-intervention, depending on the source of the data.

Quality of Evidence

The quality of the trials was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (21) presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

Literature searching and back-searching identified 410 citations published between January 1, 1950 and March 17, 2009. Of these, 410 citations, 77 were retrieved as full texts. Of these full texts, 13 RCTs (14;22-33) met the inclusion criteria along with the three aforementioned Cochrane systematic reviews. (11;12;20) Twenty-four trials were excluded on the basis of short duration (15;17;34-55), an additional 10 trials were excluded as they were published in abstract form only (56-65), and one trial was excluded due to low sample size (66). The remaining trials were excluded on the basis of inappropriate interventions. One systematic review was excluded because the majority of trials it included would not have met the inclusion criteria of this review. (19) The level of evidence of the 16 citations included in this review is summarized in Table 1.

Trial design and population characteristics, results, and GRADE assessments are summarized below, according to outcome and intervention comparison. Patient and study design characteristics of all trials are further summarized in Appendix 2. Meta-analyses for all outcomes and comparisons are summarized in Appendix 3 and individual forest plots are provided in Appendix 4. Individual GRADE tables are provided in Appendix 5.

Table 1: Level of evidence of included studies

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	3
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT	2	13
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	
Retrospective review, modelling	4d	
Case series presented at international conference	4(g)	
	Total	16

* RCT refers to randomized controlled trial.
† g indicates grey literature.

Pulmonary Function

CCPT vs. PEP

Four RCTs examining CCPT vs. PEP met the inclusion criteria for this review, totalling 86 participants analyzed with a mean age of 11.94 years of age and ranging from 6–21 years. (22-25). Three of these four RCTs (23-25) were randomized cross-over trials that compared one month of PEP treatment with one month of CCPT, with no washout or lead-in period. The remaining trial by McIlwaine (22) was a matched-pair, parallel RCT in which patients underwent PEP or CCPT treatment for 1 year.

Three of the four RCTs (22;24;25) were included in a fixed-effects meta-analysis by Cochrane (12) along with three additional RCTs (56-58) reported only in abstract form (totalling 164 participants). No overall differences between CCPT compared to PEP were demonstrated for % predicted FEV-1, FVC or FEF_{25-75} (Appendix 4, Figure 1). Removing the abstracts from meta-analysis had little effect with no significant differences observed across all three outcomes of pulmonary function (Appendix 4, Figure 2).

In contrast to the results of meta-analysis, significant differences between CCPT and PEP therapy (in favour of PEP) were observed in the trial by McIlwaine (22), specifically for the outcomes of FEV-1 and FVC (Appendix 4, Figure 3). This trial was the only long-term, parallel RCT of the four trials reaching full publication (the remaining were all of cross-over design). However, one of the trials reported in abstract, by Gaskin (58), a parallel RCT that compared 2 years of CCPT to 2 years of PEP (n=61), showed no significant difference.

The trial by Steen et al. (23) was the only trial of the four meeting the inclusion criteria that was not summarized in meta-analysis (sufficient data was unavailable). This trial similarly found no significant difference in % predicted FEV-1 or FVC between CCPT and PEP alone, PEP followed by PDP, and PEP followed by FET (*P*-value for comparisons not reported but less than 0.05 was considered significant; results averaged over 4-week study period; Appendix 4, Table 1). (23)

The quality of the combined evidence (comprised solely of the McIlwaine study) was moderate according to GRADE criteria (Appendix 5, Table 1). Because the trial by McIlwaine was a long-term, parallel RCT, all additional included trials were excluded from quality assessment on the basis of overwhelming methodological inferiority (short-term, cross-over, etc.). The body of evidence was downgraded on the basis of directness (the generalizability of the trial was in question due to the young age of participants and the old age of the trial itself).

CCPT vs. HFCC/MP

Two RCTs that examined CCPT vs. HFCC (14) or vs. MP (26) met the inclusion criteria for this review totalling 97 participants analyzed with mean age of 18.7 years in the HFCC/MP group and 17.4 years in the CCPT group (age ranges not available). Both studies were conducted during two-week hospitalizations for acute pulmonary exacerbation and both were parallel RCTs. It should be noted that Bauer combined the results of their parallel sample with a cross-over sample of patients who were hospitalized for a second time. (26)

Both RCTs were included in a fixed-effects meta-analysis by Cochrane (12), along with an additional trial (59) reported only in abstract (totalling 145 participants). No overall differences between CCPT and HFCC/MP were found in terms of % predicted FEV-1, FVC, or $FEF_{25-75\%}$ (Appendix 4, Figure 4). Removing the abstract from meta-analysis had little effect with no differences still being observed in % predicted FEV-1, FVC, or $FEF_{25-75\%}$ (Appendix 4, Figure 5).

The quality of the combined evidence (comprised of the two RCTs meeting the inclusion criteria) was low according to GRADE criteria (Appendix 5, Table 2). The body of evidence was downgraded on the basis of methodological quality (there was a general lack of allocation concealment and blinding, no ITT analyses were present in any studies, no sample size/power calculations were reported, and the trial by Bauer combined the results of a parallel sample with that of an overlapping cross-over sample) and directness (the generalizability of trials was largely in question due to the old age of trials and because both trials were conducted in patients during short-term hospitalizations and thus no long-term data was available).

CCPT vs. AOD

Three RCTs examining CCPT vs. AOD met the inclusion criteria for this review, totalling 69 participants analyzed with a mean age of 12.91 years and ranging from 5–44 years. (27-29) All three trials were of parallel design. Two of these three RCTs compared CCPT to handheld AODs in participants hospitalized over a 2-week period for acute pulmonary exacerbation (27;29), while the final trial compared CCPT to IPV over 6 months. (29) Two of the three RCTs (28;29) were combined in a Cochrane fixed effects meta-analysis (totalling 38 participants). (12) No overall differences were found between CCPT and AOD in terms of % predicted FEV-1, FVC and $FEF_{25-75\%}$.

The remaining trial by Gondor (27) was not included in meta-analysis (12) because sufficient data was not available. Gondor found no significant difference between CCPT and AOD at the end of a 2-week study period in terms of % predicted FEV-1, FVC or $FEF_{25-75\%}$ according to a repeated-measures analysis of variance (ANOVA; *P*-values not reported but <0.05 was considered significant; baseline values for pulmonary function were similar between groups). (27)

The quality of the combined evidence (comprised of the three RCTs that met the inclusion criteria) was very low according to GRADE criteria (Appendix 5, Table 3). The body of evidence was downgraded on the basis of methodological quality (due to a general lack of allocation concealment and blinding, no ITT analyses were present in any studies, trials were likely underpowered, and one of the trials by Homnick [30] analyzed multiple admissions in one study population) and directness (the generalizability of trials was largely in question due to the young age of participants, the old age of the trials themselves, and the lack of long-term data for trials using the most common AODs such as the Flutter or the Acapella).

AOD vs. PEP

Three RCTs that examined AOD vs. PEP met the inclusion criteria for this review, totalling 96 participants analyzed with a mean age of 18.8 years (age range not reported). (31-33) All three trials used handheld AODs. Two of three RCTs were of parallel design with one comparing PEP to AOD over 13 months (32) and the other comparing PEP to AOD over 12 months. (31) The third was a randomized cross-over trial comparing 2 weeks of alternating therapy separated by a 1-week washout and with a 1-week lead-in period. (33)

Two of three of the above RCTs, (31;32) both of parallel design, were combined in a fixed-effects meta-analysis by Cochrane (74 participants analyzed). (20) No overall differences were observed for % predicted FEV-1, FVC or $FEF_{25-75\%}$ (Appendix 4, Figure 7).

The cross-over trial by van Winden was not included in meta-analysis (sufficient data was not available). This trial similarly showed no significant differences across all outcomes of pulmonary function after 2 weeks of alternating therapy according to a paired t-test (*P*-vales not reported but statistical significance was assumed at a two-sided *P*-value of 0.01; a smaller *P*-value was chosen according to power calculations presented in the paper; Appendix 4, Table 2). (33)

The quality of the combined evidence (comprised of the two parallel RCTs that met the inclusion criteria) was moderate according to GRADE criteria (Appendix 5, Table 4). The body of evidence was downgraded only on the basis of consistency, as results for the primary outcomes were fairly inconsistent between the two parallel RCTs (Appendix 4, Figure 7). This may be explained by a higher proportion of dropouts in the trial by McIlwaine, (31) or by the fact that these two trials analyzed distinct populations with respect to age (one trial examined children while the other adults). As there were two long-term, parallel RCTs available for the comparison of AOD vs. PEP, the trial by van Winden was excluded from quality assessment on the basis of overwhelming methodological inferiority (short-term, cross-over, etc.).

HFCC vs. AOD

One RCT examining HFCC vs. AOD met the inclusion criteria for this review, totalling 24 participants analyzed with ages ranging from 9–39 years. (30) The trial, by Oermann, was a randomized cross-over trial that compared 4 weeks of HFCC to 4 weeks of handheld AOD, separated by a 2-week washout period and with a 2-week lead-in period. Oermann reported no significant differences in % predicted FEV-1, FVC or $FEF_{25-75\%}$ at the end of the study period according to a repeated-measures ANOVA (*P*-values not reported but <0.05 considered significant; Appendix 4, Figure 8). (30)

The quality of the evidence was very low according to GRADE criteria (Appendix 5, Table 5). The quality of evidence was downgraded on the basis of study design (cross-over), methodological quality (lack of allocation concealment and blinding, no sample size or power calculations) and sparsity of evidence (only one trial for this comparison).

Number of Days in Hospital

CCPT vs. AOD

Homnick reported no difference in the number of days per participant in hospital when comparing CCPT to IPV (5.6 ± 6.1 vs. 3.9 ± 4.5, respectively, *P*-value 0.55). (28) Gondor reported no significant difference between CCPT and AOD in mean days in hospital for patients hospitalized due to acute pulmonary exacerbation (16.6 ± 6.8 vs. 17.9 ± 5.1 days, respectively, *P*-value not reported).

Number of Admissions

CCPT vs. PEP

The trial by McIlwaine reported no difference in number of hospitalizations between the CCPT group and PEP (11 hospitalizations vs. 13, respectively; *P*-value not reported). (22)

AOD vs. PEP

McIlwaine reported that the number of hospitalizations resulting from deterioration of pulmonary status differed significantly between therapy arms with 5 hospitalizations from the PEP group and 18 from the AOD group (*P*-value=0.03). (31) Newbold reported 6 hospitalizations in the PEP group and 14 in the AOD group (*P*-value not reported); however, no significant differences were seen in the mean number of hospitalizations due to pulmonary exacerbation for individuals in the PEP group (mean 0.3 ± 0.7) and AOD group (mean 0.7 ± 1.0; *P*-value=0.2).

Adherence to Therapy and Individual Preference

CCPT vs. PEP

Three of four RCTs reported on measures of patient preference. (22-24) Responses regarding PEP treatment were consistently favourable across trials. Participants in the PEP group who had received pre-study CCTP in the parallel RCT by McIlwaine reported via questionnaire that they preferred PEP treatment to CCPT. (22) McIlwaine also reported that 92% of the CCPT group adhered to treatment compared to 96% adherence in the PEP group over the course of the study. (22) Nine out of 16 participants in the cross-over trial by Tyrrell used PEP exclusively 6 months following trial completion, while 4/16 participants used it in addition to CCPT, and 3/16 found no benefit from it. (24). On completion of the cross-over trial by Steen, 23 of 24 participants chose PEP in combination with FET as their long-term physiotherapy program. (23)

CCPT vs. HCFF/MP

Bauer obtained telephone follow-up from 38 of 41 participants and found that after trial participation, 16 of 28 patients who received MP preferred MP, 3 of 8 patients who received MP preferred CCPT, 9 of 28 patients had no preference (Bauer 1994). (26) Arens reported that 22 of 25 patients in the HFCC group expressed satisfaction and would continue using HFCC therapy for future acute pulmonary exacerbations. Satisfaction was, however, not assessed in the CCPT group (14)

CCPT vs. AOD

Homnick reported that all eight individuals in the IPV group wished to continue therapy. Participants in the IPV group were further given a survey to evaluate patient satisfaction on a 10-point scale. Results regarding IPV therapy were generally favourable; however, The CCPT group were not questioned thus not allowing for comparison. (28)

HFCC vs. AOD

Oermann reported the results of a 17-item patient satisfaction survey that evaluated three domains – efficacy, convenience, and comfort – according to a five-point Likert-type scale. (30) HFCC scored significantly higher than handheld AOD in efficacy (4.1 vs. 3.28, *P*-value <0.02) but scored significantly lower than AOD in convenience (2.88 vs. 4.26, *P*-value<0.02). There were no significant differences in regards to comfort. In this same study, self-reported compliance rates, as determined from participant diaries, were 88% and 92% for HFCC and AOD respectively. Lastly, of the 24 participants who completed both therapy types, 12/24 preferred HFCC, citing efficacy as the main reason, 9/24 preferred AOD, and 3/24 preferred CCPT.

AOD vs. PEP

McIlwaine reported on patient adherence according to patient diaries and found 95.6% adherence in the PEP group vs. 93.8% in handheld AOD (*P*-values not reported). (31) van Winden reported that 10 of 22 patients preferred PEP compared to 11/22 patients who preferred handheld AOD and 1/22 patient with no preference. (33) Newbold reported no significant differences between PEP and handheld AOD groups in adherence throughout the study (all *P*-values>0.3).

Quality of Life

AOD vs. PEP

Newbold reported no significant difference in mean slope in overall scores for the Quality of Well-Being (QWB) Scale (*P*-value=0.3) or for the Chronic Respiratory Disease Questionnaire (CRQ) (*P*-value=0.1)

between PEP and handheld AOD. (32) No significant differences were found for the mean slope of scores in each of the four dimensions of the QWB (all *P*-values>0.1) or the CRQ (all *P*-values>0.4) nor were there any between-group differences in the change in overall or change in dimension scores from first to final visit of the QWB (all *P*-values>0.1) or CRQ (all *P*-values>0.1).

Adverse Events

All Studies

Adverse events were sporadically reported and generally mild to negligible. McIlwaine reported no adverse events in either CCPT or PEP groups. (22) Arens found that one patient in the HFCC group and two patients in the CCPT developed mild hemoptysis during the study. Some patients in the HFCC group reported occasional mild chest pain and nausea which resolved after the first 2 to 3 days of therapy. (14) Homnick reported one case of minor hemoptysis during the fourth week of IPV therapy which was treated and the participant completed the study without incident. (28) Five patients in the trial by van Winden reported dizziness when using handheld AOD; however, dizziness improved following reinstruction on how to properly use the device.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Literature Review

A literature review was conducted and no cost-effectiveness (cost-utility) economic analyses were identified on the use of ACDs for the treatment of CF.

Device Costs for Airway Clearance Technologies

Costs for ACDs were estimated by technology class and obtained from correspondence with device manufacturers and literature from American thoracic societies. (67;68) There were five device classes considered in this review: handheld AOD, stationary AOD, HFCC, MP, and PEP. Device costs for the HFCC group were the highest averaging around $15,000 per vest. The cost of maintenance and vest re-sizing were included in the lifetime warranty of these products. The cheapest devices were found in the PEP and handheld AOD categories, with an average cost of approximately $60 per device. According to manufacturers, PEP and AOD (handheld and stationary) devices were replaced every two to three years. In the current economic analysis, an average maintenance cost was assigned as the need to replace these devices every 2.5 years, except in the case of stationary AODs which were assigned a replacement cost of every 3 years.

Cases of Cystic Fibrosis in Ontario

The prevalence of CF differed by age group, with the largest number of patients (cases) found in Ontario in 2002 for the 12-to-17 age group (230 cases per 100,000); the lowest number of patients was for the 50-to-71 age group (21 cases per 100,00). (9) The incidence of CF in Ontario in 2002 was estimated as 46 new cases per year. This rate was calculated by using the incidence of CF in Canada in 2002 (120 cases) and multiplying by the proportion of the Canadian population found in Ontario (38.5% in 2006). (9;69) To estimate the cost of ACDs for Ontario, the population of interest was restricted to ages 6 to 71, with the prevalence of CF being 1,047 cases in Ontario in 2002.

Estimated Costs in Ontario

To estimate the cost of airway clearance devices in Ontario, it was assumed that all prevalent and incident cases of CF would be supplied with a device from the technology classes defined above. The resulting device costs for CF patients of ages 6 to 71 are summarized in Table 2 (sorted according to disease prevalence and incidence). Maintenance costs were shown for the prevalent cases only, as the estimates represented yearly costs potentially incurred using the perspective of the Ontario Ministry of Health. Cost ranges are shown for categories in which more than one device contributed to the average cost.

Handheld AOD and PEP devices were found to be the least devices for CF according to budget impact projections. For example, using PEP devices, the total annual cost would be approximately $94,600, of which about $2,900 would be attributable to new (incident) cases of CF. The Ontario Assistive Devices Program spent a total of about $16,000 in fiscal 2008-09 on postural drainage boards ($13,335; n=17) and MP devices ($2,630; n=6) for CF patients in Ontario. Postural drainage boards, however, are now obsolete and are no longer manufactured. Similarly, at least one MP device sold in Ontario was no longer manufactured and only available as a refurbished model (according to the manufacturer). The clinical efficacy of MP devices is further unsupported by evidence.

Table 2: Cost of airway clearance devices: Budget impact projections and annual cost

			Prevalence		Incidence
Device class	**Cost**	**Unit cost**	**Device Cost**	**Maintenance**	**New Costs**
AOD-handheld	Average	$58	$60,923	$24,369	$2,686
	Range	[$38–$95]	[$40K–$100K]	[$16K–$4 K]	[$1,774–$4,391]
AOD-stationary	Average	$10,761	$11,267,165	$3,755,722	$496,740
HFCC	Average	$15,607	$16,340,263	*	$720,399
	Range	[$13K–$18K]	[$13.8M–$18.9M]		[$608K–$832K]
MP	Average	$1,442	$1,509,774	$603,910	$66,562
PEP	Average	$63	$65,516	$26,206	$2,888

* Lifetime warranty and size replacement were provided by the manufacturer for each vest purchased (according to at least one manufacturer)

Abbreviations: K, thousand; M, million

Conclusions

There is currently a lack of sufficiently powered, long-term, parallel randomized controlled trials investigating the use of ACDs in comparison to other airway clearance techniques. While much of the current evidence suggests no significant difference between various ACDs and alternative therapies/technologies, at least according to outcomes of pulmonary function, there is a strong possibility that past trials were not sufficiently powered to identify a difference. Unfortunately, it is unlikely that there will be any future trials comparing ACDs to CCPT seeing as withholding therapy using an ACD may be seen as unethical at present. Conclusions of clinical effectiveness are as follows:

1. Moderate quality evidence suggests that PEP is at least as effective, or more effective, than CCPT according to the primary outcomes of pulmonary function.
2. Moderate quality evidence suggests that there is no significant difference between PEP and handheld AODs according to the primary outcomes of pulmonary function; however, secondary outcomes may favour PEP.
3. Low quality evidence suggests that there is no significant difference between AODs or HFCC/MP and CCPT, according to both primary and secondary outcomes.
4. Very low quality evidence suggests that there is no significant difference between handheld AOD and CCPT according to the primary outcomes of pulmonary function.
5. Adverse events arising from the use of airway clearance devices are mild or negligible, and easily managed by discontinuing device use and treating symptoms.
6. Budget impact projections show that PEP and handheld AODs are highly economically feasible.

Appendices

Appendix 1: Literature Search Strategies

Search date: March 17, 2009

Databases searched: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library (all via OVID); EBSCO CINAHL, International Agency for Health Technology Assessment/Centre for Reviews and Dissemination

Database: Ovid MEDLINE(R) <1950 to March Week 1 2009>

Search Strategy:

1 exp Cystic Fibrosis/ (23021)
2 (cystic fibrosis or cf or mucoviscidosis or pancrea* fibrocystic disease).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (38891)
3 1 or 2 (38891)
4 exp Respiratory Therapy/ or exp Mucociliary Clearance/ (71676)
5 ((positive adj2 expiratory pressure) or (mucociliary adj2 clearance) or (mucous adj2 clearance)).mp. (5981)
6 (chest wall oscillat* or (high frequency chest adj2 compression*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (123)
7 ((hpep or pep) adj2 (device* or mask* or bottle* or therap*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (60)
8 (Airway adj2 (oscillat* or clearance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (383)
9 (percussive or percussion).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2458)
10 (acapella or flutter or cornet* or rc-cornet* or SmartVest or vest or pari or Frequencer or p-neb or PercussiveNeb or PercussiveTech HF or Fluid Flo or Universal Ventilator or Percussionator or IMPULSATOR or Phasitron or Resistex or Percussionaire or CoughAssist or In-Exsufflator or Cofflator).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7962)
11 exp Respiration Disorders/th [Therapy] (25338)
12 or/4-11 (93898)
13 3 and 12 (1014)
14 limit 13 to (english language and humans) (826)
15 limit 14 to (controlled clinical trial or meta analysis or randomized controlled trial) (121)
16 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (39945)
17 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (738)
18 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (78422)
19 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (568186)
20 exp Double-Blind Method/ (100000)
21 exp Control Groups/ (1162)
22 exp Placebos/ (27650)
23 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (170423)
24 or/15-23 (740696)
25 14 and 24 (166)

Database: EMBASE <1980 to 2009 Week 11>

Search Strategy:

1 exp Cystic Fibrosis/ (22942)
2 (cystic fibrosis or cf or mucoviscidosis or pancre* fibrocystic disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (33957)
3 1 or 2 (33957)
4 exp Lung Clearance/ (2122)
5 exp Artificial Ventilation/ (54117)
6 exp Mucociliary Clearance/ (1727)
7 exp postural drainage/ (331)
8 exp Airway Obstruction/th [Therapy] (882)
9 exp Breathing Disorder/th [Therapy] (5394)
10 ((positive adj2 expiratory pressure) or (mucociliary adj2 clearance) or (mucous adj2 clearance)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (17248)
11 (chest wall oscillat* or (high frequency chest adj2 compression*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (77)
12 ((hpep or pep) adj2 (device* or mask* or bottle* or therap*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (58)
13 (Airway adj2 (oscillat* or clearance)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (412)
14 (percussive or percussion).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1734)
15 (acapella or flutter or cornet* or rc-cornet* or SmartVest or vest or pari or Frequencer or p-neb or PercussiveNeb or PercussiveTech HF or Fluid Flo or Universal Ventilator or Percussionator or IMPULSATOR or Phasitron or Resistex or Percussionaire or CoughAssist or In-Exsufflator or Cofflator).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7243)
16 or/4-15 (69737)
17 3 and 16 (1139)
18 exp Evidence Based Medicine/ (295568)
19 Randomized Controlled Trial/ (166828)
20 exp Randomization/ (26635)
21 exp RANDOM SAMPLE/ (1437)
22 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (300625)
23 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (674)
24 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (65700)
25 Double Blind Procedure/ (71767)
26 exp Triple Blind Procedure/ (13)
27 exp Control Group/ (3058)
28 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (215231)
29 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (434129)
30 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (285235)
31 or/18-30 (802853)
32 17 and 31 (262)
33 limit 32 to (human and english language) (245)

CINAHL

#	Query	Limiters/Expanders	Last Run Via	Results
S29	S17 and S28	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	51
S28	(S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	130239
S27	control* N2 clinical trial*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	2148
S26	(MH "Placebos") or (MH "Control (Research)")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	5152
S25	(MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	16154
S24	meta analy* or metaanaly* or pooled analysis or (systematic* N2 review*) or published studies or medline or embase or data synthesis or data extraction or cochrane	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	28725
S23	(MH "Systematic Review")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	4389
S22	(MH "Meta Analysis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	7618
S21	health technolog* N2 assess* or rct*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	2669
S20	random* or sham*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	86463
S19	(MH "Random Assignment") or (MH "Random Sample+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	37599
S18	(MH "Professional Practice, Evidence-Based+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	20763
S17	S3 and S16	Limiters - Published Date from: 198001-200912; English Language Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	217
S16	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	17362
S15	(acapella or flutter or cornet* or rc-cornet* or SmartVest or vest or pari or Frequencer or p-neb or PercussiveNeb or PercussiveTech HF or Fluid Flo or Universal Ventilator or Percussionator or IMPULSATOR or Phasitron or Resistex or Percussionaire or CoughAssist or In-Exsufflator or Cofflator)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	1215

S14	(percussive or percussion)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	338
S13	(Airway and (oscillat* or clearance))	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	382
S12	((hpep or pep) and (device* or mask* or bottle* or therap*)).	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	124
S11	chest wall oscillat* or (high frequency chest N2 compression*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	39
S10	((positive N2 expiratory pressure) or (mucociliary N2 clearance) or (mucous N2 clearance))	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	1202
S9	(MH "Airway Obstruction+/TH")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	344
S8	(MH "Respiration Disorders+/TH")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	3688
S7	(MH "Drainage, Postural")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	81
S6	(MH "Oscillator") or (MH "Chest Physical Therapy")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	178
S5	(MH "Respiratory Therapy+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	13721
S4	(MH "Mucociliary Clearance")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	146
S3	(S1 or S2)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	2635
S2	cystic fibrosis or mucoviscidosis or pancrea* fibrocystic disease	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	2635
S1	(MH "Cystic Fibrosis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL;Pre-CINAHL	2343

Appendix 2: Study Characteristics

Table A1: Design and patient characteristics of included studies

Trial	Design	N* (Completed)	Mean Age (Range)	Intervention	Arm 1	Arm 2	ITT
Tyrrell 1986	Crossover	19 (16)	13.0 (10–18)	CCPT 1 mo X PEP 1 mo No washout	PD&P and coughing	Astra Meditec PEP	No
Van Asperen 1987	Crossover	13 (10)	NR (7–18)	CCPT 1 mo X PEP 1 mo No washout	PD&P and coughing	Astra Meditec PEP	No
Steen 1991	Crossover	28 (24)	14.0 (8–21)	CCPT 1 mo X PEP 1 mo No washout	PD&P and FET	Astra Meditec PEP or VitaPEP	No
McIlwaine 1997	Matched-pair parallel†	40 (36)	CCPT: 9.8 (6–14) PEP: 10.4 (6–17)	CCPT 12 mo vs. PEP 12 mo	PD&P + vibration on expiration, forced expiration and coughing	Astra Meditec PEP	No
Arens 1994	Parallel	50 (46)	CCPT: 18.0 HFCC: 22.9	CCPT (mean 16.2 d) vs. HFCC (mean 16 d)	PD&P	ThAIRapy vest	No
Bauer 1994	Parallel	54 (51) + 22 X-over	CCPT: 17.0 MP: 15.9	CCPT (mean 12.5 d) vs. MP (mean 11.4 d)	Manual percussion	Vibracare Percussor or Model 9000 Percussor	No
Homnick 1995	Parallel	20 (16)	CCPT: 10.0 (5–18) AOD: 12 (5–24)	CCPT 6 mo vs. AOD 6 mo	PD&P	Percussinator IPV	No
Homnick 1998	Parallel	22 [33]†	CCPT: 12.0 (7–21) AOD: 16.1 (8–44)	CCPT (mean 8.8 d) vs. AOD (mean 8.9 d)	PD&P	Flutter	No
Gondor 1999	Parallel	23 (20)	CCPT: 13.8 (8–16) AOD: 11.9 (5–21)	CCPT (mean 17.9) vs. AOD (mean 16.6)	PD&P, clapping and coughing	Flutter	No
van Winden 1998	Crossover	22 (22)	12 (7–17)	PEP 2 wk X AOD 2 wk 1 wk lead-in/ washout	Astra Meditec PEP	Flutter	No
McIlwaine 2001	Parallel	40 (32)	PEP: 10.7 (7–16) AOD: 11.90 (7–16)	PEP 12 mo vs. AOD 12 mo	Astra Meditec PEP	Flutter	No
Newbold 2005	Parallel	43 (42)	PEP: 28 (≥18) AOD: 31 (≥18)	PEP 13 mo vs. AOD 13 mo	Astra Meditec PEP	Flutter	No
Oermann 2001	Crossover	29 (24)	23 (9–39)	HFCC 4 wk X AOD 4 wk 2 wk lead-in/washout	ThAIRapy Vest	Flutter	Yes

*Sample randomized (sample that completed study) †Matching was done according to FEV-1 (within 15% of predicted value), sex, and age (within 3 years)

33 hospitalizations were analyzed from 22 patients

Abbreviations: AOD, airway oscillating devices; CCPT, conventional chest physiotherapy; d, days; HFCC, high frequency chest compression; IPV, intrapulmonary percussive ventilator; ITT, intent-to-treat analysis; mo, months; N, sample size; PD&P, postural drainage and percussion; PEP, positive expiratory pressure; wk, week; X, cross;

Appendix 3: Results

Table A2: Summarization of results for primary outcomes across all trials by comparison and subgroupings

Outcome or Subgroup	No. of Studies	Estimate of Effectiveness (95% CI)	*P*-value	Heterogeneity (I^2)	GRADE
CCPT vs. PEP					
Cochrane					
FEV-1	6	0.08 (-1.45 to 1.62)	0.91	46%	
FVC	6	0.38 (-1.56 to 2.23)	0.70	63%	N/A
$FEF_{25-75\%}$	4	-0.44 (-3.38 to 2.50)	0.77	36%	
Full publications only					
FEV-1	3	-0.50 (-3.93 to 2.92)	0.77	77%	
FVC	3	-0.86 (-4.66 to 2.95)	0.66	74%	
$FEF_{25-75\%}$	2	-0.12 (-6.22 to 5.98)	0.97	0%	N/A
Long-term, parallel RCTs only					
FEV-1	1	-8.25 (-15.77 to -0.75)	0.03	N/A	
FVC	1	-8.74 (-16.03 to -1.45)	0.02	N/A	1 Trial
$FEF_{25-75\%}$	1	-3.56 (-13.30 to 6.18)	0.47	N/A	MODERATE
CCPT vs. HFCC/MP					
Cochrane					
FEV-1	3	-1.76 (-4.67 to 1.16)	0.24	0%	
FVC	3	-1.42 (-5.17 to 2.33)	0.46	70%	
$FEF_{25-75\%}$	2	0.49 (-2.54 to 3.52)	0.75	0%	N/A
Full publications only					
FEV-1	3	-2.10 (-5.49 to 1.29)	0.23	0%	
FVC	3	-3.86 (-8.05 to 0.33)	0.07	0%	3 Trials
$FEF_{25-75\%}$	2	0.49 (-2.54 to 3.52)	0.75	0%	LOW
CCPT vs. AOD					
2 of 3 RCTs/Cochrane					
FEV-1	2	0.80 (-5.79 to 7.39)	0.81	0%	3 Trials
FVC	2	6.06 (-2.42 to 14.55)	0.16	12%	LOW
$FEF_{25-75\%}$	2	1.26 (-7.56 to 10.09)	0.78	0%	
AOD vs. PEP					
Long-term, parallel RCTs only/Cochrane					
FEV-1	2	0.29 (-4.17 to 4.75)	0.90	73%	
FVC	2	-0.55 (-4.60 to 3.50)	0.79	77%	2 Trials
$FEF_{25-75\%}$	2	0.10 (-4.86 to 5.06)	0.97	0%	MODERATE
AOD vs. HFCC/MP					
Long-term, parallel RCTs only/Cochrane					
FEV-1	1	-1.6 (-3.44 to 0.24)	0.09	N/A	
FVC	1	-1.80 (-4.32 to 0.72)	0.08	N/A	1 Trial
$FEF_{25-75\%}$	1	-1.40 (-3.07 to 0.27)	0.16	N/A	VERY LOW

Bolding indicates significant difference

Positive summary statistics favour the former intervention

Abbreviations: AOD, airway oscillating devices; CCPT, conventional chest physiotherapy; CI, confidence interval; HFCC, high frequency chest compression; MP, mechanical percussion; N/A: not applicable; PEP, positive expiratory

Appendix 4: Forrest Plots

Figure A1: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to PEP: all trials including abstracts

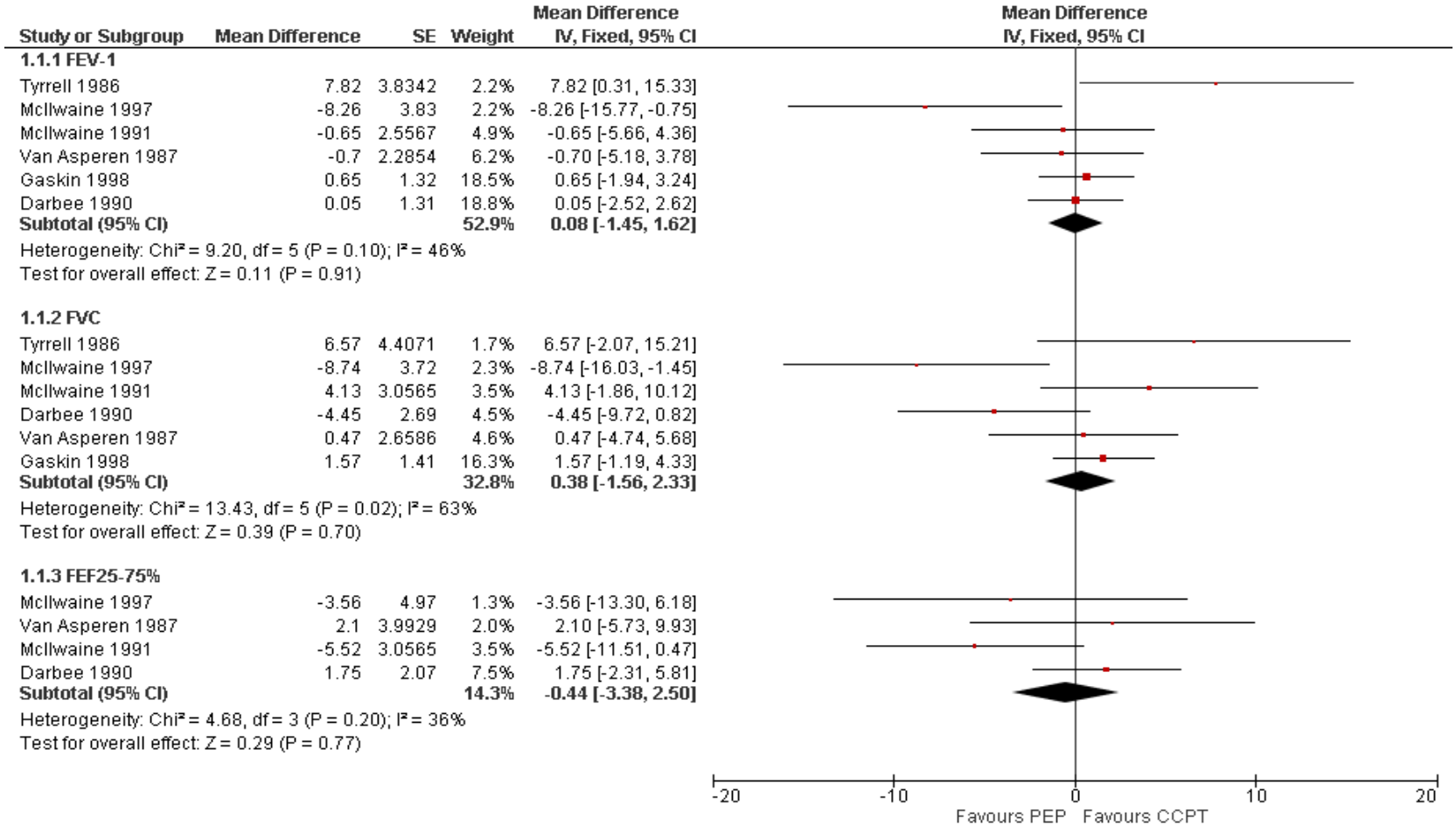


Figure A2: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to PEP: full publications only

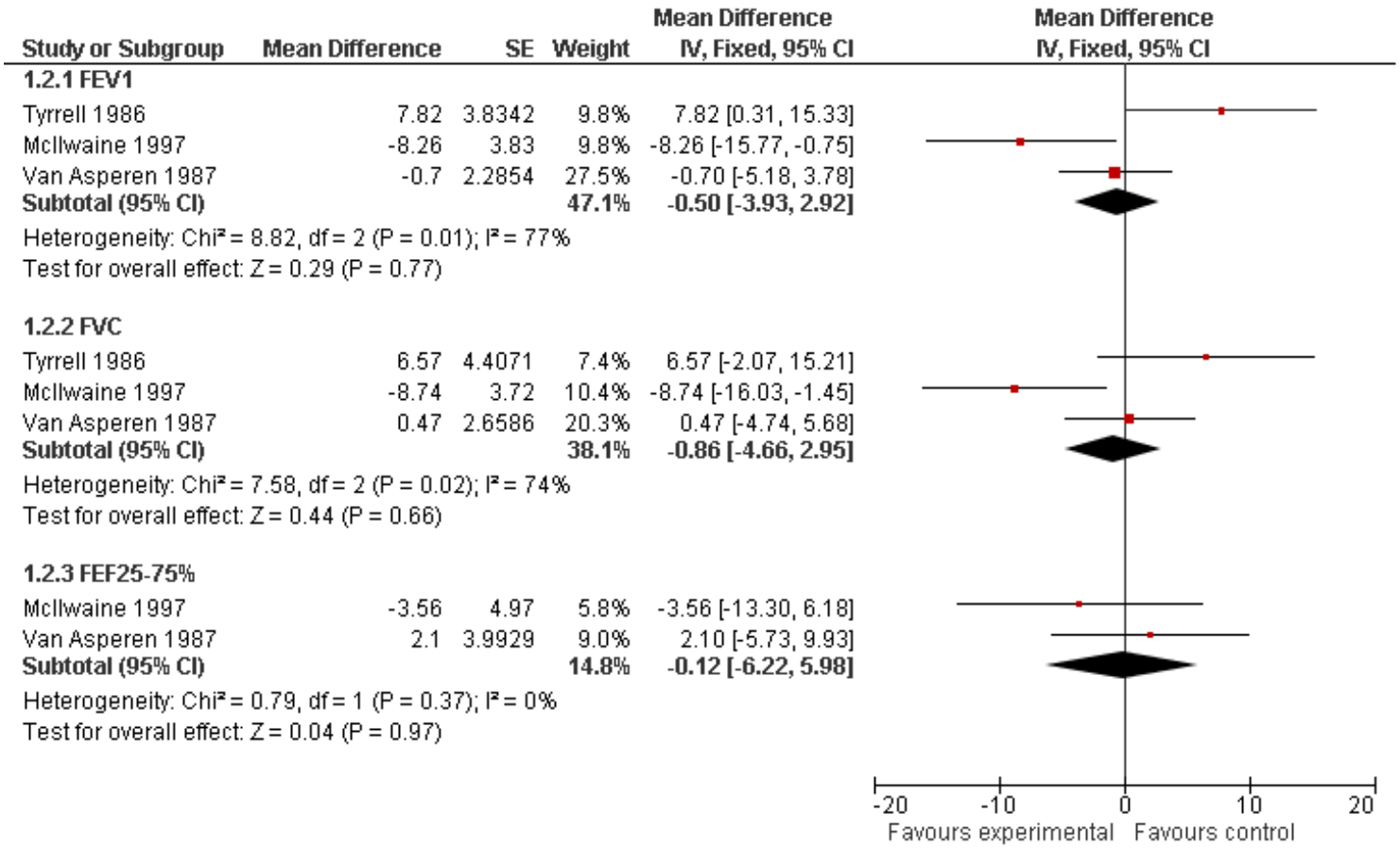


Figure A3: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to PEP: long-term, parallel RCTs only

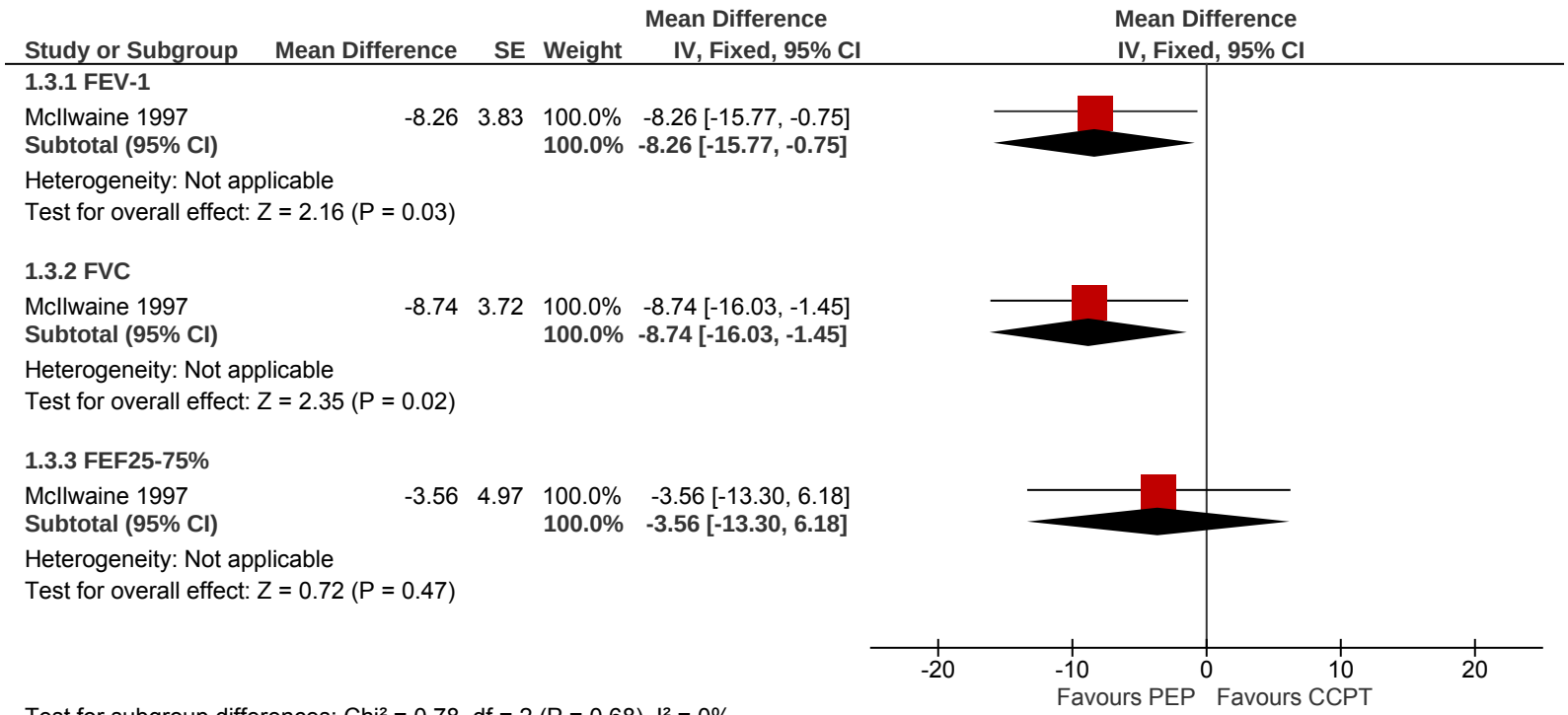


Table A3: Results of pulmonary function outcomes for the trial by Steen: CCPT vs. PEP

	Intervention				
Outcome	CCPT + FET (control)	PEP → CCPT	PEP alone	PEP + FET	FET alone
% predicted FEV-1	60 (23)	58 (28)	61 (32)	55 (28)	69 (26)
% predicted FVC	78 (23)	73 (27)	79 (27)	64 (30)	74 (28)

All values are % predicted measurements averaged over 4 weeks of treatment and are presented as mean (±SD)

No significant differences observed at *P*-value <0.05

Abbreviations: +, in combination with; →, followed by; CCPT, conventional chest physiotherapy; FET, forced expiration technique; PEP, positive expiratory pressure;

Figure A4: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to HFCC/MP: all trials including abstracts

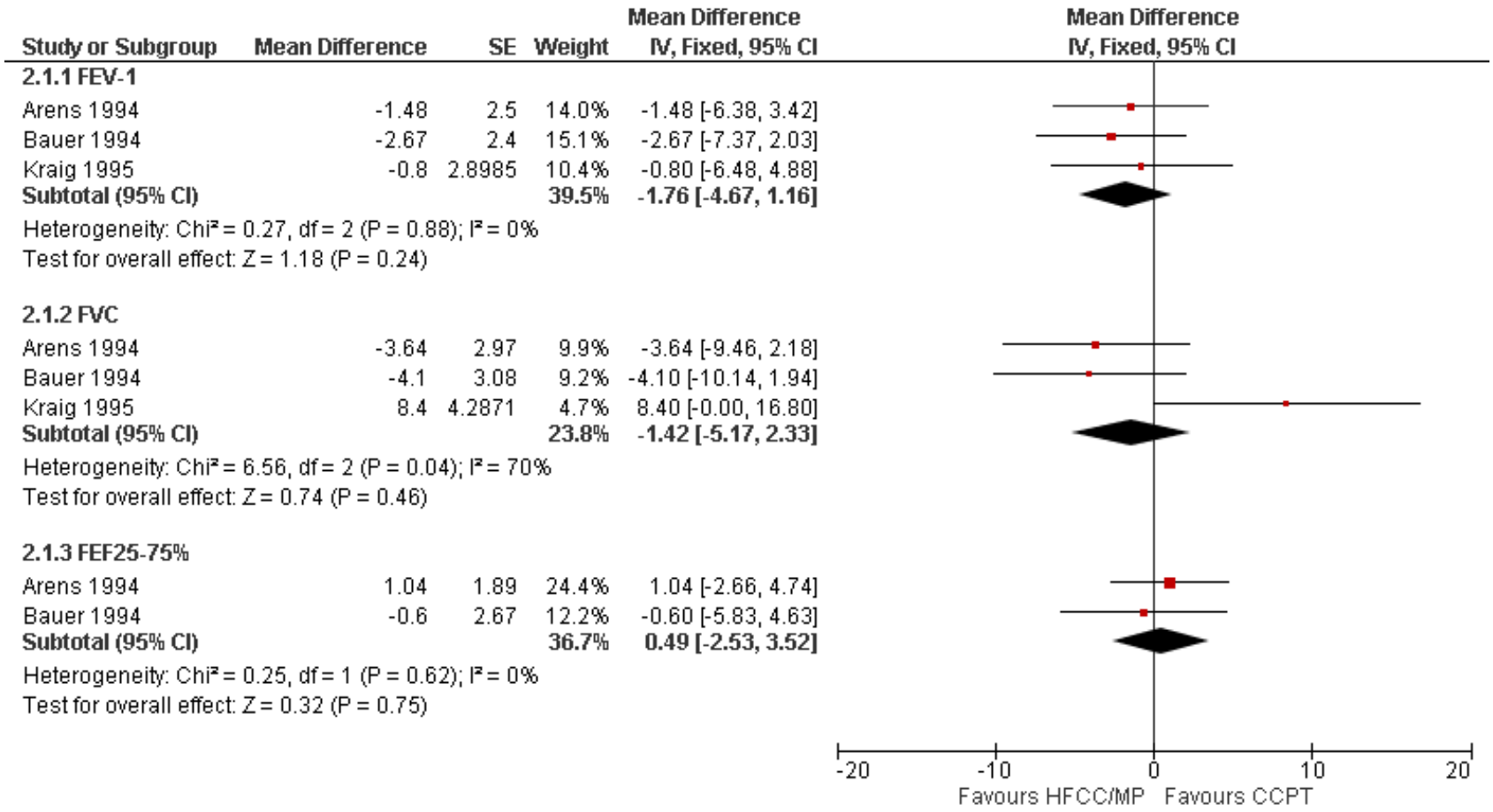


Figure A5: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to HFCC/MP: full publications only

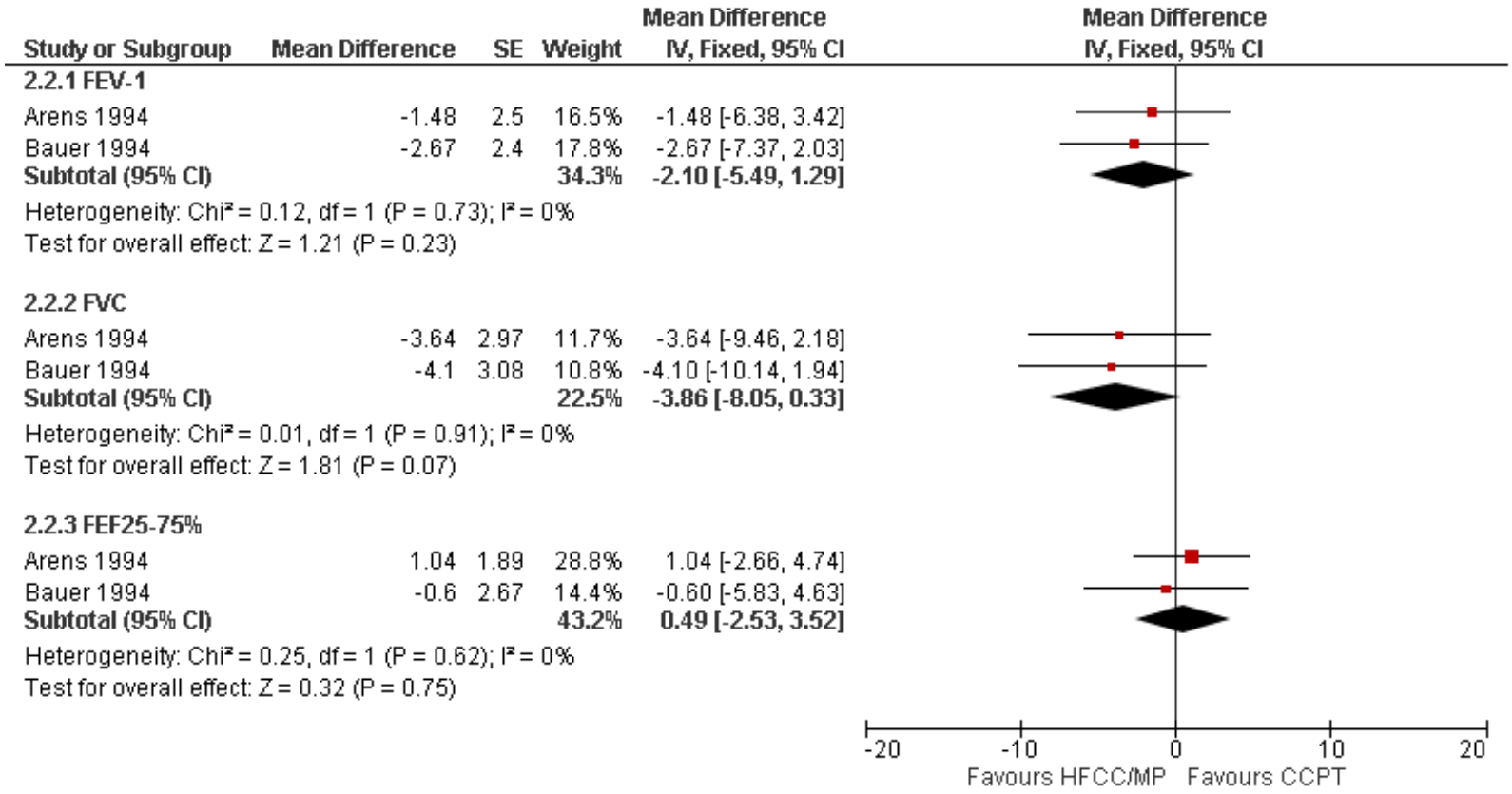


Figure A6: Meta-analysis of pulmonary function outcomes for trials comparing CCPT to AOD

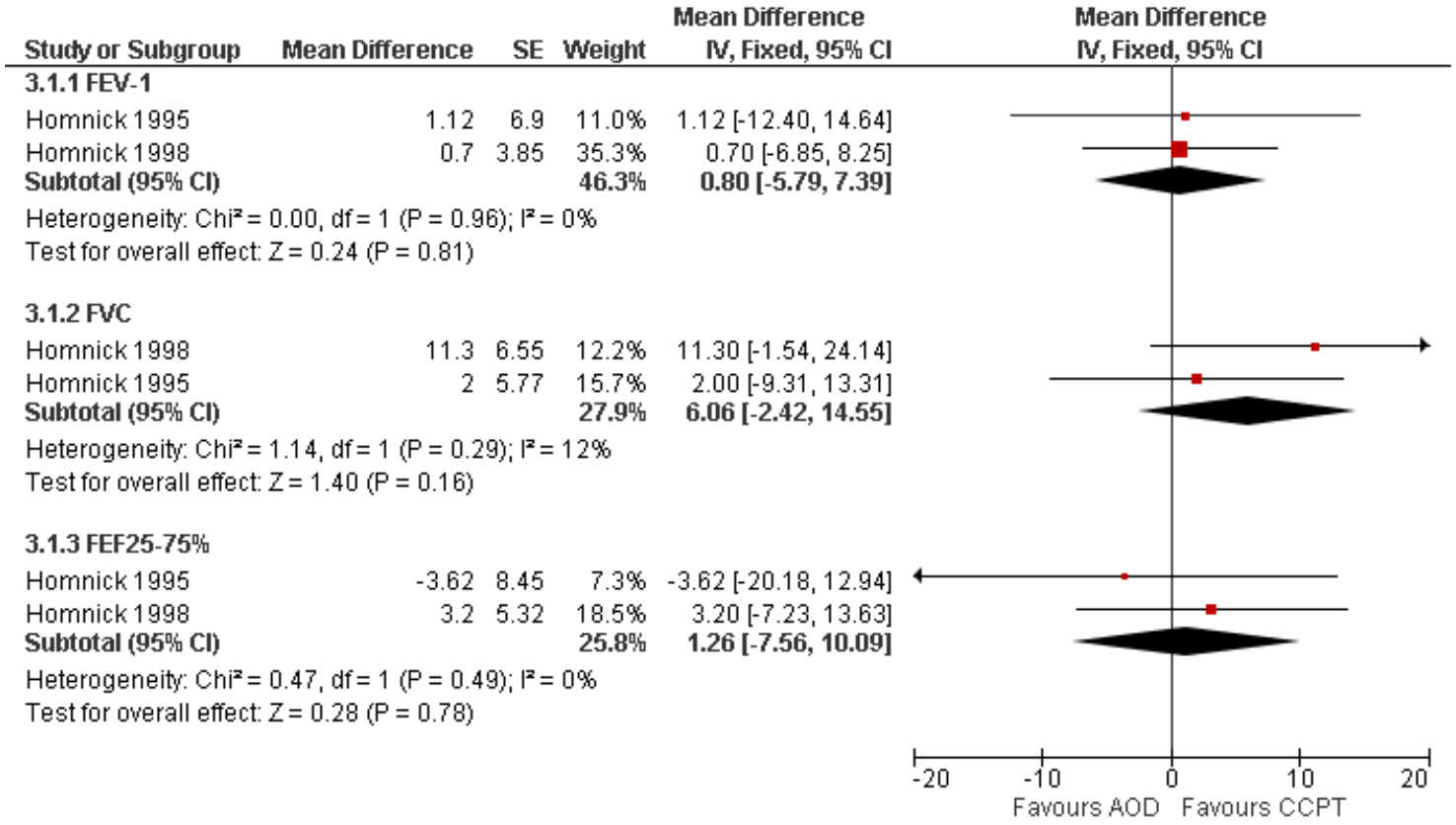


Figure A7: Meta-analysis of pulmonary function outcomes for trials comparing PEP to AOD

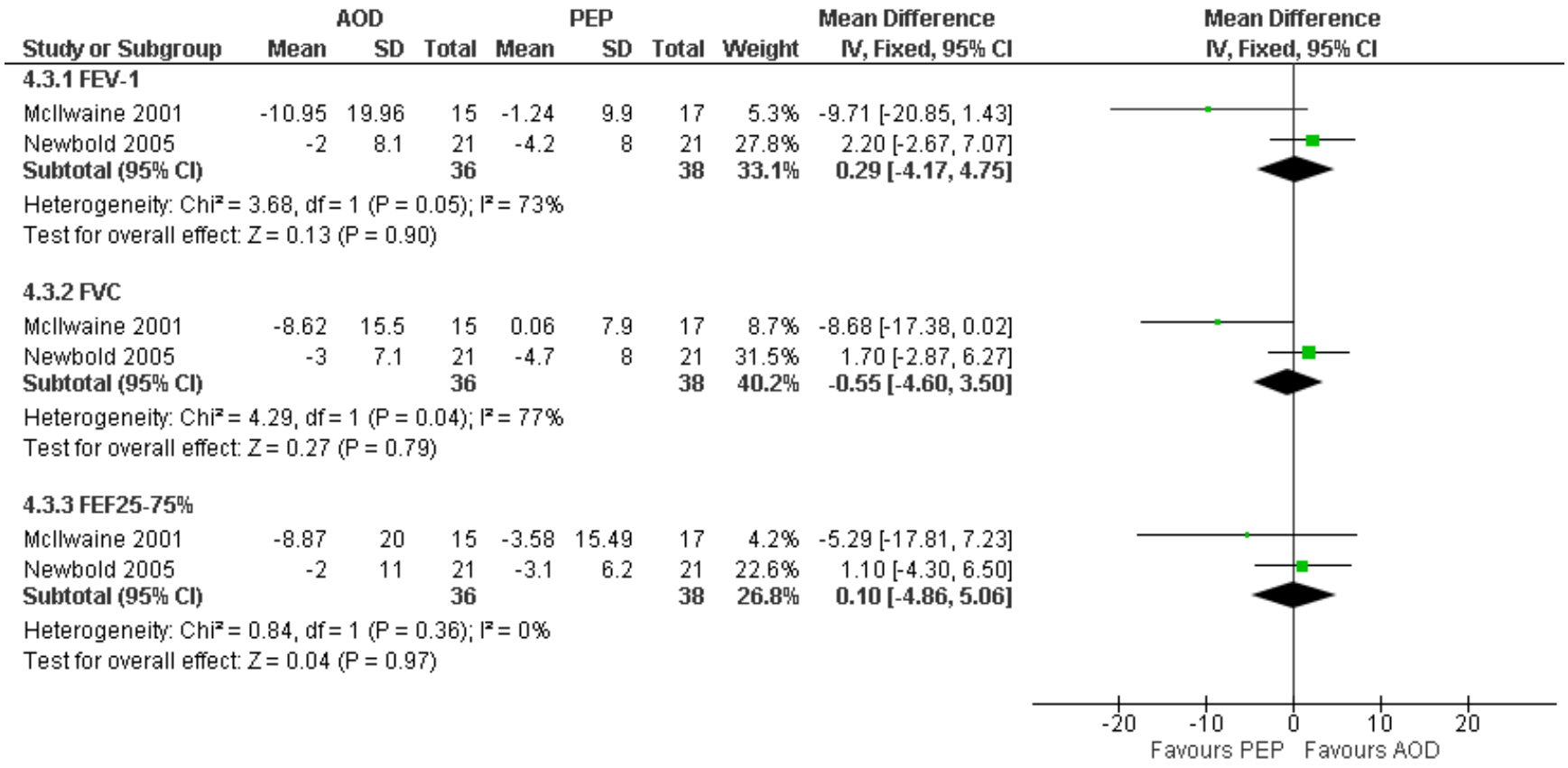
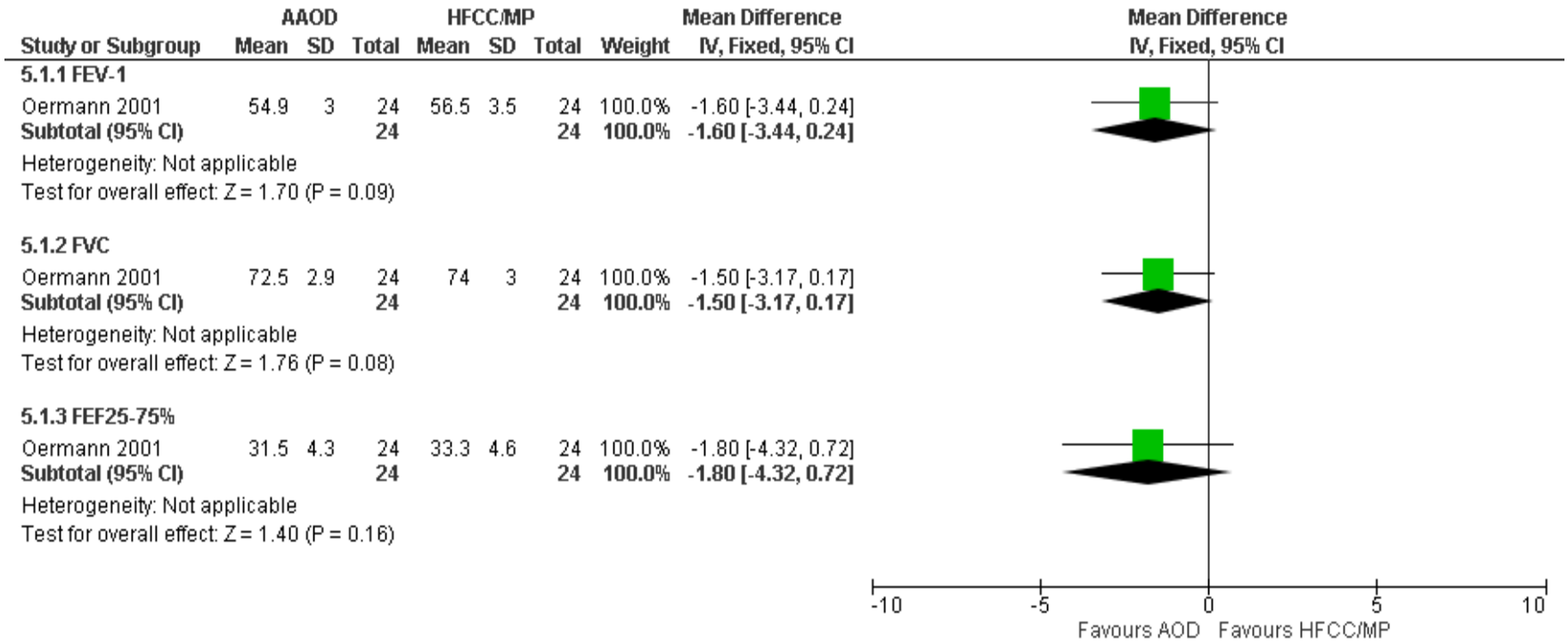


Table A4: Results of pulmonary function outcomes for the trial by van Winden: handheld AOD vs. PEP

	Outcome		
Intervention	% predicted FEV-1	% predicted FVC	% predicted $FEF_{25–75\%}$
PEP	86 (4)	97 (3)	55 (5)
AOD	88 (4)	99 (4)	54 (5)

All values are % predicted measurements taken at the end of the 2-week study period and are presented as mean (±SD)
No significant differences observed at *P*-value <0.01 Abbreviations: AOD, airway oscillating device; PEP, positive expiratory pressure

Figure A8: Results of pulmonary function outcomes for the trial by Oermann: HFCC vs. handheld AOD



Appendix 5: Results of GRADE Analysis

Table A5: GRADE analysis of included trials: CCPT vs. PEP

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Overall Quality
McIlwaine 1997	Parallel RCT	Physicians and pulmonary function technicians blinded to therapy group No ITT analysis (but few drop-outs) No sample size/power calculation		Generalizability of trials in question: Participant age ≤17; not reflective of modern median age of CF survivor Trial >10 years old	Sparse evidence	
	HIGH	**HIGH**	**HIGH**	**MODERATE**	**MODERATE**	**MODERATE**

Abbreviations: ITT, intent-to-treat analysis; RCT, randomized controlled trial; X, cross

Table A6: GRADE analysis of included trials: CCPT vs. HFCC/MP

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Overall Quality
Arens 1994 Bauer 1994	Parallel RCTs	Lack of allocation concealment and blinding No ITT analysis Parallel sample combined with crossover sample No sample size/power calculations **MODERATE**		Generalizability of trials in question: Both trials conducted in patients during hospitalizations for pulmonary exacerbation No long-term data Trials >10 years old **LOW**	No other factors to report.	
	HIGH		**MODERATE**		**LOW**	**LOW**

Abbreviations: ITT, intent-to-treat analysis; RCT, randomized controlled trial; X, cross

Table A7: GRADE analysis of included trials: CCPT vs. AOD

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Overall Quality
Homnick 1995 Homnick 1998 Gondor 1999	Parallel RCTs	Lack of allocation concealment and blinding Multiple admissions analyzed No ITT analysis No sample size/power calculations (small sample sizes)		Generalizability of intervention in question: No long-term trials using Flutter (both trials using Flutter were conducted during 2-week hospitalizations for pulmonary exacerbation) Age generally under 21 Trials >10 years old	No other factors to report.	
	HIGH	**MODERATE**	**MODERATE**	**LOW**	**LOW**	**LOW**

Abbreviations: ITT, intent-to-treat analysis; RCT, randomized controlled trial

Table A8: GRADE analysis of included trials: handheld AOD vs. PEP

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Overall Quality
McIlwaine 2001	RCTs	Descriptions of randomization & concealment/ blinding were provided where possible 20% dropout in 1 trial and no ITT 1 trial reported sample size calculations	Divergent results	Ages well represented across trials Trials <10 years old	No other factors to report.	
Newbold 2005						
	HIGH	**HIGH**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**

Abbreviations: ITT, intent-to-treat analysis; RCT, randomized controlled trial

Table A9: GRADE analysis of included trials: HFCC vs. handheld AOD

Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Overall Quality
Oermann 2001	X-over	Lack of allocation concealment and blinding No sample size/ power calculation ITT analysis provided		Wide age range Trial <10 years old	Sparse evidence (1 trial)	
	MODERATE	**LOW**	**LOW**	**LOW**	**VERY LOW**	**VERY LOW**

Abbreviations: ITT, intent-to-treat analysis; X = cross

References

(1) Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. Chest 2004; 125(1 Suppl):1S-39S.

(2) Zach MS. Lung disease in cystic fibrosis--an updated concept. Pediatr Pulmonol 1990; 8(3):188-202.

(3) Coutinho HD, Falcao-Silva VS, Goncalves GF. Pulmonary bacterial pathogens in cystic fibrosis patients and antibiotic therapy: a tool for the health workers. Int Arch Med 2008; 1(1):24.

(4) Cantin A. Cystic fibrosis lung inflammation: early, sustained, and severe. Am J Respir Crit Care Med 1995; 151(4):939-41.

(5) Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. Pediatr Pulmonol 1997; 24(2):137-42.

(6) Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989; 245(4922):1059-65.

(7) Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989; 245(4922):1073-80.

(8) Dupuis A, Hamilton D, Cole DE, Corey M. Cystic fibrosis birth rates in Canada: a decreasing trend since the onset of genetic testing. J Pediatr 2005; 147(3):312-5.

(9) Canadian Cystic Fibrosis Foundation. Report of the Canadian Patient Data Registry 2002 [Internet]. Toronto: The Foundation. 2002. [cited: 2009 Apr 11]. 8 p.
Available from: www.fibrosekystique.ca/pdf/Lay%20CPDR%20ReportE.pdf

(10) Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev 2009; Issue 1. Art. No.: CD002769. DOI: 10.1002/14651858.CD002769.pub3.

(11) Elkins MR, Jones A, van der SC. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev 2006; Issue 2. Art. No.: CD003147. DOI: 10.1002/14651858.CD003147.pub3.

(12) Main E, Prasad A, Schans C. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. Cochrane Database Syst Rev 2005; Issue 1. Art. No.: CD002011. DOI: 10.1002/14651858.CD002011.pub2.

(13) Cystic Fibrosis Foundation. Patient Registry: Annual Data Report 2007 [Internet]. Bethesda, MD: The Foundation. 2008. [cited: 2009 Apr 11]. 19 p.
Available from: www.cff.org/UploadedFiles/research/ClinicalResearch/2007-Patient-Registry-Report.pdf

(14) Arens R, Gozal D, Omlin KJ, Vega J, Boyd KP, Keens TG et al. Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. Am J Respir Crit Care Med 1994; 150(4):1154-7.

(15) Braggion C, Cappelletti LM, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross-over randomized study. Pediatr Pulmonol 1995; 19(1):16-22.

(16) Desmond KJ, Schwenk WF, Thomas E, Beaudry PH, Coates AL. Immediate and long-term effects of chest physiotherapy in patients with cystic fibrosis. J Pediatr 1983; 103(4):538-42.

(17) Kluft J, Beker L, Castagnino M, Gaiser J, Chaney H, Fink RJ. A comparison of bronchial drainage treatments in cystic fibrosis. Pediatr Pulmonol 1996; 22(4):271-4.

(18) Reisman JJ, Rivington-Law B, Corey M, Marcotte J, Wannamaker E, Harcourt D et al. Role of conventional physiotherapy in cystic fibrosis. J Pediatr 1988; 113(4):632-6.

(19) Thomas J, Cook DJ, Brooks D. Chest physical therapy management of patients with cystic fibrosis: A meta-analysis. Am J Respir Crit Care Med 1995; 151(3 I):846-50.

(20) Morrison L, Agnew J. Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev 2009; Issue 1. Art. No.: CD006842. DOI: 10.1002/14651858.CD006842.pub2.

(21) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454):1490.

(22) McIlwaine PM, Wong LT, Peacock D, Davidson AG. Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. J Pediatr 1997; 131(4):570-4.

(23) Steen HJ, Redmond AO, O'Neill D, Beattie F. Evaluation of the PEP mask in cystic fibrosis. Acta Paediatr Scand 1991; 80(1):51-6.

(24) Tyrrell JC, Hiller EJ, Martin J. Face mask physiotherapy in cystic fibrosis. Arch Dis Child 1986; 61(6):598-600.

(25) Van Asperen PP, Jackson L, Hennessy P, Brown J. Comparison of a positive expiratory pressure (PEP) mask with postural drainage in patients with cystic fibrosis. Aust Paediatr J 1987; 23(5):283-4.

(26) Bauer ML, McDougal J, Schoumacher RA. Comparison of manual and mechanical chest percussion in hospitalized patients with cystic fibrosis. J Pediatr 1994; 124(2):250-4.

(27) Gondor M, Nixon PA, Mutich R, Rebovich P, Orenstein DM. Comparison of Flutter device and chest physical therapy in the treatment of cystic fibrosis pulmonary exacerbation. Pediatr Pulmonol 1999; 28(4):255-60.

(28) Homnick DN, White F, de CC. Comparison of effects of an intrapulmonary percussive ventilator to standard aerosol and chest physiotherapy in treatment of cystic fibrosis. Pediatr Pulmonol 1995; 20(1):50-5.

(29) Homnick DN, Anderson K, Marks JH. Comparison of the flutter device to standard chest physiotherapy in hospitalized patients with cystic fibrosis: a pilot study. Chest 1998; 114(4):993-7.

(30) Oermann CM, Sockrider MM, Giles D, Sontag MK, Accurso FJ, Castile RG. Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: a pilot study. Pediatr Pulmonol 2001; 32(5):372-7.

(31) McIlwaine PM, Wong LT, Peacock D, Davidson AGF. Long-term comparative trial of positive expiratory pressure versus oscillating positive expiratory pressure (flutter) physiotherapy in the treatment of cystic fibrosis. J Pediatr 2001; 138(6):845-50.

(32) Newbold ME, Tullis E, Corey M, Ross B, Brooks D. The Flutter device versus the PEP Mask in the treatment of adults with cystic fibrosis. Phys Canada 2005; 57(3):199-207.

(33) van Winden CM, Visser A, Hop W, Sterk PJ, Beckers S, de Jongste JC. Effects of flutter and PEP mask physiotherapy on symptoms and lung function in children with cystic fibrosis. Eur Respir J 1998; 12(1):143-7.

(34) Darbee JC, Kanga JF, Ohtake PJ. Physiologic evidence for high-frequency chest wall oscillation and positive expiratory pressure breathing in hospitalized subjects with cystic fibrosis. Phys Ther 2005; 85(12):1278-89.

(35) Falk M, Kelstrup M, Andersen JB, Kinoshita T, Falk P, Stovring S et al. Improving the ketchup bottle method with positive expiratory pressure, PEP, in cystic fibrosis. Eur J Respir Dis 1984; 65(6):423-32.

(36) Hofmeyr JL, Webber BA, Hodson ME. Evaluation of positive expiratory pressure as an adjunct to chest physiotherapy in the treatment of cystic fibrosis. Thorax 1986; 41(12):951-4.

(37) Lagerkvist AB, Sten GM, Redfors SB, Lindblad AG, Hjalmarson O. Immediate changes in blood-gas tensions during chest physiotherapy with positive expiratory pressure and oscillating positive expiratory pressure in patients with cystic fibrosis. Resp Care 2006; 51(10):1154-61.

(38) Marks JH, Hare KL, Saunders RA, Homnick DN. Pulmonary function and sputum production in patients with cystic fibrosis: a pilot study comparing the PercussiveTech HF device and standard chest physiotherapy. Chest 2004; 125(4):1507-11.

(39) McCarren B, Alison JA. Physiological effects of vibration in subjects with cystic fibrosis. Eur Respir J 2006; 27(6):1204-9.

(40) Mortensen J, Falk M, Groth S, Jensen C. The effects of postural drainage and positive expiratory pressure physiotherapy on tracheobronchial clearance in cystic fibrosis. Chest 1991; 100(5):1350-7.

(41) Pfleger A, Theissl B, Oberwaldner B, Zach MS. Self-administered chest physiotherapy in cystic fibrosis: a comparative study of high-pressure PEP and autogenic drainage. Lung 1992; 170(6):323-30.

(42) Varekojis SM, Douce FH, Flucke RL, Filbrun DA, Tice JS, McCoy KS et al. A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. Resp Care 2003; 48(1):24-8.

(43) Warwick WJ, Wielinski CL, Hansen LG. Comparison of expectorated sputum after manual chest physical therapy and high-frequency chest compression. Biomed Instrum Techn 2004; 38(6):470-5.

(44) Lannefors L, Wollmer P. Mucus clearance with three chest physiotherapy regimes in cystic fibrosis: a comparison between postural drainage, PEP and physical exercise. Eur Respir J 1992; 5(6):748-53.

(45) van Der Schans CP, van der Mark TW, de VG, Piers DA, Beekhuis H, nkert-Roelse JE et al. Effect of positive expiratory pressure breathing in patients with cystic fibrosis. Thorax 1991; 46(4):252-6.

(46) Placidi G, Cornacchia M, Cappelletti LM, Mastella G, Assael BM, Braggion C. Short-term effects of positive airway pressure on sputum clearance by directed coughing: A cross-over, randomized study [Abstract]. Pediatr Pulmonol 2001;(Suppl 22):313-4.

(47) Konstan MW, Stern RC, Doershuk CF. Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. J Pediatr 1994; 124(5 I):689-93.

(48) Majaesic CM, Montgomery M. Reduction in sputum viscosity using high frequency chest compressions (HFCC) compared to conventional chest physiotherapy (CCP) [abstract]. Pediatric Pulmonol 1996; Suppl. 13:308.

(49) Maxwell M, Redmond A. Comparative trial of manual and mechanical percussion technique with gravity-assisted bronchial drainage in patients with cystic fibrosis. Arch Dis Child 1979; 54(7):542-4.

(50) Newhouse PA, White F, Marks JH, Homnick DN. The intrapulmonary percussive ventilator and flutter device compared to standard chest physiotherapy in patients with cystic fibrosis. Clin Pediatr (Phila) 1998; 37(7):427-32.

(51) Rossman CM, Waldes R, Sampson D, Newhouse MT. Effect of chest physiotherapy on the removal of mucus in patients with cystic fibrosis. Am Rev Respir Dis 1982; 126(1):131-5.

(52) Scherer TA, Barandun J, Martinez E, Wanner A, Rubin EM. Effect of high-frequency oral airway and chest wall oscillation and conventional chest physical therapy on expectoration in patients with stable cystic fibrosis. Chest 1998; 113(4):1019-27.

(53) Cantin AM, Bacon M, Berthiaume Y. Mechanical airway clearance using the frequencer electro-acoustical transducer in cystic fibrosis. Clin Invest Med 2006; 29(3):159-65.

(54) Hansen LG, Warwick WJ. High-frequency chest compression system to aid in clearance of mucus from the lung. Biomed Instrum Technol 1990; 24(4):289-94.

(55) Lyons E, Chatham K, Campbell I, Prescott R. Evaluation of the flutter VRP1 device in young adults with cystic fibrosis [abstract]. 11th International Cystic Fibrosis Congress; 1992; Dublin, Ireland 1992: AHP30. 92.

(56) Darbee J, Dadparvar S, Bensel K, Jehan A, Watkins M, Holsclaw D. Radionuclide assessment of the comparative effects of chest physical therapy and positive expiratory pressure mask in cystic fibrosis [Abstract]. Pediatr Pulmonol 1990; Suppl5:251.

(57) McIlwaine P, Davidson A. Comparison of positive expiratory pressure and autogenic drainage with conventional percussion and drainage therapy in the treatment of cystic fibrosis [abstract]. Proceedings of the 17th European Cystic Fibrosis Conference; 1991 Jne 18-21; Copenhagen, Denmark. 1991: S8,4.

(58) Gaskin L, corey M, Shin J, Reismann J, Thomas J, Tullis D. Long-term trial of conventional postural drainage and percussion vs. positive expiratory pressure [abstract]. Pediatr Pulmonol 1998; Suppl 17:345.

(59) Kraig R, Kirkpatrick K, Howard D, Ter-Pogossian M, Kollef M. A direct comparison of manual chest percussion with acoustic percussion, an experimental treatment for cystic fibrosis [abstract]. Am J Respir Crit Care Med 1995; 151(4):A738.

(60) Hare K, Homnick D, Cucos D, Marks J. The PercussiveTech HF device compared to standard chest phystiotherapy in hospitalized patients with cystic fibrosis [abstract]. Pediatr Pulmonol 2002; Suppl 24:315.

(61) Constantini D, Brivio A, Brusa D, Delfino R, Fredella C. PEP-mask versus postural drainage in CF infants a long-term comparative trial [abstract]. Pediatr Pulmonol 2001; Suppl 22:308, A400.

(62) Pryor J, Tannenbaum E, Cramer D, Scott S, Burgess J, Gyi K. A comparison off five airway clearance techniques in the treatment of people with cystic fibrosis [abstract]. J Cyst Fibros 2006; 5(Suppl):S76.

(63) Warick W, Wielnski C, Hansen L. Matched pair comparison of manual chest physical therapy (CPT) and the therapy bronchial drainage vest (ThBVD) system [abstract]. Pediatr Pulmonol 1990;(Suppl 5):177.

(64) Modi A, Sontag M, Koenig J, Accurso F, Quittner A, Investigators and Coordinators of the Airway Secretion Clearance Study. Adherence to airway clearance therapies in patients with cystic fibrosis [abstract]. J Cyst Fibros 2006; 5(Suppl):S97.

(65) Gotz M, Wolkerstorfer A. Physiotherapy in cystic fibrosis: Intrapulmonary percussive ventilation (IPV) versus positive expiratory pressure (PEP) [abstract]. Pediatr Pulmonol 1995; 20(Suppl 12):267.

(66) Padman R, Geouque DM, Engelhardt MT. Effects of the flutter device on pulmonary function studies among pediatric cystic fibrosis patients. Del Med J 1999; 71(1):13-8.

(67) American Thoracic Society. Secretion clearance devices: coverage policies/cost [Internet]. [updated 2009; cited 2009 Nov 5]. Available from: www.thoracic.org/sections/career-development/practitioners-page/practice-tips/articles/tip22.html

(68) California Thoracic Society. Airway clearance devices: limited evidence for what is 'the best method' [Internet]. Tustin, CA: The Society. 2009. [cited: 2009 Nov 5]. 5 p. Available from: www.thoracic.org/sections/chapters/thoracic-society-chapters/ca/publications/resources/respiratory-disease-adults/Airway%20Clearance%20Devices.pdf

(69) Statistics Canada. Population by year, by province and territory [Internet]. [updated 2009; cited 2009 May 12]. Available from: www40.statcan.gc.ca/l01/cst01/demo02a-eng.htm