

## **Appendices for On-Line supplement.**

### **Study design**

Inclusion criteria: a confirmed diagnosis of CF, FEV<sub>1</sub> > 45% predicted as calculated by Wang reference equations;<sup>1</sup> a willingness to adhere to the prescribed treatment regimen, study visits, and study procedures. Exclusion Criteria were: diagnosis of Allergic Broncho-Pulmonary Aspergillosis, positive culture for *Burkholderia cepacia* complex within the previous year; active treatment for Non-Tuberculosis Mycobacteria; use of intravenous antibiotics within the previous 14 days of enrollment; initiation and or change in maintenance therapy within 14 days of enrollment; use of systemic corticosteroids (1mg/kg if < 20 kg or 20 mg of prednisone per day) within 14 days of enrollment; concurrent participation in another interventional study; haemoptysis of over 20 milliliters on more than 2 occasions within the previous 30 days; pneumothorax in the preceding six months; or presence of a condition or abnormality that in the opinion of the site CF physician would compromise the safety of the patient.

79 participants (73%) commencing the study were using PEP as their primary airway clearance technique (ACT), although, the method of performing PEP was not standardised across the participants. Other ACTs used at enrollment included, 11 participants were using postural drainage and percussion with no tip, 5 were using oscillating PEP devices, 4 were performing the Active Cycle of Breathing Technique, 4 were performing Autogenic Drainage, 2 were using a High Frequency Chest Wall Oscillation device and 2 were primarily using exercise as their ACT. To avoid any potential bias from using PEP, we included a washout period where the participants had to change to another technique for two months prior to visit 2. At visit 2, the subjects were taught either HFCWO or PEP, both to be performed in a standard method as per study Protocol. Training had been given during the 2 day training session training given to Principal Investigators and Research Coordinators. Thus the study authors took many steps to minimise any effect from subjects entering the study using PEP. In addition in Canada as part of our Physiotherapy Standard of Care, each of the participants enrolled in the study would have known at least 1 -2 other ACTs than PEP and were not dependent on a knowledge of only one technique.

Visit 2 was the beginning of the one year study period. Assessments including pulmonary function tests, satisfaction questionnaires and health Related quality of life scores were performed at 3 monthly intervals with visit 3 at 3 months, visit 4 at 6 months, visit 5 at 9 months and visit 6 at 12 months.

### **Blinding**

Every effort was made to ensure that the Physicians and Respiratory Therapists were blinded as to which technique the study participants were performing. Any clinic papers relating to ACT had labels affixed indicating that this patient was on the Vest study, do not ask any questions about their ACT. In addition, participants were told not to divulge to anyone which ACT they were performing. Physicians were not allowed to ask the subjects which ACT technique they were doing.

### **PEP technique**

There are many PEP devices on the market. The original PEP mask was made by Astra-Meditec and consisted of an Ambu mask to which an inspiratory valve and an expiratory valve are attached. On the expiratory valve, a resistor is attached to create a back pressure of between 10 – 20 cms H<sub>2</sub>O. As the Astra-Meditec device is not available in Canada an alternative device called the TheraPEP<sup>®</sup> was used. It is based on the same physiological principle that the Astra-Meditec

uses. The TheraPEP<sup>®</sup> consists of an inspiratory one-way valve and a set of expiratory resistors. The expiratory resistor used is the one which creates a back pressure of between 10 – 20 cm H<sub>2</sub>O with tidal volume breathing. As the original PEP Mask studies were performed using a facemask and not a mouthpiece, for the purpose of this study we choose to perform PEP using a mask. This helps to ensure that a closed system was kept intact through a series of 12 – 15 breathes through the PEP mask. The regimen used is as follows: Participants were instructed to sit with back straight, and elbows resting on a table. They were asked to hold the mask tight against face with both hands and inspire a slightly larger than normal sized breath (using abdominal breathing) through the mask. They were told that expiration should be slightly active (not forced) against the mask, to create a back pressure of between 10-20 cm of water as measured by manometer. This was repeated for 15 breaths. The mask was then removed from the face and the participant instructed to perform 2 - 3 huffs from a high lung volume to a mid lung volume, followed by a cough and expectoration of any mucus produced. Participants were then to pause for one to two minutes and concentrate on doing relaxed abdominal breathing. The above procedure was to be repeated 6 times.

### **HFCWO technique**

The HFCWO device used in this study was the inCourage System (ICS)<sup>®</sup> by RespirTech. This device consists of an air-pulse generator which delivers high frequency air pulses to an inflatable vest that the subject wears. The device has two user-controlled operating adjustments: frequency and pressure. The frequency control determines the air-pulse frequency and is adjustable from 6 to 15Hz. The pressure control adjusts the amount of external chest wall pressure with mean chest wall pressure adjustable from 0 to 15 cm H<sub>2</sub>O.

The regimen used was as follows: Participants were instructed to sit comfortably wearing the appropriate size jacket (The participants brought their jacket back at each clinic visit to ensure proper sizing as the participants grew over the year). While wearing the jacket, participants were instructed to breathe normally. For the purposes of this study, the 30 minute pre-programmed ramped Quick Start Program was used. This consists of a programmed ramping up and down between the frequencies of 6 – 15 Hz over a 5-minute period with a pressure set between 60% - 80% as tolerated. This was repeated 6 times. At the end of each 5-minute period, the device automatically paused and the participants were instructed to perform 2 – 3 huffing maneuvers.

### **Data Safety Monitoring Board**

This committee operated under the FDA guidelines for the Establishment and Operation of Clinical Trial Data Monitoring Committees. The committee consisted of a CF Centre Physician who was knowledgeable with clinical trials, a research Physiotherapist with relevant expertise in the area of study and a Methodologist who was knowledgeable about statistical methods for clinical trials. They were an international group from Ireland, England and Australia. The committee were emailed after every cluster of 50 subjects have been enrolled and received SAE's at 3 monthly intervals or sooner if there are more than 10 SAE's within the 3 month period.

They communicated regularly either by email and had teleconferences as issues arose. They had a yearly face to face meeting with the study steering committee. When the DSMB noticed a disproportionate number of pulmonary exacerbations in one arm of the study compared to the

other arm, they requested an interim analysis on the pulmonary function. As there did not appear to be any differences in the pulmonary function between groups, they reported that the study could continue with the number enrolled to completion. Ethic Boards, Health Canada and the FDA were notified of the number of serious adverse events due to pulmonary exacerbations in each group. No further action was taken.

## **Adverse Events.**

A total of 363 adverse events were reported throughout the study period. All 91 patients had at least one adverse event with a median of 4 events (lower quartile: 2, upper quartile:6). A total of 41 Serious Adverse Events (28 patients) were reported throughout the study period, 25 serious adverse events were reported as pulmonary exacerbations (table 2). In terms of the relationship to the study device: 2 events were reported as related, both events occurred in the same patient (HFCWO group) and were reported as abdominal pain during treatment session. Both events were reported as mild, not serious and did not require hospitalization. One event was reported as probably related (PEP group) and consisted of persistent symptoms of an exacerbation not responding to non-pharmacological treatments. The event was reported as severe and serious and the subject was hospitalized for a pulmonary exacerbation. Seventy-six events were reported as possibly related and 284 events were reported as not related. No deaths occurred during the course of the study.

## Adverse Event Categories

### **Adverse Events**

Upper airway (cold, sore throat, sinusitis, allergy/sneezing), ear infection, runny nose and dry cough)

Lower Airway (cough, SOB, chest pain, mucus, crackles, secretions, hemoptysis, chest infection, pneumonia, de  
change in sputum, bronchospasm)

GI ( abdominal pain, nausea, vomiting, gastro)

Systemic (fever, decrease appetite, decrease exercise tolerance)

### **Serious adverse events**

Treating physician diagnosed Pulmonary Exacerbation

First Growth of Pseudomonas

Other (headache, polypectomy)

---

### **Table. Definition of a pulmonary exacerbation.**

---

The presence of a pulmonary exacerbation is established by the following:

One of the major criteria alone OR two of the minor signs/symptoms and fulfillment of symptom duration

Major Criteria: One finding alone establishes the presence of a pulmonary exacerbation

1. Decrease in FEV1 of  $\geq 10\%$  from best baseline within past 6 months, unresponsive to bronchodilator.
2. Oxygen saturation  $< 90\%$  on room air or  $\geq 5\%$  decline from previous baseline
3. New lobar infiltrate(s) or atelectasi(e)s on chest radiograph
4. Hemoptysis (more than streaks on more than one occasion in past week)

Minor Signs/Symptoms: (Two are required with duration criteria in absence of major criteria)

1. Increased work of breathing or respiratory rate
  2. New or increased adventitial sounds on lung exam
  3. Weight loss  $\geq 5\%$  of body weight or decrease across one major percentile in weight percentile for age within the past 6 months
  4. Increased cough
-

- 
- 5. Decreased exercise tolerance or level of activity
  - 6. Increased chest congestion or change in sputum
- Symptom Duration: (Required with two minor signs in absence of major criteria)  
Duration of symptoms  $\geq 3$  days or significant symptom severity.
- 

When a subject was prescribed an antibiotic, the prescribing Physician completed an antibiotic utilization form. This form included the signs and symptoms listed in the definition of a pulmonary exacerbation table above. Antibiotic Utilization form completion was also verified from source documents and from cross referencing with use of antibiotics listed under Conmeds in the Electronic database.

**Results.**

As noted in Figure 1. 133 subjects were screened and 107 subjects were enrolled into the study. There were 26 screen failures at visit 1 due to not meeting the inclusion criteria. The primary reasons were; i) Subjects were either judged not clinically stable on examination due to having a respiratory exacerbation, ii) They had a respiratory exacerbation within the previous two weeks, iii) They had a change in medications within the previous two weeks.

**Table 2A. Cystic Fibrosis Questionnaire reported for the following Domains**

	N	Physical	Emotional	Treatment burden	Respiratory	Digestion/weight
<b>PEP</b>	58	-0.84 ±3.3	0.48 ±11.9	-2.55 ±20.6	2.98 ±17.0	-3.28 ±19.0
<b>HFCWO</b>	66	-3.04 ±13.0	-3.13 ±11.6	-3.60 ±18.2	0.19 ±17.1	-2.21 25.1

Data reported as mean (SD) change from baseline (visit 2 -6) in each Domain.

1. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;15:75±88