EFFECTIVENESS OF THE FLUTTER DEVICE VERSUS THE PEP MASK IN THE TREATMENT OF ADULT CYSTIC FIBROSIS

by

Mary Ellen Newbold

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Rehabilitation Science
University of Toronto

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Effectiveness of the Flutter Device Versus the PEP Mask in the Treatment of Adult Cystic Fibrosis

Mary Ellen Newbold, M.Sc. (2001)
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University of Toronto

Purpose: The purpose of this study was to evaluate the effectiveness of the Flutter Device versus the PEP Mask in the treatment of adult Cystic Fibrosis. Methods: 42 adults mean age 29 (+/- 8.4) years participated in a 13-month randomized controlled trial. Pulmonary function tests, the Quality of Well-Being Scale (QWB) and the Chronic Respiratory Disease Questionnaire (CRQ) were administered 1-month post-recruitment and every 3 months thereafter. Results: Using linear regression, the mean slope of FEV1 % predicted was -1.97 (+/- 8.14) for the Flutter group and -4.16 (+/- 8.04) for the PEP group (p = 0.384). There was no significant difference in the slopes of the QWB (p = 0.295) or CRQ (p = 0.980) total scores. Conclusions: There was no difference in the effectiveness of the Flutter Device and the PEP Mask over a 13-month period. Large studies are needed to confirm the results of this study.

* abstract cannot exceed 150 words (School of Graduate Studies)
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- Patients of the Adult Cystic Fibrosis Clinic, St. Michael's Hospital, Toronto
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS AND SYMBOLS</td>
<td>xii</td>
</tr>
</tbody>
</table>

## 1.0 BACKGROUND INFORMATION

1.1 CYSTIC FIBROSIS

1.2 INTRODUCTION TO THE PHYSIOTHERAPY TREATMENT OF CYSTIC FIBROSIS

1.3 RESEARCH PLANS

1.4 CONVENTIONAL PHYSIOTHERAPY

1.5 THE PEP MASK
   1.5.1 Action of the PEP Mask
   1.5.2 Clinical Studies on the PEP Mask

1.6 THE FLUTTER DEVICE
   1.6.1 Action of the Flutter Device
   1.6.2 Clinical Studies on the Flutter Device

1.7 OUTCOME MEASURES IN CYSTIC FIBROSIS
   1.7.1 Definition and Properties of Outcome Measures
   1.7.2 Conceptual Framework for Outcome Measures in Cystic Fibrosis
   1.7.3 Outcome Measures in Cystic Fibrosis
1.7.4 Measures of Impairment in Cystic Fibrosis

1.7.4 a) sputum volume/weight
1.7.4 b) chest radiograph scoring systems
1.7.4 c) pulmonary function tests
1.7.4 d) exercise testing
  1.7.4 d) i) maximal exercise tests
  1.7.4 d) ii) submaximal exercise tests

1.7.5 Measures of Functioning and Disability in Cystic Fibrosis:
Health-Related Quality of Life Measures

1.7.5 a) Child Health Questionnaire
1.7.5 b) Short Form-36
1.7.5 c) Cystic Fibrosis Quality of Life Questionnaire
1.7.5 d) A new CF-specific quality of life measure
1.7.5 e) Functional Status Index
1.7.5 f) Quality of Well-Being Scale
1.7.5 g) Chronic Respiratory Questionnaire

1.7.6 Outcome Measures in Cystic Fibrosis: Concluding Remarks

2.0 METHODS

2.1 SUBJECTS

2.1.1 Sampling and Recruitment
2.1.2 Inclusion and Exclusion Criteria

2.2 OUTCOME MEASURES

2.2.1 Primary Outcome Measures
2.2.2 Secondary Outcome Measures
2.2.3 Descriptive Data

2.3 PROTOCOL

2.3.1 Baseline Assessment and Patient Instruction
  2.3.1 a) Flutter Device Technique
  2.3.1 b) PEP Mask Technique
2.3.2 Follow-up Assessments

2.4 CO-INTERVENTION AND CONTAMINATION

2.5 DATA MANAGEMENT AND ANALYSIS
3.0 RESULTS

3.1 SAMPLE CHARACTERISTICS

3.2 PRIMARY OUTCOME MEASURES
3.2.1 Mean Pulmonary Function Data at Each Follow-up Visit
3.2.2 Change in Pulmonary Function Data from Recruitment to Each Follow-up Visit
3.2.3 Change in Individual's FEV₁ % predicted From One Visit to the Next
3.2.4 Estimate of the Annual Change in Pulmonary Function Data
3.2.5 Slope of Pulmonary Function Data

3.3 SECONDARY OUTCOME MEASURES
3.3.1 Quality of Well-Being Scale
3.3.2 Chronic Respiratory Questionnaire
3.3.3 Adherence
3.3.4 Exercise
3.3.5 Number of Hospitalizations for Pulmonary Exacerbation

4.0 DISCUSSION

4.1 EFFECT ON PULMONARY FUNCTION
4.2 EFFECT ON HEALTH-RELATED QUALITY OF LIFE
4.3 EFFECT ON ADHERENCE
4.4 EXERCISE AND THE NUMBER OF HOSPITAL ADMISSIONS
4.5 LIMITATIONS OF THE CURRENT STUDY
4.6 FUTURE DIRECTIONS

REFERENCES

APPENDICES
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Summary of Studies Involving the Flutter Device</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Summary of Studies on Chest Radiograph Scoring Systems</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Summary of Studies on Maximal and Submaximal Exercise Tests</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Scoring of the CRQ</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Subject Characteristics at Recruitment (Baseline)</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>Sample Size at Each Follow-up Assessment</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>Mean Pulmonary Function Test Values at Each Follow-up Visit</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>Summary of Flutter Subjects Missing Follow-up Visits</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>Summary of PEP Subjects Missing Follow-up Visits</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>Change in Mean Pulmonary Function Data from Recruitment to each Follow-up Visit</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>Change in Individual's FEV$_1$ % predicted From One Visit to the Next</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>Mean Estimated Annual Change in Pulmonary Function Data</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>Slope of Pulmonary Function Data (by visit)</td>
<td>96</td>
</tr>
<tr>
<td>14</td>
<td>Estimated Slope of Pulmonary Function Data (for one year)</td>
<td>97</td>
</tr>
<tr>
<td>15</td>
<td>Slope of Pulmonary Function Data (for one year)</td>
<td>97</td>
</tr>
<tr>
<td>16</td>
<td>Summary of Mean Total QWB Scores</td>
<td>98</td>
</tr>
<tr>
<td>17</td>
<td>Summary of Mean QWB Symptom/Problem Scores</td>
<td>98</td>
</tr>
<tr>
<td>18</td>
<td>Summary of Mean QWB Mobility Scores</td>
<td>99</td>
</tr>
<tr>
<td>19</td>
<td>Summary of Mean QWB Physical Scores</td>
<td>99</td>
</tr>
<tr>
<td>Page</td>
<td>Summary of Mean QWB Social Scores</td>
<td>100</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>21</td>
<td>Change in QWB Scores from the First Follow-up Visit to the Final Assessment</td>
<td>100</td>
</tr>
<tr>
<td>22</td>
<td>Summary of Mean Total CRQ Scores</td>
<td>103</td>
</tr>
<tr>
<td>23</td>
<td>Summary of Mean CRQ Dyspnea Scores</td>
<td>103</td>
</tr>
<tr>
<td>24</td>
<td>Summary of Mean CRQ Fatigue Scores</td>
<td>104</td>
</tr>
<tr>
<td>25</td>
<td>Summary of Mean CRQ Emotional Function Scores</td>
<td>104</td>
</tr>
<tr>
<td>26</td>
<td>Summary of Mean CRQ Mastery Scores</td>
<td>105</td>
</tr>
<tr>
<td>27</td>
<td>Change in CRQ Scores from the First Follow-up Visit to the Final Assessment</td>
<td>105</td>
</tr>
<tr>
<td>28</td>
<td>Summary of Adherence Analysis</td>
<td>108</td>
</tr>
<tr>
<td>29</td>
<td>Summary of Analysis of Exercise Habits</td>
<td>111</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean FEV(_1) (% predicted) Over Time</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Mean FVC (% predicted) Over Time</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>A) Mean FEV(_1) (litres) Over Time</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>B) Mean FVC (litres) Over Time</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A) Mean FEF(_{25-75}%) (% predicted) Over Time</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>B) Mean FEF(_{25-75}%) (litres) Over Time</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Change in Mean FEV(_1) (% predicted) From Recruitment</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>A) Change in Mean FVC (% predicted) From Recruitment</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>B) Change in Mean FEF(_{25-75}%) (% predicted) From Recruitment</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>A) Change in Mean FEV(_1) (litres) From Recruitment</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>B) Change in Mean FVC (litres) From Recruitment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C) Change in Mean FEF(_{25-75}%) (litres) From Recruitment</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mean Total QWB Score Over Time</td>
<td>101</td>
</tr>
<tr>
<td>9</td>
<td>A) Mean QWB Symptom/Problem Score Over Time</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>B) Mean QWB Physical Score Over Time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C) Mean QWB Mobility Score Over Time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D) Mean QWB Social Score Over Time</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Mean Total CRQ Score Over Time</td>
<td>106</td>
</tr>
</tbody>
</table>
A) Mean CRQ Dyspnea Score Over Time
B) Mean CRQ Fatigue Score Over Time
C) Mean CRQ Emotional Function Score Over Time
D) Mean CRQ Mastery Score Over Time

Noncompliance with Therapy
# LIST OF APPENDICES

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Quality of Well-Being Scale</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>The Chronic Respiratory Questionnaire</td>
<td>157</td>
</tr>
<tr>
<td>3</td>
<td>Sample of a Daily Diary (one month)</td>
<td>169</td>
</tr>
<tr>
<td>4</td>
<td>Data Collection Forms</td>
<td>172</td>
</tr>
<tr>
<td>5</td>
<td>Information Form</td>
<td>179</td>
</tr>
<tr>
<td>6</td>
<td>Consent Form</td>
<td>180</td>
</tr>
<tr>
<td>7</td>
<td>Patient Instructions – Flutter Device</td>
<td>182</td>
</tr>
<tr>
<td>8</td>
<td>Patient Instructions – PEP Mask</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>Collection of Subjective Comments Regarding Therapy</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>and Other Important Notes</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>arterial blood gas</td>
<td></td>
</tr>
<tr>
<td>ACB</td>
<td>Active Cycle of Breathing</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>Autogenic Drainage</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>Autoimmune Deficiency Syndrome</td>
<td></td>
</tr>
<tr>
<td>am</td>
<td>morning</td>
<td></td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
<td></td>
</tr>
<tr>
<td>CAFT</td>
<td>Canadian Aerobic Fitness Test</td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td>Cough Clearability Index</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
<td></td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic Fibrosis Transmembrane Conductance Regulator</td>
<td></td>
</tr>
<tr>
<td>CHQ</td>
<td>Child Health Questionnaire</td>
<td></td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
<td></td>
</tr>
<tr>
<td>C-N</td>
<td>Chrispin-Norman CXR Scoring System</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>Conventional Physiotherapy</td>
<td></td>
</tr>
<tr>
<td>CRQ</td>
<td>Chronic Respiratory Disease Index Questionnaire</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>chest radiograph</td>
<td></td>
</tr>
<tr>
<td>Dco</td>
<td>single-breath diffusing capacity for carbon monoxide</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
<td></td>
</tr>
<tr>
<td>e.g.</td>
<td>for example</td>
<td></td>
</tr>
<tr>
<td>etc.</td>
<td>and so forth</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>FET</td>
<td>Forced Expiratory Technique</td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td>forced expiratory volume in one second</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
<td></td>
</tr>
<tr>
<td>FEF₂₅-₇₅%</td>
<td>mean forced expiratory flow during the middle half of FVC</td>
<td></td>
</tr>
<tr>
<td>FSI</td>
<td>Functional Status Index</td>
<td></td>
</tr>
<tr>
<td>GER</td>
<td>gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>GHPM</td>
<td>General Health Policy Model</td>
<td></td>
</tr>
<tr>
<td>HFCC</td>
<td>High Frequency Chest Compression</td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>water</td>
<td></td>
</tr>
<tr>
<td>HRQOL</td>
<td>health-related quality of life</td>
<td></td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (a unit of frequency in cycles per second)</td>
<td></td>
</tr>
<tr>
<td>ICC</td>
<td>intraclass correlation coefficient</td>
<td></td>
</tr>
<tr>
<td>ICIDH-2</td>
<td>International Classification of Functioning, Disability and Health</td>
<td></td>
</tr>
<tr>
<td>i.e.</td>
<td>that is</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>litres</td>
<td></td>
</tr>
<tr>
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<td>litres per second</td>
<td></td>
</tr>
<tr>
<td>lat</td>
<td>lateral CXR</td>
<td></td>
</tr>
<tr>
<td>ml</td>
<td>millilitres</td>
<td></td>
</tr>
<tr>
<td>ml/kg/min</td>
<td>millilitres per kilogram of total body weight per minute</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Northern CXR Scoring System</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>number of subjects or sample size</td>
<td></td>
</tr>
<tr>
<td>NIH</td>
<td>National Institute of Health CXR Scoring System</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>no significant/not significant</td>
<td></td>
</tr>
<tr>
<td>NSD</td>
<td>no significant difference</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>OCD</td>
<td>Oxygen Cost Diagram</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>level of significance (alpha), probability of rejecting a true null hypothesis (Type I Error)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>postural drainage</td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>positive expiratory pressure</td>
<td></td>
</tr>
<tr>
<td>% predicted</td>
<td>percent predicted</td>
<td></td>
</tr>
<tr>
<td>PFTs</td>
<td>pulmonary function tests</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>acid/base balance</td>
<td></td>
</tr>
<tr>
<td>pm</td>
<td>afternoon/evening</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>physical therapy or physiotherapy</td>
<td></td>
</tr>
<tr>
<td>pts</td>
<td>patients</td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
<td></td>
</tr>
<tr>
<td>QBW</td>
<td>Quality of Well-Being Scale</td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>Pearson’s correlation coefficient</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
<td></td>
</tr>
<tr>
<td>SGRQ</td>
<td>St. George’s Respiratory Questionnaire</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36</td>
<td></td>
</tr>
<tr>
<td>S-K</td>
<td>Shwachman-Kulczycki CXR Scoring System</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>statistically significant</td>
<td></td>
</tr>
<tr>
<td>SSD</td>
<td>statistically significant difference</td>
<td></td>
</tr>
<tr>
<td>VO$_2$max</td>
<td>maximal oxygen uptake</td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
<td></td>
</tr>
<tr>
<td>Wmax</td>
<td>maximum exercise capacity</td>
<td></td>
</tr>
</tbody>
</table>
yrs  
&  
~  
=  
>  
≥  
<  
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+  
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+/−  

years
and
approximately
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greater than
greater than or equal to
less than
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negative
positive
question, query	imes
with or without, plus or minus
1.0 BACKGROUND INFORMATION

This chapter provides an overview of Cystic Fibrosis (CF). Airway clearance is an important component of the treatment of CF. Done on a regular basis, it has been shown to help slow the rate of decline in lung function (Thomasi et al., 1995a; Zach, 1990). The purpose of this study was to evaluate the effectiveness of two different airway clearance techniques in the treatment of adult CF - the Flutter Device in comparison to the PEP Mask. The physiotherapy treatments of CF and the outcome measures relevant to this study are systematically reviewed.

1.1 CYSTIC FIBROSIS

Cystic Fibrosis is an inherited disease that is characterized by a defect in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) (Davis et al., 1996). CFTR is a transmembrane protein that assists with fluid balance across epithelial cells by acting as a chloride channel and by inhibiting sodium absorption (Davis et al., 1996). In CF, mutation of the CFTR causes defective chloride transport and sodium absorption across the epithelial cells of the pancreas and the respiratory, hepatobiliary, gastrointestinal and reproductive systems (Davis et al., 1996). The degree and severity of organ system involvement and clinical presentation of CF is variable depending upon the type of CFTR mutation (Davis et al., 1996). Since the discovery of the CF gene in 1989, over 400 different mutations have been identified (Davis et al., 1996).

The most serious single manifestation of CF is pulmonary disease; thick, sticky secretions reduce mucociliary clearance and eventually there is widespread small airway obstruction, air trapping and atelectasis (Jankowski, 1987). Over time, chronic obstruction and
infection of the airways cause bronchiectasis and fibrosis to develop (Jankowski, 1987). Acute pulmonary exacerbations occur throughout the course of CF (Ramsey, 1996). During these exacerbations, patients may experience such signs and symptoms as increased shortness of breath, increased cough and sputum, fever, weight loss and a decrease in pulmonary function (Ramsey, 1996). This drop in lung function may be reversible (at least partially) with therapy (Ramsey, 1996). However, patients do experience a progressive decline in pulmonary function over time (Davis et al., 1996). This eventually impacts their ability to perform everyday activities, such as work, school, caring for children, and even activities many people take for granted such as bathing independently. Complications such as massive hemoptysis and pneumothorax may also occur (Davis et al., 1996). In end stage lung disease, alveolar hypoxia causes pulmonary vascular constriction, which may eventually result in cor pulmonale (Davis et al., 1996). In summary, pulmonary disease is the primary cause of morbidity and mortality in CF (Davis et al., 1996; Ramsey, 1996).

The median survival age of people with CF has greatly improved over the last three decades. In 1960, the median survival age of a patient with CF was only six years (Tullis and Guyatt, 1995). In 1992, the Canadian Cystic Fibrosis Data Registry of the Canadian CF Foundation reported that the median survival age of a patient with CF was 32 years (National Report of the Canadian Cystic Fibrosis Data Registry, 1992). This improvement in survival is attributed to improved drug therapy, nutrition and physiotherapy (Tullis and Guyatt, 1995; Wong et al., 1993).

It is important to study the effectiveness of treatments in adults with CF because of improved survival i.e. 50% of patients with CF live beyond age 32 (National Report of the Canadian Cystic Fibrosis Data Registry, 1992). Although an estimated 70% of people are diagnosed with CF in the first year of life (Lewis, 2000), others are diagnosed later in life and
well into adulthood. Noone and Knowles (2000) stated that approximately 8% of patients are diagnosed after age 10, while D.E. Tullis stated that approximately 10% of people with CF are diagnosed over the age of 18 (personal communication, November 1999).

1.2 INTRODUCTION TO THE PHYSIOTHERAPY TREATMENT OF CYSTIC FIBROSIS

It has been shown that the removal of mucus from the airways helps slow the rate of decline in lung function (Thomas et al., 1995a; Zach, 1990). Numerous physiotherapy techniques exist whose intent is to aid secretion clearance; however, the literature supporting the efficacy of these techniques is controversial, largely due to methodological limitations. Patients are encouraged to perform some form of airway clearance one to two times per day, or more frequently at times of pulmonary exacerbation. Conventional physiotherapy, the PEP Mask and the Flutter Device are physiotherapy techniques that will be reviewed in detail in this paper.

Compliance with any physiotherapy treatment routine is an issue in the treatment of adults for several reasons. Adult lifestyles often demand independence and convenience in a treatment technique. If a patient does not adhere to an effective treatment routine because it is perceived to be too time consuming, dependent upon others, inconvenient or noisy, then it will not help them to maintain or improve their health. Most literature suggests that CF patient compliance rates range from 26 to 47% (Williams, 1994; Muszynski-Kwan et al., 1988; Passero et al., 1981). In 1994, a survey of 229 adult CF patients at the Wellesley Hospital in Toronto found that 30% of these patients were performing ineffective or no chest physiotherapy or exercise (Veress et al., 1994). This self-reported data is likely an
underestimation of the magnitude of this problem. These results demonstrate the need for an effective physiotherapy technique(s) that will be attractive to adults and thereby improve adherence.

1.3 RESEARCH PLANS

It is evident that there is a need for an airway clearance technique that is effective in slowing the rate of decline in lung function and that maximizes adherence. Many adults with CF consider conventional physiotherapy to be an unattractive option because it may cause uncomfortable side effects, it is less portable, less independent and it is often time consuming. The PEP Mask has been shown to be as effective as conventional physiotherapy (Gaskin et al., 1998; McIlwaine et al., 1997), and both it and the Flutter Device are independent and portable treatment techniques that are quite easy to learn and perform. Many adults find these techniques well suited to their busy lifestyles for these reasons.

Few patients at the Adult Cystic Fibrosis Clinic at St. Michael's Hospital in Toronto, Ontario (formerly at The Wellesley Hospital in Toronto, Ontario) were using the Flutter Device because of the lack of evidence to support its effectiveness with long-term use or as a sole method of treatment. However, patient interest and demand for this technique was strongly evident. In response to this issue, a randomized controlled trial was designed to evaluate the effectiveness of the Flutter Device in comparison to the PEP Mask. This study allowed the introduction of the Flutter Device to adult CF patients in a controlled manner using appropriate measures to evaluate outcomes.
OBJECTIVE

To evaluate the effectiveness of the Flutter Device in comparison to the PEP Mask in the treatment of adult Cystic Fibrosis.

NULL HYPOTHESES:

1. There will be no significant difference between the Flutter Device group and the PEP Mask group as measured by the effect on lung function over the study duration.

2. There will be no significant difference in the impact these techniques have on health-related quality of life as measured by the Quality of Well-Being Scale and the Chronic Respiratory Questionnaire.

3. There will be no significant difference between the two groups in the level of adherence to therapy as measured by patient diaries and subjective comments.

Conventional physiotherapy, the PEP Mask and the Flutter Device are now systematically reviewed.

1.4 CONVENTIONAL PHYSIOTHERAPY

Postural drainage and percussion/vibration are the oldest accepted methods of airway clearance used in the treatment of CF. Together they are commonly referred to as standard or conventional physiotherapy (CPT).

Postural drainage (PD) allows gravity to enhance the mucociliary escalator. There is evidence to suggest that PD is effective in those patients whose mucociliary clearance is impaired and who produce a significant amount of sputum (Thomas et al., 1995a; Bauer et al., 1994; McIntosh and Kelsey, 1990; Desmond et al., 1983; Wong et al., 1977; Blake, 1975;
Shapiro et al., 1975). Sputum production is said to be significant at a volume of greater than 30 millilitres (ml) per day (Wong et al., 1977). In CF, mucus forms and collects in the distal airways where there are greater surface tension forces. Therefore, the use of PD alone is not optimal. Percussion and/or vibration act on the thixotropic nature of mucus, and are often used in combination with PD. This helps to loosen secretions in the distal airways and move them to the upper airways where they can be coughed and expectorated (Desmond et al., 1983). The efficacy of CPT in the treatment of CF has been well documented (e.g. Thomas et al., 1995a; Reisman et al., 1988; Desmond et al., 1983). As alternative therapies have been introduced, their effectiveness has traditionally been compared to CPT.

Vibration can be performed manually or mechanically. There is no evidence in the CF literature that specifically examines the effectiveness of manual vibration on secretion clearance. However, the physiologic rationale and clinical usefulness of mechanical vibration was examined by Thomas et al (1995b) in a literature review. Articles published between 1966 and 1993 containing experimental and quasi-experimental designs were collected. Six of the 17 studies reviewed examined its effectiveness in the CF population. There is some evidence that secretion clearance may be assisted by mechanical vibration at lower frequencies (less than 60 Hz), but high frequency vibration (100 Hz) can cause adverse reactions such as decreased tidal volume and respiratory rate, and complaints of increased shortness of breath. Thomas et al. (1995b) concluded that there is insufficient evidence to support the use of mechanical vibration.

There have been reports in the literature, of patients experiencing adverse effects while performing CPT. Some studies have shown that CF patients with moderate to severe lung disease may experience oxygen desaturation (Pryor et al., 1990; McDonnell et al., 1986). There is also great debate as to whether or not PD induces or aggravates gastroesophageal
reflux (GER). Work by Button et al. (1995) has shown that CPT increases acid reflux in some infants with CF, and that modified PD positions with percussion/vibration may be more appropriate during the first year of life. Vandenplas et al. (1991) also reported that aspiration from GER may occur during the head-down PD positions. Currently there is no evidence to suggest that the possible presence of GER in an infant, child or adult should be an absolute contraindication for CPT. However, if a patient experiences either of these two adverse effects during treatment, it could be uncomfortable, detrimental to their health, and it may discourage compliance.

Thomas et al. (1995a) examined studies published between 1966 and 1993 of any combination of CPT, positive expiratory pressure therapy (the PEP Mask), the forced expiratory technique (FET, now known as the Active Cycle of Breathing or ACB), autogenic drainage (AD), or exercise. The PEP Mask will be described shortly. Briefly, the FET or ACB is a method of airway clearance that combines breathing control, deep breathing exercises and forced expirations (huffing) to mobilize secretions centrally. In AD, patients use tidal volume breaths at different lung volumes and expiratory flow rates to mobilize the mucus centrally. Thomas et al. (1995a) only included randomized controlled trials. Of the 456 citations found, 35 of these met the inclusion criteria. These studies were divided into seven different groups according to which combination of techniques they compared:

1. CPT versus no therapy
2. CPT versus the PEP Mask
3. CPT versus CPT and exercise
4. CPT versus FET
5. CPT versus cough
6. CPT versus AD
7. manual versus mechanical percussion/vibration

A meta-analysis was performed on each of these groups using the pooled effect size technique. The results showed that CPT resulted in significantly greater sputum production than no
treatment, and that CPT and exercise is associated with significant increases in FEV₁ over CPT alone. This overview found no other significant differences between the techniques compared. The investigators concluded that more research is needed to evaluate the effectiveness of these and other airway clearance techniques in the CF population.

The results of work by Bauer et al. (1994) comparing mechanical and manual percussion concurred with the findings of the four trials reviewed by Thomas et al. (1995a) in their meta-analysis. The authors noted that patient preference for one form of treatment over the other is dependent on individual perceptions of comfort, benefit and convenience.

Finally, van der Schans et al. (2001) completed a systematic review for the Cochrane Database to determine the effectiveness and acceptability of chest physiotherapy compared to no treatment or spontaneous cough alone to improve mucus clearance in CF. The airway clearance techniques considered for review were: CPT, PEP therapy, high pressure PEP therapy, ACB, AD, exercise and oscillating therapies such as the Flutter, thoracic oscillation and oral oscillation. The PEP Mask (PEP therapy) and the Flutter Device will soon be described in detail. The ACB and AD were described briefly above. High pressure PEP therapy is a modification of the PEP Mask technique. It is performed with forceful expirations through a PEP Mask to obtain high pressure (40 to 120 cmH₂O). The ThAIRapy Vest® is an example of a device that provides thoracic oscillation, or high frequency chest compression (HFCC). It consists of an inflatable vest and a large-volume variable-frequency air pulse delivery system which provides oscillation to the chest wall. Oral oscillation is an intervention that provides oscillation to the airways via the mouth. It will not be discussed further in this paper. Searches for randomized or quasi-randomized clinical trials were conducted in Medline from 1966 to February 2000, in Embase from 1974 to 1995 and from the abstract books of the three major CF conferences (the North American CF Conference, the International CF
Conference and the European CF Conference). One hundred and twenty studies were identified for potential inclusion in this review; however 107 of these could not be included because they lacked a "no treatment" or "spontaneous coughing" control group. Two of the remaining studies were not clinical trials, two used diagnoses other than CF, one did not evaluate chest physiotherapy, and one had no data. The seven remaining studies were cross-over designs with a control period, but they could not be included in this review. Hence, no randomized controlled trials or cross-over trials were eligible for inclusion in this review. Van der Schans et al. concluded that there is no good scientific evidence to support airway clearance techniques in CF. However, they did conclude that short-term cross-over trials suggest that airway clearance techniques might have beneficial effects in patients with CF.

Compliance with CPT can be poor because patients often require assistance from another person. It can be time consuming for both the patient and their helper, and it may require equipment that can be bulky, noisy, expensive, and that may require an electrical outlet. Without adherence to an effective airway clearance technique(s), the goals of maintaining or improving pulmonary health and health-related quality of life may be unrealistic.

1.5 THE PEP MASK

The PEP Mask (by Astra Meditec®) was the first device designed for positive expiratory pressure or PEP therapy. It is a portable, hand-held device that is used independently in a comfortable sitting position. Several other PEP devices have been developed in response to increased popularity and in efforts to reduce consumer costs. However, the PEP Mask has been investigated the most, and only it will be discussed in detail.

The PEP Mask consists of a mask and two one-way valves - one for inspiration and one for expiration. One of eight resistors is placed in the expiratory valve. The resistors range
in diameter from 1.5 to 5 mm, in 0.5-mm increments. In order to determine which resistor is correct, a manometer is inserted in the expiratory valve just proximal to the resistor. The patient seals the mask over his/her mouth and nose, and using tidal volume breathing, breathes in and out actively (but not forcefully) through it. The correct diameter of resistor should create a low PEP of 10 to 20 cmH\textsubscript{2}O during the middle part of exhalation. Once the proper resistor has been determined, the manometer can be removed from the system.

One treatment session consists of approximately six cycles of 10 to 15 breaths in and out through the PEP Mask, one to three forced expirations, and coughing to clear the secretions that have been mobilized to the central airways. One treatment session requires approximately 20 minutes, and it is suggested that patients perform this twice daily. There is no evidence to support the duration and frequency of this treatment.

No complications from the PEP Mask have been reported in the literature. However, it should not be used in a patient who has acute sinusitis, epistaxis, ear infection, recent facial, oral or skull surgery or injury, active hemoptysis or unresolved pneumothorax (Mahlmeister et al., 1991).

1.5.1 Action of the PEP Mask

Positive expiratory pressure therapy may stem from pursed lip breathing (Mahlmeister et al., 1991). Increased intrathoracic pressure can compress unstable airways during exhalation. Therefore, many patients with unstable airways (e.g. CF, COPD) actually discover pursed lip breathing on their own. It is believed that by breathing out through pursed lips (or a fixed resistance such as a PEP device), the expiratory airflow meets some resistance at the mouth, which transmits back pressure that splints the airways open.

Falk et al. (1984) was the first to describe PEP therapy as an airway clearance technique in CF. As a patient breathes out through a resistance, positive expiratory pressure
(PEP) is created which stabilizes the airways and prevents early airway closure. Collateral ventilation is increased and subsequently pressure builds up behind mucus obstructions. Tyrrell et al. (1986) also believed a pressure gradient builds up behind mucus plugs because more air is allowed to enter the small airways through collateral channels during inspiration than escapes during expiration. This forces mucus centrally so that it can be expectorated.

A study by Mortensen et al. (1991) evaluated the effect of the PEP Mask and several other techniques on tracheobronchial clearance in CF patients. Ten patients with CF (age range 15 to 26 years) inhaled a radioaerosol on three occasions; each separated by 48 hours. After this inhalation, each patient was randomized to 20 minutes of PEP Mask and FET, PD and FET, or spontaneous coughing in an upright position (control). Tracheobronchial clearance was measured with a gamma camera every 30 minutes for three hours after each treatment. Thirty minutes after treatment and one hour after treatment, approximately four to five times more radioactivity was cleared from the lung after PEP and FET, and PD and FET than after control. However, only PEP and FET increased clearance more than control at three hours. The authors concluded that airway clearance in CF patients is faster with 20 minutes of PEP and FET or PD and FET than with no treatment. However, no significant differences were found between the effects of PEP and FET or PD and FET.

1.5.2 Clinical Studies on the PEP Mask

As stated above, Falk et al. (1984) was the first to describe PEP (15 to 30 cm H₂O) as an airway clearance technique in CF. The acute effects of four different treatments were examined using a randomized cross-over design in 14 CF patients. The treatments compared were a) CPT, b) PD and periodic application of the PEP Mask, c) PEP Mask in a sitting position, and d) FET in a sitting position. Falk et al. found that treatments b) and c) produced more sputum than treatment d) and even more so than treatment a) (p < 0.05). They reported
that PEP therapy was well accepted by the patients, and that they consistently performed treatment c).

Davidson et al. (1988) conducted a randomized cross-over design trial to compare PEP, AD and CPT. Eighteen CF patients (divided into three groups) did each technique for two months, with one month of CPT in between each two-month trial. Pulmonary function tests were done at the start of the study and at the beginning and end of each two-month trial period. Davidson et al. reported no significant difference in pulmonary function during the study period, but that AD showed greater ability than CPT to mobilize sputum.

Steen et al. (1991) recruited 28 patients with CF (age range 8 to 21 years) to participate in a randomized cross-over trial which compared four different airway clearance regimens. The regimens evaluated were: 1) a combination of PD and FET 2) five minutes of PEP Mask followed by PD, percussion and FET 3) PEP Mask only and 4) PEP Mask and FET. Five subjects also completed a fifth treatment regimen of FET only. Each treatment program lasted one month and there were no wash-out periods between techniques. Twenty-four subjects completed the trial. There was no significant difference between any of the treatment regimens in change in pulmonary function or the weight of sputum produced within two hours post-treatment. At the end of the study, 23 of the subjects indicated that they would prefer to use a combination of PEP Mask and FET, and the authors stated that the PEP Mask should be used in conjunction with other techniques depending on the needs of the individual.

Evans and Herried (1994) randomized 15 subjects with CF to three months with both the PEP Mask and their current routine or the PEP Mask only. No significant difference was found in their pulmonary function; however patients preferred the PEP Mask.

Braggion et al. (1995) did a randomized cross-over study to examine the short-term efficacy of PEP therapy, postural drainage, high frequency chest compression and no treatment
in patients admitted to hospital for treatment of an acute pulmonary exacerbation. Sixteen patients with CF were randomized to two days per therapy. There were no reported differences in the short-term efficacy using wet and dry sputum weights as the primary outcome measures, and lung function and subjective efficacy score (patient and physiotherapist) as secondary measures.

Robins et al. (1996) reported their experience with 12 children with CF using the PEP Mask. The mean change in pulmonary function measures was not significantly different one year prior to using the PEP Mask and subsequently during one year while using the PEP Mask (spirometry was tested once per month). Robins et al. suggested that therapy with the PEP Mask was similar to CPT.

Button et al. (1998) did a study to evaluate the effects of a change from postural drainage to PEP therapy in children with CF and symptoms of gastroesophageal reflux. Six patients (mean age 13.5 +/- 2.3 years, range 10.5 to 16.0) with CF and GER were changed from their routine treatment sessions of PD, percussion, vibration, deep breathing exercises, relaxed breathing, forced expirations and coughing to the PEP Mask. Patients evaluated their symptoms of GER with a visual analogue scale from -5 for maximal discomfort to +5 for maximal comfort with therapy (0 meant indifference). All six patients reported a decrease in symptoms of GER with the PEP Mask (mean score for PD was -3.8 (range -2 to -5) versus +4.3 (range +3 to +5) for PEP Mask, p<0.001). Forced vital capacity and FEV₁ improved after patients were switched to the PEP Mask. Mean FEV₁ (percent predicted) rose from 43.8 +/-9.6 % in the six months before cessation of PD to 61.5 +/-12.7 % in the six months after PEP Mask was started (p<0.001). The improvement in lung function seemed to plateau after approximately six months of starting the PEP Mask, and was maintained for the remaining 18 months of the study period. There was also a significant reduction in the number of hospital
bed days after starting PEP Mask (PD: 105 +/- 17 (range 87-135) days per year; PEP Mask: 36 +/- 29 (range 9-83) days per year, p<0.0005). Button et al. (1998) concluded that PEP therapy may be more appropriate than PD in some patients with CF and symptomatic GER, and suggested that the role of GER in the deterioration of lung function should be further evaluated.

Wong et al. (1999) also evaluated GER during PEP therapy and CPT. Ten patients (mean age 13.2 years) with CF and suspected GER had esophageal pH monitoring for 48 hours. During this time they received two sessions of CPT (in a head down position) and two sessions of PEP therapy (in an upright position) in a randomized order. Patients were asked to huff and cough during each PD position and with each PEP cycle. The number of reflux episodes and the fractional reflux time were both increased during CPT and PEP therapy, but there was no significant difference between the two types of therapy. The authors found that the reflux episodes appeared to be associated with coughing.

McIlwaine et al. (1997) conducted a one-year trial of PD and percussion versus the PEP Mask in 40 patients with CF (22 males, age range 6 to 17 years, FEV1 range 37 to 115% predicted). The patients were paired according to their FEV1 (within 15%), sex and age (within three years) and then randomly assigned to either CPT or the PEP Mask. Thirty-six patients completed the trial, resulting in 18 subjects per treatment group. Two subjects were withdrawn because of nonattendance and two were withdrawn because they did not comply with their prescribed therapy. Patients were deemed noncompliant if they did less than 85% of twice daily therapy over a one-month period. Least squares regression was used to determine the slope for the rate of decline in the pulmonary function data. The PEP Mask group improved in % predicted FEV1 +5.98, FVC +6.57, and FEF25-75% +3.32, whereas the CPT group declined in % predicted FEV1 -2.28, FVC -2.17, and FEF25-75% -0.24. The difference
between the two groups was significant for FEV\textsubscript{1} (p = 0.04) and FVC (p = 0.02). The number of hospitalizations was not significantly different (13 for PEP group, 11 for CPT group).

McIlwaine et al. (1997) used a monthly questionnaire that asked patients about their physical activity level, impression of the physiotherapy technique, adverse reactions, how they were feeling, amount of cough and sputum, and a summary of reasons for compliance or noncompliance. Subjectively, the patients preferred the PEP Mask to CPT because they found it was easier to perform and they felt it mobilized greater quantities of sputum. They concluded that the PEP Mask was superior to CPT in maintaining lung function in CF patients, and that the patients preferred the PEP Mask due to its independence and time efficiency.

Gaskin et al. (1998) conducted a two-year randomized controlled trial of CPT versus the PEP Mask with 66 CF patients (34 males, 44 adults, mean age 21.6 years (+/- 8.3, range 11 to 45), mean FEV\textsubscript{1} 65.3 and 70.2 % predicted). Over the two-year period, the rate of decline in % predicted FEV\textsubscript{1} per year was -2.11 for the CPT group and -2.76 for the PEP group. The change in % predicted FEV\textsubscript{1} was similar when the analysis was conducted with only those subjects under 19 years of age (-1.65 % predicted per year for the CPT group and -1.58 % predicted per year for the PEP group). Gaskin et al. used the QWB as a secondary outcome measure. They reported that the baseline QWB score was similar between the PEP and CPT groups, and that there was no change in either group seen throughout the duration of the study. The authors concluded that the PEP Mask is a valid alternative to conventional physiotherapy.

1.6 THE FLUTTER DEVICE

The Flutter VRP1 Device\textsuperscript{©} (Flutter Device or Flutter) is a relatively new device for airway clearance that was developed in Switzerland in the early 1980's. The primary difference between the Flutter Device and the PEP Mask is that the Flutter Device creates
oscillating PEP. It is attractive to adults because it is used in a comfortable sitting position and it is an independent, portable and quiet technique that is easy to learn. Several other oscillating PEP devices have been developed in response to increased popularity. However, the Flutter Device has been investigated the most, and only it will be discussed in detail.

The Flutter is a pipe-like device that contains a cone and a steel ball, and it has a perforated cover. As a patient breathes out through the Flutter, the expiratory airflow against the ball creates PEP. Positive expiratory pressure builds and pushes the ball up towards the perforated cover. The expiratory pressure then decreases and the ball drops. This cycle happens repeatedly in each exhalation, creating an oscillation in endobronchial pressure and intermittent accelerations in expiratory airflow. This is the "flutter" effect (McIlwaine et al., 2001).

One treatment session with the Flutter Device takes approximately 20 minutes, during which the following cycle is repeated numerous times. The first stage of each cycle is referred to as the "loosening" breaths. The patient inhales deeply and holds his/her breath for two to three seconds, and then actively (but not too forcefully) exhales through the Flutter, slightly further than one would exhale during a normal breath. These "loosening" breaths are repeated five to 15 times. After this, the patient is instructed to take one to three deep breaths (filling their lungs completely), and exhale more quickly and forcefully through the Flutter. This may precipitate coughing. If no coughing is precipitated, the patient should cough purposefully and clear any secretions that have been mobilized to the central airways. With each breath out through the Flutter, the patient should keep his/her cheeks as stiff as possible, and the patient should adjust the degree of tilt of the Flutter at the mouth in order to maximize the vibrations that are felt within the airways. Patients are advised to perform this technique twice daily. There is no evidence to support the duration and frequency of this treatment.
No adverse effects of Flutter use have been reported in the literature. Although not
reported in the literature, similar to the PEP Mask, the Flutter should likely not be used by an
individual with acute sinusitis, ear infection, epistaxis, recent facial, oral or skull surgery or
injury, active hemoptysis or unresolved pneumothorax.

1.6.1 Action of the Flutter Device

There is disagreement in the literature regarding the amount of PEP, the frequency of
oscillation and the variability of the airflow that is created with the Flutter. McIlwaine et al.
(2001) stated that the PEP varies between 0.8 and 25 cm H₂O, Homnick et al. (1998) stated
that it varies between approximately 10 to 25 cm H₂O, while Newhouse et al. (1998) stated that
it varies between approximately 20 to 25 cm H₂O. Langenderfer (1998) stated that the Flutter
creates an intermittent PEP of approximately 18 to 22 cm H₂O, that may go up to 35 cm H₂O
with a forced expiration. Blackney and Chipps (1999) reported that the peak pressure for the
Flutter Device ranges from 20 to 24 cm H₂O, that the pressure amplitude ranges from 2 to 5 cm
H₂O, and that the frequency of oscillation ranges from 1200 to 1800 cycles per minute.
Lindemann (1992, from App et al., 1998) stated that the oscillation frequency is dependent on
the airflow through the device and the angle at which the Flutter is used. Further research is
required to clarify the relationship between the angle of inclination of the Flutter at the mouth,
airflow and the PEP and oscillation frequency produced.

<table>
<thead>
<tr>
<th>Angle of the Flutter</th>
<th>Expiratory Pressure (cm H₂O)</th>
<th>Oscillation Frequency (Hz)</th>
<th>Airflow (L/second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 30 degrees</td>
<td>12 - 75</td>
<td>15 - 32</td>
<td>1.6 - 5.5</td>
</tr>
<tr>
<td>0 degrees</td>
<td>10 - 70</td>
<td>9 - 22</td>
<td>1.6 - 5.5</td>
</tr>
<tr>
<td>- 30 degrees</td>
<td>8 - 60</td>
<td>2 - 10</td>
<td>1.6 - 5.5</td>
</tr>
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The theory behind the Flutter is that PEP stabilizes the airways and prevents early airway closure, and the oscillations or interruptions of expiratory airflow help to mechanically rupture the rigid mucus gel and thus reduce its viscoelasticity (App et al., 1998; Dasgupta et al., 1998).

App et al. (1998) studied the effect of the Flutter on CF sputum in both an in vivo and an in vitro experiment. The in vivo experiment was a randomized cross-over design that evaluated the effect of the Flutter versus AD on the sputum viscoelasticity of CF patients. Fourteen CF patients did Flutter or AD treatment twice daily for four weeks with a one-week wash-out period prior to each therapy interval. Sputum was collected after each therapy session and its viscoelasticity was evaluated using a magnetic microrheometer. The findings revealed that the sputum viscoelasticity was significantly lower after therapy with the Flutter than after AD (p < 0.01). Therefore, App et al. suggested that the Flutter Device is capable of reducing the viscoelasticity of sputum in vivo, and thus improving airway clearance. In the in vitro experiment, humidified air was passed through a Flutter Device over CF sputum lining an acrylic tube. The generated flow rate was approximately 1.5 L/second and the median frequency of oscillation was 19 Hz. Sputum elasticity was measured by a filancemeter. The results showed that sputum elasticity was significantly decreased by the oscillations generated by the Flutter at 15 and 30 minutes (p < 0.001). The decrease was greater after 30 minutes than after 15 minutes (p < 0.01). App et al. stated that the mechanism(s) for the reduction in viscoelasticity by mechanical oscillation are unknown. However, they suggested that it may involve the disruption of the physical entanglements of the mucus glycoproteins and other macromolecules, the disruption of disulfide bridges, or even the break-down of larger molecules such as DNA (deoxyribonucleic acid) or F-actin, which are present in CF sputum as a byproduct of infection and which increase the viscoelasticity of mucus. App et al. concluded
that applied oscillations are capable of decreasing mucus viscoelasticity at frequencies and amplitudes achievable with the Flutter Device.

Dasgupta et al. (1998) also conducted an in vitro study on the Flutter and its effect on the viscoelasticity of the sputum of CF patients. Similar to the study by App et al. (1998), humidified air was passed through a Flutter Device at 1.5 L/second. The Flutter was kept at an elevation of 30 degrees above horizontal, and the oscillation frequency was approximately 19 Hz with an amplitude of +/- 0.5 L/second. Dasgupta et al. also used a control which was the same set up but with the steel ball removed from the Flutter. The viscoelasticity of the mucus was measured with a magnetic micro rheometer. Mucus rigidity was defined as the vector sum of viscosity and elasticity reported in a log scale, and the loss tangent was defined as the ratio of viscosity to elasticity. The cough clearability index, or CCI (a derived parameter) was calculated from the mucus rigidity and loss tangent data. The calculation of CCI is based on relationships established in in vitro experiments involving mucus clearance in model studies of simulated cough. Dasgupta et al. found that the use of 30 minutes of Flutter oscillations on CF sputum samples resulted in only small, nonsignificant decreases in mucus rigidity compared to baseline (p = 0.19), and nonsignificant changes in CCI (p = 0.39). However, they concluded that the changes in the viscoelasticity of Flutter treated sputum are related to the oscillations of airflow generated through the Flutter. Similar to App et al., Dasgupta et al. assumed that the oscillations produced by the Flutter physically break the macromolecular backbone linkages and/or disrupt the physical entanglements of the viscous mucus gel. A decrease in mucus rigidity is related to a lower viscoelasticity, and is predictive of enhanced mucus clearance from the lungs of CF patients. The authors discussed the fact that the model they used did not incorporate a flexible wall, as airway walls are flexible. For example, during a cough, the pressure outside the airways becomes greater than the pressure inside the airways, and the
airway walls are pushed inwards. This can accelerate airflow and enhance clearance. Therefore, a greater effect on the viscoelasticity of sputum might be seen in a flexible wall model. However, Dasgupta et al. believed that the PEP feature of the Flutter would counteract this and minimize airway collapse, and they anticipated that the oscillations would be dampened as they are transmitted down the airways. Finally, they stated that further in vivo evaluation of the Flutter Device is needed.

1.6.2 Clinical Studies on the Flutter Device

The trials completed to assess the effectiveness of the Flutter have been limited to date. The characteristics of studies involving the Flutter Device are presented in Table 1. The methodological quality of most of these studies is flawed due to small sample sizes, short study durations, unreliable outcome measures and poorly described methods and patient characteristics. Until further research is completed on the Flutter Device, evidence-based decisions can not be made.

Of note, McIlwaine et al. (2001) conducted a one-year randomized controlled trial comparing the PEP Mask to the Flutter Device with 40 CF patients (age range 7 to 17 years, 24 boys, FEV₁ 47 to 107 % predicted). All of the subjects were using the PEP Mask before the study began. Three patients were withdrawn from the PEP group either because of noncompliance with treatment or nonattendance at clinic. Noncompliance was defined as per the CPT versus PEP study by McIlwaine et al. (1997) i.e. noncompliance was defined as less than 85% adherence to twice daily physiotherapy over a one-month period. Five patients in the Flutter group withdrew themselves from the study because they felt the Flutter was ineffective. McIlwaine et al. (2001) reported that these five patients had a mean decline in FEV₁ of -10.0 % predicted at the time of withdrawal. The results for the 32 subjects who completed the trial
were that FVC decreased significantly more in the Flutter group (-8.62 +/- 15.5 % predicted) than in the PEP group (+0.06 +/- 7.9 % predicted) (p = 0.05). The Flutter group had a greater decline in FEV₁ and FEF₂₅₋₇₅% than the PEP group; however this difference was not significant (p = 0.08). The mean annual rate of decline in FEV₁ % predicted was -10.95 (+/- 19.96) % predicted for the Flutter group and -1.24 (+/- 9.9) % predicted for the PEP group. The slope of FEF₂₅₋₇₅% % predicted was -8.87 (+/- 20) % predicted for the Flutter group and -3.58 (+/- 15.49) % predicted for the PEP group. The number of hospital admissions due to pulmonary exacerbation was significantly different between the two groups: 18 for the Flutter group versus five for the PEP group (p = 0.03). The level of compliance (recorded by patients with a diary) was reported as 95.6% in the PEP group and 93.8% in the Flutter group. Therefore, McIlwaine et al. (2001) concluded that the PEP Mask is more effective at maintaining pulmonary function and that it is less costly than the Flutter Device.
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>n</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindemann 1992</td>
<td>randomized cross-over</td>
<td>A Flutter B autogenic drainage</td>
<td>sputum weight</td>
<td>20 CF</td>
<td>1 treatment</td>
<td>NSD between A or B</td>
</tr>
<tr>
<td>Lyons et al. 1992</td>
<td>randomized cross-over</td>
<td>A ACB B Flutter C Flutter &amp; ACB D Sham Flutter &amp; ACB</td>
<td>sputum weight peak expiratory flow visual analogue scale of subjective findings</td>
<td>12 CF</td>
<td>4 days (1 day per technique)</td>
<td>SSD less sputum weight produced with B NSD in other measures</td>
</tr>
<tr>
<td>Girard and Terri 1994</td>
<td>one group pretest-posttest</td>
<td>Flutter</td>
<td>FEV₁, FVC, peak expiratory flow subjective reports</td>
<td>20 asthma</td>
<td>30 to 45 days</td>
<td>SSD improvement in all measures</td>
</tr>
<tr>
<td>Greger et al. 1994</td>
<td>1. Daily cross over 2. One group pretest-posttest</td>
<td>1. Flutter +/- inhalation therapy 2. Flutter</td>
<td>pulmonary function values, specific airway flow resistance &amp; conductance</td>
<td>10 asthma</td>
<td>1. 1 treatment 2. 3 to 4 days</td>
<td>1. No significant influence on basal obstruction 2. No increase in bronchial hyperreactivity</td>
</tr>
<tr>
<td>Konstan et al. 1994</td>
<td>randomized A B C (6 possible sequences)</td>
<td>A cough B PD, with 1 minute percussion/vibration C Flutter</td>
<td>sputum weight (wet &amp; dry)</td>
<td>17 CF (age 8 to 38)</td>
<td>patients came 3 times/week &amp; did A, B, C in random order, in 2nd week the order was reversed (2 weeks total)</td>
<td>SSD C &gt; A or B NSD between A or B</td>
</tr>
<tr>
<td>Pryor et al. 1994</td>
<td>randomized cross-over</td>
<td>A ACB plus Flutter B ACB</td>
<td>pulmonary function oxygen saturation sputum weight subjective report</td>
<td>20 CF</td>
<td>1 day per technique</td>
<td>SSD in pulmonary function, 24 hour sputum weight or oxygen saturation SSD in sputum weight B&gt;A during treatment 17/20 preferred B</td>
</tr>
<tr>
<td>Swift et al. 1994</td>
<td>one group pretest-posttest</td>
<td>A Baseline B Flutter C Sham Flutter</td>
<td>peak expiratory flow amount of salbutamol required subjective report</td>
<td>20 asthma</td>
<td>3 weeks (1 week per arm)</td>
<td>NSD in PEFR or salbutamol required B subjectively useful by 6th day</td>
</tr>
</tbody>
</table>
Table 1: Summary of Studies Involving the Flutter Device

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</thead>
<tbody>
<tr>
<td>Bodie et al. 1995</td>
<td>single case alternating A, B or B, A</td>
<td>A conventional PT B Flutter</td>
<td>sputum volume patient preference</td>
<td>4</td>
<td>24 hour period</td>
<td>sputum volume produced by B &gt; that produced by A patients preferred B</td>
</tr>
<tr>
<td>Ambrosino et al. 1995</td>
<td>randomized cross-over B Flutter</td>
<td>A conventional PT B Flutter</td>
<td>expiratory flows oxygen saturation sputum volume visual analogue scale of sense of congestion</td>
<td>14 non-CF who produce sputum (&gt;25 mL/day)</td>
<td>2 sessions per treatment</td>
<td>NS difference between A or B B as effective as A in relieving symptoms of chest congestion</td>
</tr>
<tr>
<td>Geouque and Engelhardt 1998</td>
<td>A B C</td>
<td>A Flutter B conventional PT C PEP therapy</td>
<td>pulmonary function resp assessment (resp rate, oxygen saturation, cough, auscultation, general comments)</td>
<td>6 CF</td>
<td>1 month per therapy</td>
<td>NSD between A, B or C patients preferred A</td>
</tr>
<tr>
<td>Giles et al. 1996</td>
<td>randomized cross-over with 2 week washout period A Flutter B conventional PT</td>
<td>A Flutter B conventional PT</td>
<td>pulmonary function sputum weight (wet &amp; dry) subjective questionnaire</td>
<td>14 CF</td>
<td>4 weeks per therapy</td>
<td>SSD in FVC with A &gt; pre-study NSD in other measures patients preferred A</td>
</tr>
<tr>
<td>Gondor et al. 1996</td>
<td>randomized controlled A Flutter B conventional PT</td>
<td>A Flutter B conventional PT</td>
<td>pulmonary function exercise tolerance (6-minute walk test) health-related quality of life (QWB scale)</td>
<td>14 CF</td>
<td>14 days</td>
<td>NSD between A or B</td>
</tr>
<tr>
<td>Hornick and Marks 1996</td>
<td>randomized controlled A Flutter B conventional PT</td>
<td>A Flutter B conventional PT</td>
<td>pulmonary function in hospital for acute pulmonary exacerbation</td>
<td>14 CF</td>
<td>duration of hospital admission</td>
<td>NSD between A or B</td>
</tr>
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<tr>
<td>Newhouse et al. 1998</td>
<td>randomized cross-over</td>
<td>A Flutter B conventional PT C Intrapulmonary Percussive Ventilator</td>
<td>pulmonary function (done pre-, 1- &amp; 4- hours post-treatment) oxygen saturation (during treatment) sputum weight (wet, collected over 4-hour period post-treatment)</td>
<td>8 CF (age 9 to 25)</td>
<td>1 session per treatment, on 3 separate days during 3 successive weeks</td>
<td>SS increase from baseline in: FVC with A at 1 hour, FEV₁ with A &amp; C at 1 hour, FEV₁ with A at 4 hours. NSD in sputum weight between treatments at 4 hours NSD in pulmonary function between treatments at 1 and 4 hours trend (NS) to transiently lower oxygen saturation with B, neither severe nor prolonged</td>
</tr>
<tr>
<td>van Winden et al. 1998</td>
<td>randomized cross-over</td>
<td>A Flutter with FET B PEP Mask with FET (patients did FET during washout periods)</td>
<td>pulmonary function oxygen saturation peak expiratory flow symptoms</td>
<td>22 CF (age 7 to 17)</td>
<td>Flutter or PEP Mask 2 times/day for 2 weeks with a 1 week washout period before each session</td>
<td>NSD in pulmonary function after a single session or after 2 weeks with either A or B no difference in acceptability or subjective efficacy (10 preferred B, 11 preferred A) NSD between A or B in oxygen saturation before or after therapy</td>
</tr>
<tr>
<td>App et al. 1998</td>
<td>randomized cross-over</td>
<td>A autogenic drainage B Flutter</td>
<td>FEV₁, FVC sputum volume &amp; weight sputum viscoelasticity (using a magnetic micrometer)</td>
<td>14 CF (age 7 to 41)</td>
<td>4 weeks per therapy with a 1 week washout period before each session</td>
<td>NS changes in FEV₁, FVC or sputum volume sputum viscoelasticity was significantly lower after therapy with B versus A</td>
</tr>
<tr>
<td>Hornick et al. 1998</td>
<td>1st subject randomized, then alternate assignment to A or B</td>
<td>A Flutter B conventional PT</td>
<td>pulmonary function (done on admission, weekly &amp; at discharge) Swachman score (done at admission &amp; discharge)</td>
<td>22 CF in hospital for acute pulmonary exacerbation, total of 33 hospitalizations (age 8 to 44)</td>
<td>duration of hospital admission</td>
<td>significant improvement in pulmonary function and Swachman score in both A &amp; B from admission to discharge NSD between A or B in amount of improvement</td>
</tr>
<tr>
<td>Author</td>
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</table>
| Dasgupta et al. 1998 | in vitro          | A baseline - no treatment applied  
B 30 minute application of oscillations generated by airflow through the Flutter (~19 Hz, flow rate 1.5 L/sec, amplitude +/- 0.5 L/sec, Flutter at +30 degrees)  
C incubation with a mucolytic (rhDNase)  
D combination of Flutter oscillations & normal saline  
E combination of Flutter oscillations & mucolytic (rhDNase) | sputum rigidity (viscosity & elasticity)  
cough clearability index (predicted from sputum rigidity & models with simulated cough) | sputum samples from 19 CF (age 18 to 37) divided into smaller samples for study | n/a            | B & C alone did not result in a significant reduction in the rigidity of CF sputum  
E significantly reduced sputum rigidity  
predict increased clearability of sputum  
D did not significantly change sputum rigidity  
NSD change in cough clearability with B or C  
SS change in cough clearability with E |                                                                                                                                     |
| Gondor et al. 1999    | randomized controlled | A conventional PT  
B Flutter | pulmonary function  
6-minute walk test | 23 CF in hospital for acute pulmonary exacerbation (age 5 to 21) | conventional PT or Flutter 4 times/day for 14 days | B had higher FEV₁ and FVC than A after 1 week of treatment  
NSD between A or B after 2 weeks of treatment |                                                                                                                                     |
| Padman et al. 1999   | randomized A B C | A Flutter  
B PEP therapy  
C conventional PT | pulmonary function  
resp assessment (resp rate, heart rate, oxygen saturation, auscultation, cough, medications)  
subjective comments compliance (home tracking log) | 6 CF (age 5 to 17) | 3 treatments per day, 1 month per therapy (washout period with C, time not defined) | NS changes in pulmonary function, resp assessment  
all patients preferred the "new therapies" A & B - "felt physically better, able to expectorate mucus more easily, felt more in control of their therapy"  
compliance results (from home tracking log) not given |
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</tr>
</thead>
<tbody>
<tr>
<td>McIlwaine et al. 2001</td>
<td>randomized controlled</td>
<td>A Flutter B PEP Mask</td>
<td>FEV₁, FVC, FEF₂₅₋₇₅% number hospital admissions due to pulmonary deterioration compliance</td>
<td>32 CF</td>
<td>1 year</td>
<td>FVC decreased significantly more in group A: -8.62 (±/-15.5) % for A versus +0.06 (±/-7.9) % for B (p = 0.05) greater decrease in FEV₁ in group A but NSD: -10.95 (±/-19.96) % for A versus -1.24 (±/-9.9) % for B (p = 0.08) greater decrease in FEF₂₅₋₇₅% in group A but NSD: -8.87 (±/-20) % for A versus -3.58 (±/-15.49) % for B (p = 0.08) A required 18 admissions, B required 5 admissions level of compliance: 93.8% for A versus 95.6% for B</td>
</tr>
</tbody>
</table>

**Legend:**
- NS = no significant
- SS = statistically significant
- NSD = no significant difference
- SSD = statistically significant difference
- > = greater than
- & = and
The next section briefly reviews the definition and properties of outcome measures, a conceptual framework for outcome measures in CF, what outcome measures are commonly used in CF practice and research, and finally, which outcome measures were chosen for this study.

1.7 OUTCOME MEASURES IN CYSTIC FIBROSIS

1.7.1 Definition and Properties of Outcome Measures

An outcome measure is defined as a measurement tool (such as an instrument, questionnaire or rating form) that is used to document change in one or more patient characteristics over time (Cole et al., 1994). When choosing a measure for clinical or research purposes, the following properties should be considered: the purpose of its use, the population it is intended for, the time it takes to complete, the cost, what training is necessary, and the scaling and scoring of the tool (Cole et al., 1994). Most importantly, a measure should possess the following properties: reliability, validity, and responsiveness (Cole et al., 1994). These concepts will be introduced briefly; however the different procedures used for evaluating and expressing these properties will not be reviewed in this paper.

Reliability is a fundamental way to reflect the amount of error, random and systematic, inherent in any measure (Streiner and Norman, 1995). Reliability can be reported in several ways; however the most appropriate form of the reliability coefficient can be debated (Streiner and Norman, 1995). The classic definition of reliability is the ratio of variance between patients to error variance (Streiner and Norman, 1995). This coefficient is known as an intraclass correlation coefficient or ICC. A measure will have a certain degree of reliability when applied to specific populations under specific conditions (Streiner and Norman, 1995). Test-retest reliability is the degree to which scores are stable or consistent over time (Currier,
Intra-rater reliability measures the degree of agreement between observations made by the same rater on two different occasions, and inter-rater reliability indicates the amount or degree of agreement between observers (Currier, 1990). For the purpose of this paper, Pearson correlation coefficient and ICC values above 0.75 were considered indicative of good reliability (Streiner and Norman, 1995; Portney and Watkins, 1993b), values between 0.40 and 0.75 moderate reliability (Portney and Watkins, 1993b), and values below 0.40 poor reliability.

Internal consistency is another form of reliability (Streiner and Norman, 1995). It refers to the way individual items of the measure correlate with each other and with the total score (Streiner and Norman, 1995). Measures of internal consistency (Cronbach's alpha for example) represent the average of the correlations among all the items in a measure (Streiner and Norman, 1995). If the internal consistency is too high, it may suggest that items are redundant, and therefore that some items are unnecessary (Streiner and Norman, 1995).

Validity is the extent to which a test measures what it is intended to measure (Streiner and Norman, 1995). It concerns the objectives of a test and the ability to make inferences from test scores or measurements (Portney and Watkins, 1993a). A measure must be reliable (i.e. relatively free from error) in order to be valid, but a test with strong reliability does not necessarily have strong validity (Portney and Watkins, 1993a). In other words, a test with low reliability will automatically have low validity, whereas a test with strong reliability does not necessarily have strong validity (Portney and Watkins, 1993a).

There are generally four types of validity: face validity, content validity, criterion validity and construct validity (Portney and Watkins, 1993a). These various types of validity all address the same issue, that is, the degree of confidence that can be placed in the inferences that are drawn from test results (Streiner and Norman, 1995). The choice of which type of validity is required depends on the purpose of the instrument (Portney and Watkins, 1993a).
For some tests, more than one type of validity will be used (Portney and Watkins, 1993a). Face validity is a judgement whether the instrument appears to be assessing the desired qualities, while content validity is a judgement whether the instrument samples all the relevant content or domains (Streiner and Norman, 1995). Criterion validity is the correlation of a scale with some other measure that evaluates the same trait, ideally a "gold standard" criterion which is accepted in the area (Streiner and Norman, 1995). There are two different types of criterion validity, concurrent and predictive (Streiner and Norman, 1995). When the new measure and the criterion measure are given and correlated at relatively the same time, it is considered concurrent criterion validity (Streiner and Norman, 1995). With predictive criterion validity, the criterion is not available until some time in the future, i.e. one must wait for the criterion to confirm or disconfirm the predictions (Streiner and Norman, 1995). Construct validity is used when no other criterion or measure exists (Streiner and Norman, 1995). The attribute being measured is linked to a hypothesis/theory/construct, and tests are done to see if the expected relationships are found between the measure and the hypothesis/theory/construct (Streiner and Norman, 1995). Therefore, content validity is part of construct validity, because the content that represents a construct must be defined (Portney and Watkins, 1993a). Construct validation is never fully achieved because of the abstract nature of constructs (Portney and Watkins, 1993a). Work to validate an instrument provides evidence to support or refute the theory behind the construct (Portney and Watkins, 1993a). Some authors have evaluated longitudinal validity by correlating the change in one measure with the change in another measure (P. Stratford, personal communication, August 2001). In this paper, these correlations will be discussed under validity. However, there is some controversy regarding correlating changes in one measure with changes in another measure, as this may threaten the assumption of independence inherent in correlation analysis.
The terms responsiveness and sensitivity have both been used to refer to the ability of a measure to detect statistically significant change or the effect of a treatment (Streiner and Norman, 1995). However, these terms have also been defined as a measure’s ability to detect clinically important change, even if that change is small (Beaton et al., 1997; Wright and Young, 1997; Liang, 1995; Guyatt et al., 1989a; Kazis et al., 1989). Therefore, a distinction can be made between statistically significant change and clinically important change. A measure that detects statistically significant change may not detect clinically important change (change that is important to patients/providers), and conversely, change that may be clinically important may not always be statistically significant (Wright and Young, 1997; Liang, 1995; Kazis et al., 1989). Liang (1995) distinguished the terms sensitive versus responsive. He stated that statistical techniques capture whether a measure is sensitive i.e. whether it detects any statistical change, but that they are not good at capturing responsiveness to a clinically meaningful or important change i.e. distinguishing clinically relevant change from irrelevant change (Liang, 1995). There is no "gold standard" or consensus on what methods/statistics should be used to evaluate responsiveness (Beaton et al., 1997; Liang, 1995; Streiner and Norman, 1995; Guyatt et al., 1989a). However, change scores and a form of effect size, that is, the observed change divided by some measure of variance, are generally reported (Kazis et al., 1989; Cohen, 1988). Responsiveness may also be considered a specific form of validity i.e. validity is whether a measure detects what it is supposed to detect, and measures are supposed to pick up clinical change (D. Beaton, personal communication, 1998).

In summary, clinicians and researchers must consider the psychometric properties of outcome measures and choose the best possible outcome measure for their population and purpose(s).
1.7.2 Conceptual Framework for Outcome Measures in Cystic Fibrosis

The World Health Organization (WHO) published a pre-final draft of the International Classification of Functioning, Disability and Health (ICIDH-2) in December 2000. The purpose of the ICIDH-2 is to provide a standard framework and common language for the description of health and health-related states (World Health Organization, 2000).

The ICIDH-2 organizes information in two parts: functioning and disability, and contextual factors. Functioning and disability is broken down into two components: body functions and structure, and activities and participation. Body functions are the physiological functions of body systems (including psychological functions). Body structures are anatomical parts of the body such as organs and limbs. Activity is the execution of a task or action by an individual, and participation is involvement in a life situation. Impairments are defined as problems in body function or structure. Activity limitations are difficulties an individual may have in executing activities, and participation restrictions are problems an individual may experience in involvement in life situations. To summarize, functioning refers to all body functions and structures, activities and participation (non-problematic aspects of health or health-related states), while disability refers to impairments, activity limitations or participation restrictions (problems). Contextual factors consist of personal factors and environmental factors (both in an individual’s immediate and general environment) that can facilitate or hinder functioning and disability.

The ICIDH-2 considers an individual’s functioning and disability as an interaction between health conditions (diseases, disorders, injuries, etc.) and contextual factors. The ICIDH-2 will be used as the conceptual framework with which the outcome measures will be discussed.
1.7.3 **Outcome Measures in Cystic Fibrosis**

Numerous outcome measures have been employed in CF practice and research throughout the years. Some of these outcome measures have been validated for use in this special population, while others have been examined to a lesser extent. This section reviews the outcome measures used in this study, specifically pulmonary function tests and two health-related quality of life measures - the Quality of Well-Being Scale (QWB) and the Chronic Respiratory Questionnaire (CRQ). Outcome measures not used in this study (i.e. sputum volume/weight, chest radiograph scoring systems, exercise tests and other health-related quality of life measures) will be discussed briefly.

1.7.4 **Measures of Impairment in Cystic Fibrosis**

Sputum volume/weight, chest radiograph scores, pulmonary function tests and exercise tests are outcome measures that attempt to provide information related to an individual's level of impairment secondary to CF.

1.7.4 a) **Sputum Volume/Weight**

Sputum volume and/or weight have been used as outcome measures in many studies regarding CF and other pulmonary diseases. However, there are many discrepancies in the way this data is collected, and no studies have been published that report the reliability, validity or responsiveness of sputum volume/weight as an outcome measure. It is a poor outcome measure of impairment as it is impossible to know what change in volume/weight reflects a true change in impairment.

1.7.4 b) **Chest Radiograph Scoring Systems**

The pathophysiology of the respiratory disease in CF is reflected in radiographic changes (Ruzal-Shapiro, 1998). Chest radiographs (CXRs) may help in the diagnosis of CF, and they play a role in the longitudinal assessment of patients (Ruzal-Shapiro, 1998).
However, the rate of progression of CF is highly variable, both clinically and radiographically, and a CXR may not change even with acute clinical exacerbations (Ruzal-Shapiro, 1998). Chest radiograph scoring systems have been created to help quantify the lung abnormalities (i.e. impairment) that occur secondary to pulmonary disease (Eichner et al., 1996). However, they have not been shown to be helpful in defining acute clinical exacerbations (Ruzal-Shapiro, 1998).

The CXR scoring systems used most frequently in clinical practice and research in CF are the Brasfield, the Wisconsin, the Shwachman-Kulczycki, the Chrispin-Norman, the Northern, and the National Institute of Health CXR scoring systems (e.g. Hyland et al., 1995; Conway et al., 1994; Wong et al., 1993; Te Meermann et al., 1985). The results of numerous studies on these CXR scoring systems are summarized in Table 2. Some authors suggest that CXR scoring systems are not as sensitive as pulmonary function tests in detecting small changes in pulmonary status (Grum and Lynch, 1992; Rosenberg et al., 1992), and that CXR changes may lag behind or not even agree with changes detected by pulmonary function tests (Hyland et al., 1995; Grum and Lynch, 1992; Rosenberg et al., 1992; O’Laoide et al., 1991). They may, however, be useful in infants and children who are too young to perform pulmonary function tests.
<table>
<thead>
<tr>
<th>Study</th>
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<th># of CXRs scored</th>
<th>Assessors</th>
<th>Inter-Rater Reliability</th>
<th>Intra-Rater Reliability</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brasfield et al. 1979</td>
<td>Brasfield Shwachman-Kulczycki (S-K) PFTs (on 95 pts)</td>
<td>643 CXRs 118 CF patients</td>
<td>1 pediatric radiologist, 2 physicians from Birmingham (blinded)</td>
<td>* average correlation between 3 Birmingham physicians $r = 0.91$</td>
<td>* correlation between Brasfield and FVC $r = 0.68$ S-K score $r = 0.82$</td>
<td></td>
</tr>
<tr>
<td>Brasfield et al. 1979</td>
<td>Brasfield S-K PFTs</td>
<td>rescored 20 of the above CXRs 1 year later</td>
<td>* 1 radiologist &amp; 2 physicians from Birmingham * radiologists &amp; physicians from 3 other cities or institutions (blinded)</td>
<td>* average correlation among cities/institutions $r = 0.81$ (range 0.63 to 0.93) * correlation between raters in: Birmingham $r = 0.93$ Chicago $r = 0.84$ New York $r = 0.80$ Baltimore $r = 0.85$</td>
<td>* average correlation of 3 raters from Birmingham $r = 0.91$</td>
<td></td>
</tr>
<tr>
<td>Brasfield et al. 1980</td>
<td>Brasfield</td>
<td>40 CXRs, scored on 2 occasions</td>
<td>* 5 large centres: pediatric radiologist, 1 pediatrician *10 small centres: 1 pediatrician * Birmingham: 2 observers (blinded)</td>
<td>* btw Birmingham observers $r = 0.94$ * btw radiologists &amp; Birmingham observers $r = 0.88$ * btw pediatricians &amp; Birmingham observers large centres: $r = 0.85 &amp; 0.85$ small centres: $r = 0.79 &amp; 0.85$</td>
<td>* Birmingham observers $r = 0.95$ * radiologists $r = 0.86$ * pediatricians: large centres $r = 0.84$ small centres $r = 0.78$</td>
<td></td>
</tr>
<tr>
<td>Te Meer et al. 1985</td>
<td>S-K Chrispin-Norman (C-N) Brasfield</td>
<td>60 CXRs 39 CF pts</td>
<td>2 radiologists (blinded)</td>
<td>S-K $r = 0.807$ C-N $r = 0.880$ Brasfield $r = 0.810$</td>
<td>* correlation of C-N with S-K $r = 0.880 &amp; 0.728$ * correlation of C-N with Brasfield $r = 0.862 &amp; 0.818$ * correlation of Brasfield with S-K $r = -0.816 &amp; -0.866$</td>
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</table>
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<th>Inter-Rater Reliability</th>
<th>Intra-Rater Reliability</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Leary et al.</td>
<td>Brasfield PFTs</td>
<td>40 pairs of CXRs</td>
<td>2 radiologists scored each</td>
<td></td>
<td></td>
<td>* correlation with FEV₁ %: initial ( r = 0.50 ), follow-up ( r = 0.68 ), combined ( r = 0.67 ) * correlation with FVC %: initial ( r = 0.61 ), follow-up ( r = 0.66 ), combined ( r = 0.65 ) over 5.9 (±2.8) yrs, correlation between change in CXR score and ( i ) ) change in FEV₁ % ( r = 0.45 ) ( ii ) ) change in FVC % ( r = 0.64 )</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td>adult CF pts</td>
<td>scored each CXR by consensus</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>mean age (yrs)</td>
<td>initial 17.5 (±5.0)</td>
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<td></td>
<td></td>
<td></td>
<td>follow-up 23.3 (±5.3)</td>
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<td></td>
<td></td>
<td>66 pairs of CXRs</td>
<td>2 raters (blinded)</td>
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<tr>
<td></td>
<td></td>
<td>adult CF pts</td>
<td>age range 18-40 yrs, mean</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>age (yrs) initial 25 (±1.7)</td>
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<tr>
<td></td>
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<td></td>
<td>follow-up 31 (±1.7)</td>
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<tr>
<td>Rosenberg et al.</td>
<td>Brasfield PFTs</td>
<td>41 CXRs</td>
<td>2 radiologists</td>
<td></td>
<td></td>
<td>* correlation between Brasfield and FEV₁ ( r = 0.63 ), FEV₁ % ( r = 0.68 ), FVC ( r = 0.55 ), FVC % ( r = 0.65 ) correlation between Brasfield and FEV₁ % in 11 pts over 5.8 (±0.5) yrs: initial ( r = 0.60 ), final ( r = 0.67 ) * but the decline/year in FEV₁ (litres) -4.2 (±0.8), in FEV₁ % -3.9 (±0.8), in Brasfield -1.9 (±0.6)</td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td>adult CF pts</td>
<td>mean age 22.7 yrs (range 17-37 yrs)</td>
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<td></td>
<td></td>
<td></td>
<td>(range 17-37 yrs)</td>
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<tr>
<td>Wong et al.</td>
<td>modified S-K</td>
<td>41 CXRs</td>
<td>S-K: ( t = 3.65 ) SSD</td>
<td></td>
<td></td>
<td>* correlation with FEV₁ % and S-K ( r = 0.78 ) ( \text{NIH} ) ( r = -0.78 ) Brasfield ( r = 0.69 ) correlation with FVC % and S-K ( r = 0.71 ) ( \text{NIH} ) ( r = -0.69 ) Brasfield ( r = 0.71 ) Kendall's coefficient of concordance ( \text{NIH} ) vs S-K 0.86</td>
</tr>
<tr>
<td>1993</td>
<td>National Institute of Health (NIH) Brasfield PFTs (on 31 pts)</td>
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<td>NIH: ( t = 0.69 ) NSD</td>
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<td></td>
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<td>Brasfield: ( t = 1.88 ) NSD</td>
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<th>Validity</th>
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</table>
| Weatherly et al. 1993 Phase 2 | Wisconsin Brasfield | 61 CXRs          | 1 pediatric radiologist, 3 pediatric respirologists (blinded) | * correlation (ranges): Wisconsin r = 0.614 to 0.757  
Brasfield r = 0.646 to 0.735  
*Kendall coefficient of concordance Wisconsin 0.714  
Brasfield 0.622 | * correlation between the average Wisconsin and Brasfield scores r = - 0.875 | * correlation between the Wisconsin and Brasfield scores r = - 0.731  
*t test of differences between system scores (Wisconsin - Brasfield)  
initial t = -1.541 NSD  
final t = 3.11 SSD  
*t test of differences between initial and final scores by system: Wisconsin t = 3.39 SSD  
Brasfield t = 1.11 NSD  
* simple linear regression: age accounted for 17.4% (p<0.0001) of variation in Wisconsin scores vs 5.8% (p=0.001) in Brasfield scores | |
| Weatherly et al. 1993 Phase 3 | Wisconsin Brasfield | 176 CXRs    | 1 pediatric radiologist, 3 pediatric respirologists (blinded) | * interobserver variability: Brasfield 23.2% or 5.8 units  
NIH 24.1% or 4.1 units  
* Brasfield ICC = 0.74  
NIH ICC = 0.73  
* correlation ranged from 0.84 to 0.87 for Brasfield | * repeated assessments by same observer can differ by up to 20% for Brasfield and NIH scores i.e. Brasfield 4.8 units, NIH 3.4 units | * correlation with FEV, +% and Brasfield r = 0.58  
NIH r = 0.52  
* correlation with FVC% and Brasfield r = 0.52  
NIH r = 0.44 | |
| Sawyer et al. 1994 | Brasfield NIH (Royal Children's Hospital (RCH)) PFTs (on 61 pts) | 82 CXRs | 1 pediatric radiologist, 2 respirologists (blinded) | * interobserver variability: Brasfield 23.2% or 5.8 units  
NIH 24.1% or 4.1 units  
* Brasfield ICC = 0.74  
NIH ICC = 0.73  
* correlation ranged from 0.84 to 0.87 for Brasfield | * repeated assessments by same observer can differ by up to 20% for Brasfield and NIH scores i.e. Brasfield 4.8 units, NIH 3.4 units | * correlation with FEV, +% and Brasfield r = 0.58  
NIH r = 0.52  
* correlation with FVC% and Brasfield r = 0.52  
NIH r = 0.44 | |
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<td><strong>Table Data</strong></td>
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<tr>
<td><strong>Radiologist</strong></td>
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<tr>
<td><strong>Breast</strong></td>
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<tr>
<td>N+</td>
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<tr>
<td>N-</td>
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<tr>
<td><strong>Mean Age</strong></td>
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<td><strong>Female</strong></td>
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<td><strong>Male</strong></td>
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<tr>
<td><strong>Contrast A.M.A.</strong></td>
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<tr>
<td>N+</td>
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<td>N-</td>
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<tr>
<td><strong>Mean Age</strong></td>
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<td><strong>Female</strong></td>
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<td><strong>Male</strong></td>
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<tr>
<td><strong>Contrast Bleeker</strong></td>
</tr>
<tr>
<td>N+</td>
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<tr>
<td>N-</td>
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<tr>
<td><strong>Mean Age</strong></td>
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<td><strong>Mean Age</strong></td>
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<td><strong>Male</strong></td>
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<th>Intra-Rater Reliability</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyland et al.</td>
<td>Wisconsin Brasfield PFTs</td>
<td>65 pairs of CXRs taken – 1 year apart adult CF pts</td>
<td>1 radiologist, 2 pulmonologists (blinded)</td>
<td>*significant correlations at individual time points for both Brasfield and Wisconsin (r ranged from 0.54 to 0.77) * correlation of changes in CXR score between reviewers Wisconsin: r = 0.26, 0.15 and 0.14 Brasfield: r = 0.17, 0.33 and 0.45</td>
<td></td>
<td>*significant correlation between both Brasfield and Wisconsin and FEV₁ (r ranged from -0.33 to -0.50) *mean decline in FEV₁ over 1 year 2.4% predicted (+/− 13.1) * mean Brasfield score increased by 2.63 (+/− 9.49) * mean Wisconsin score increased by 1.16 (+/− 11.86) * correlation between change in CXR score and change in FEV₁ Wisconsin: r = -0.07, -0.26 and 0.05 Brasfield: r = 0.02, -0.23 and -0.11</td>
</tr>
<tr>
<td>Santamaria et al.</td>
<td>Brasfield (High-resolution CT scan) Modified S-K PFTs</td>
<td>30 CXRs CF pts mean age 13.85 yrs (range 6.75 to 24 yrs)</td>
<td>1 radiologist, 1 pediatric pulmonologist (blinded) Brasfield * inter-observer coefficient of variation 10.5% * correlation coefficient 0.82 (p&lt;0.0001)</td>
<td></td>
<td></td>
<td>* correlation between Brasfield and modified S-K r = 0.50 (p=0.001) FEV₁ r = 0.60 (p&lt;0.001) PVC r = 0.60 (p&lt;0.001)</td>
</tr>
<tr>
<td>Mudge et al.</td>
<td>Chrispin-Norman</td>
<td>55 CXRs from 3 consecutive years CF patients</td>
<td>2 physicians</td>
<td>* SSD between the 2 raters (p&lt;0.001)</td>
<td></td>
<td>* NSD between the mean scores over a 3 year period, but there was a SSD between the scores from year 1 to year 3</td>
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</table>

**Legend:**
- **CXR** = chest radiograph
- **C-N** = Chrispin-Norman CXR scoring system
- **N** = Northern CXR scoring system
- **+/− lat** = with or without lateral CXR
- **NIH** = National Institute of Health CXR scoring system
- **S-K** = Shwachman-Kulczycki CXR scoring system
- **ANOVA** = analysis of variance
- **NSD** = no significant difference
- **p** = level of significance (alpha)
- **pts** = patients
- **r** = Pearson's correlation coefficient
- **SSD** = statistically significant difference
- **yrs** = years
- **α** = and
- **%** = percent predicted
1.7.4 c) Pulmonary Function Tests

Pulmonary function tests (PFTs) are performed routinely on patients with CF to measure change over time and response to various treatments. They provide an objective assessment of the extent and progress of pulmonary disease (i.e. impairment). In 1979, the American Thoracic Society published a statement on the standardization of spirometry (American Thoracic Society, 1979). This document provides information on instrument specifications and is the source for the definitions of the PFT terminology used in this paper. Forced vital capacity (FVC) is defined as the vital capacity performed with a maximally forced expiratory effort. The forced expiratory volume in one second (FEV₁) is defined as the volume of air exhaled during the first second of FVC. The mean forced expiratory flow during the middle half of the FVC is known as FEF₂₅₋₇₅%. These values can be expressed as a percentage of that predicted for the age, gender and height of an individual from standard tables (Knudson et al., 1976).

In CF, the earliest changes in pulmonary function are detected in the maximal midexpiratory flow rates (e.g. FEF₂₅₋₇₅%) which indicate small airways disease (Davis et al., 1996). As the disease progresses, a decrease is seen in FEV₁ that is indicative of airway obstruction (Davis et al., 1996). The FEV₁ decreases throughout the life of individuals with CF; however the rate at which it declines is variable (Davis et al., 1996). There is usually a drop in FEV₁ and FVC during an acute pulmonary exacerbation, which may be reversible (at least partially) (Ramsey, 1996). The average annual rate of decline in FEV₁ % predicted in CF patients is approximately -2 % predicted per year (Davis et al., 1997).

The reliability of PFTs in CF patients has been evaluated in several studies (Cooper et al., 1990; Nickerson et al., 1980). The mean value of within-subject coefficient of variation (%) has been shown to be 6.0 for FVC, 5.3 for FEV₁, and 9.3 for FEF₂₅₋₇₅% (Nickerson et al.,
Therefore, FVC and FEV\(_1\), which are more effort-dependent, show less within-subject variation than FEF\(_{25-75}\%), a more effort-independent test (Nickerson et al., 1980). Another study reported a median within-subject coefficient of variation of 5.8 for FEV\(_1\) and 11.3 for FEF\(_{25-75}\%\) (Cooper et al., 1990). This is further evidence to support that FEV\(_1\) is a more reproducible or precise measurement than FEF\(_{25-75}\%\) (Cooper et al., 1990; Nickerson et al., 1980). There are many factors that may influence the reproducibility of PFTs. For example, patient and technician training may influence the results by affecting subject effort (Nickerson et al., 1980). Other factors that may influence the performance and results of repeated PFT measurements include sputum retention, airway obstruction, poor nutrition and fatigue (Cooper et al., 1990). Even when some of these factors are controlled, CF patients have more variability in their PFTs than do their healthy matched controls (Cooper et al., 1990; Nickerson et al., 1980). However, the degree of variability in an individual is consistent (Cooper et al., 1990). The effect of age on the variability of PFTs is unclear. Cooper et al. found that older patients with CF were significantly less variable than younger children. However, Nickerson et al. found that the variability in PFTs was independent of age; children were just as reproducible as adults were. Finally, the variability of PFT results has been reported to be similar for patients with different degrees of severity of pulmonary disease (Cooper et al., 1990).

Pulmonary function tests have been well validated over the years. They have face and content validity as they are an objective and "direct" measure of the changes that occur secondary to pulmonary disease. The concurrent criterion validity of PFTs has been demonstrated as very strong correlations have been found between a decline in clinical status and pulmonary function, and the frequency of viral infection (Wang et al., 1984). PFTs have predictive criterion validity as FEV\(_1\) has been shown to be the best predictor of mortality.
Low pulmonary function values, specifically an FEV₁ < 30% predicted, and/or an FVC < 40% predicted, are predictive of mortality within two years of measurement (Kerem et al., 1992).

In summary, PFTs, particularly FEV₁, are accepted as the best overall outcome measure in CF practice and research and are recommended as part of routine care (Kerem et al., 1992).

1.7.4 d) Exercise Testing

Exercise testing is used to determine aerobic capacity. Individuals who have greater aerobic capacity require less effort in activities of daily living and other pursuits, and they have more reserve for dealing with illness (Fitness Canada, 1987). An individual who has poor aerobic capacity (i.e. impairment) may experience activity limitations and/or participation restrictions.

Maximal oxygen uptake (VO₂max) is regarded as an index of aerobic capacity (Singh et al., 1994). VO₂max can be defined as the point in exercise at which oxygen consumption plateaus and shows no further increase (or increases only slightly) with an additional workload (Webb et al., 1995; McArdle et al., 1986). It is also known as maximal oxygen consumption or maximal aerobic power (McArdle et al., 1986). The higher the VO₂max, the greater the individual’s aerobic capacity (Fitness Canada, 1987). It is usually expressed in milliliters of oxygen per kilogram of total body weight per minute (ml O₂/kg/min).

Maximal oxygen uptake can be determined directly with maximal exercise tests by measuring the air expired during the test and analyzing it to determine how much oxygen has been used. It can also be estimated from submaximal exercise tests by measuring heart rate and predicting how much oxygen has been consumed (Fitness Canada, 1987).
1.7.4  

d) i) Maximal Exercise Tests

Maximal exercise tests are the most precise method of measuring VO\textsubscript{2max} (Singh and Morgan, 1994). Maximal exercise tests are usually performed on a treadmill or cycle ergometer and the following measures may be monitored during the test: heart rate, oxygen saturation, breath by breath analysis of inspired and expired gases, and electrocardiograph changes (Boas, 1997). Many different variations of these tests can be found in the literature on CF (e.g. DeJong et al., 1997; Nixon et al., 1992; Stanghelle et al., 1986). The reliability of maximal exercise tests and the measurement of VO\textsubscript{2max} have not been addressed in the CF population. However, in any given subject, healthy or otherwise, the accuracy and reproducibility of these tests is dependent upon the individual’s effort and willingness to exercise to exhaustion (Carlson, 1995). Some aspects of the validity of VO\textsubscript{2max} measured with maximal exercise tests have been addressed in the CF population. Several studies have demonstrated that VO\textsubscript{2max} is significantly correlated to FEV\textsubscript{1} (DeJong et al., 1997; Moorcroft et al., 1997; Alison et al., 1996) and survival (Alison et al., 1996; Nixon et al., 1992). The prognostic value of exercise testing in comparison to PFTs, demographic characteristics, nutrition and sputum colonization has been assessed (Moorcroft et al., 1994). It was found that although exercise testing provided functional information, FEV\textsubscript{1} was the best prognostic indicator (Moorcroft et al., 1994). VO\textsubscript{2max} is a correlate of survival but it was no better than FEV\textsubscript{1} (Moorcroft et al., 1994). Moorcroft et al. (1997) found no relationship between the change in VO\textsubscript{2max} from maximal exercise tests and the change in FEV\textsubscript{1} in CF patients. Hence, they concluded that reduced pulmonary function does not necessarily lead to reduced VO\textsubscript{2max} (Moorcroft et al., 1997). Table 3 summarizes the results of numerous studies on maximal exercise tests and CF or other lung disease.
In summary, there is no evidence of the reliability or responsiveness of maximal exercise tests and the measurement of VO₂max in CF patients. However, there is substantial evidence that VO₂max is a valid measure in CF that has prognostic value. The cost (e.g. equipment, time) of running these tests must be considered.

1.7.4 d) ii) Submaximal Exercise Tests

There are several standardized submaximal exercise tests that are used in CF practice and research. Table 3 summarizes the results of numerous studies done on these submaximal exercise tests in patients with CF or other lung or heart disease.

The 6-minute walk test is a self-paced walk test in which the distance an individual can cover in six minutes is measured in metres (Cole et al., 1994). It is a field test for estimating the VO₂max of persons with disabilities, particularly those with heart or lung disease (Cole et al., 1994). Heart rate, oxygen saturation, respiratory rate, blood pressure and rate of perceived exertion or dyspnea may be measured throughout the test (Cole et al., 1994). In order to maximize reliability, the test should be performed three times, the third test being the most accurate reflection of the individual’s functional exercise capacity (Cole et al., 1994). The 6-minute walk test is a simple exercise test that has been well validated for use with children and adults with cardiorespiratory illness.

The 2-minute walk test is a shortened version of the 12- and 6-minute walk tests. The validity of the 2-minute walk test must be further examined in pediatric and adult CF patients prior to it being used as a primary outcome measure of activity/activity limitation in CF practice and research. The responsiveness of the 2-minute walk test must also be evaluated.

The Shuttle walk test is an incremental, externally paced field exercise test of activity for patients with chronic lung disease (Singh and Morgan, 1994). Patients are asked to walk at increasing speeds up and down a 10-meter course (Singh and Morgan, 1994). The speed of
walking is controlled by audio signals played from a tape recorder, and the speed increases every minute (Singh and Morgan, 1994). Further research is needed to assess the reliability, validity and responsiveness of the Shuttle walk test in children and adults with CF before it is used as a primary outcome measure of activity/activity limitation in CF practice or research.

The 3-minute step test can also be used to estimate maximum oxygen consumption. Different versions of this test exist. For example, the Canadian Aerobic Fitness Test (CAFT) is performed on two 20.3 centimeter steps to a six-count musical rhythm set by a cassette tape with a progressive increase in tempo (Fitness Canada, 1986). Subjects start at a certain stage depending on their age and sex (Fitness Canada, 1986). Each stage is three minutes long, and a subject may complete a maximum of three stepping stages (Fitness Canada, 1986). The test is stopped if their heart rate is equal to or exceeds the ceiling post-exercise heart rate, or if the subject is experiencing any discomfort or dizziness (Fitness Canada, 1986). The step test used in a study with CF patients required that the subjects step up and down a six-inch step in a four-step pattern (Balfour-Lynn et al., 1996). The cadence was regulated by a metronome, at a rate of 30 beats per minute (Balfour-Lynn et al., 1996). Regardless of the format of the step test, heart rate is measured throughout the test. Oxygen saturation, blood pressure and scales of dyspnea or perceived exertion can also be measured. More studies are needed to determine the reliability, validity and responsiveness of the 3-minute step test in CF patients before it is used in CF practice or research. A standardized version of this test should also be chosen, preferably one like the CAFT, so that comparisons can be made to healthy controls.
Table 3: Summary of Studies on Maximal and Submaximal Exercise Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Test(s) Evaluated</th>
<th>Population</th>
<th>Test-retest Reliability</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nixon et al. 1992</td>
<td>VO\textsubscript{2}\textsuperscript{max} maximal cycle ergometer test (Godfrey protocol)</td>
<td>109 patients with CF (mean age 17, range 7 to 35 years)</td>
<td>patients with highest levels of aerobic fitness (VO\textsubscript{2}\textsuperscript{max} &gt; 82% predicted) had survival rate of 83% at 8 years, versus 51% and 28% with middle and lowest level of fitness (VO\textsubscript{2}\textsuperscript{max} 59 to 81 and &lt; 58% predicted respectively)</td>
<td></td>
</tr>
<tr>
<td>De Jong et al. 1997</td>
<td>Maximal exercise capacity (W\textsuperscript{max}) maximal cycle ergometer test</td>
<td>14 adults with CF (mean age 25 +/- 6.8 years)</td>
<td>W\textsuperscript{max} correlated significantly with % predicted FEV\textsubscript{1} (r = 0.79)</td>
<td></td>
</tr>
<tr>
<td>Stanghellini et al. 1986</td>
<td>VO\textsubscript{2}\textsuperscript{max} maximal cycle ergometer test</td>
<td>10 children with CF (all 11 years of age)</td>
<td>VO\textsubscript{2}\textsuperscript{max} was higher in subjects with frequent habitual physical activities (r = 0.79), fair correlation between VO\textsubscript{2}\textsuperscript{max} and Shwachman scores (r = 0.58)</td>
<td></td>
</tr>
<tr>
<td>Moorcroft et al. 1997</td>
<td>VO\textsubscript{2}\textsuperscript{max} maximal cycle ergometer test</td>
<td>30 adults with CF (mean age at baseline = 19.8, at retesting = 26.1 years)</td>
<td>significant correlation between VO\textsubscript{2}\textsuperscript{max} and FEV\textsubscript{1} (r = 0.70), no relationship found between change in VO\textsubscript{2}\textsuperscript{max} and FEV\textsubscript{1} (mean interval between 2 tests was 6.3 years (range 4.5 to 7.6)</td>
<td></td>
</tr>
<tr>
<td>Alison et al. 1995</td>
<td>VO\textsubscript{2}\textsuperscript{max} maximal cycle ergometer test</td>
<td>87 adults with CF (mean age 23 +/- 6 years)</td>
<td>significant correlation between % predicted VO\textsubscript{2}\textsuperscript{max} and % predicted FEV\textsubscript{1} (r = 0.71) and survival ie. those people who had VO\textsubscript{2}\textsuperscript{max} % predicted &gt; 80% had best prognosis</td>
<td></td>
</tr>
<tr>
<td>Moorcroft et al. 1994</td>
<td>VO\textsubscript{2}\textsuperscript{max} maximal exercise test</td>
<td>87 adults with CF (mean age 19.8 years)</td>
<td>VO\textsubscript{2}\textsuperscript{max} and W\textsuperscript{max} are correlates of survival but FEV\textsubscript{1} was the only significant independent correlate of mortality</td>
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</table>
**Table 3: Summary of Studies on Maximal and Submaximal Exercise Tests**

<table>
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<tr>
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<tbody>
<tr>
<td>Marcinuk et al. 1993</td>
<td>VO\textsubscript{2}\text{max} maximal cycle ergometer test</td>
<td>6 adults with restrictive lung disease (mean age 44 +/- 15 years)</td>
<td>mean within subject coefficient of variation = 5.3% (range 5.3 to 9.5%) in subjects who had never done exercise testing - suggest no significant learning effect</td>
<td></td>
</tr>
<tr>
<td>Mungall et al. 1979</td>
<td>12-minute walk</td>
<td>13 patients with COPD (mean age 55.4, 47 to 64 years)</td>
<td>coefficient of variation over all 6 tests = +/- 8.2%, if 1st 2 tests were not counted coefficient of variation = +/- 4.2%, suggests training effect</td>
<td></td>
</tr>
<tr>
<td>Guyatt et al. 1985 a</td>
<td>6-minute walk</td>
<td>43 adults with chronic heart (18) or lung (25) disease (mean age 64.7 +/- 8.3 years)</td>
<td>results within 6% of their mean score 65% of the time and within 12% of their mean score 95% of the time</td>
<td>fair correlation between distance and cycle ergometer results i.e. exercise time to exhaustion (r = 0.58, p &lt; 0.001)</td>
</tr>
<tr>
<td>Guyatt et al. 1985 b</td>
<td>6-minute walk</td>
<td>43 adults with chronic heart (18) or lung (25) disease (mean age 64.7 +/- 8.3 years)</td>
<td>coefficient of variation = 0.07 for all 6 tests, 0.05 for tests 3 to 6 (i.e. exclude 1st 2 tests); ICC = 0.921 for all 6 tests, 0.909 for tests 3 to 6</td>
<td>fair correlation between distance and cycle ergometer results i.e exercise time to exhaustion (r = 0.579, p &lt; 0.001)</td>
</tr>
<tr>
<td>Nixon et al. 1996</td>
<td>6-minute walk</td>
<td>17 patients with severe heart/lung disease, 10 with CF (age 9 to 19 years)</td>
<td>good (r = 0.80) (in 6 of these severely ill children)</td>
<td>moderate correlation between distance and VO\textsubscript{2}\text{max} (r = 0.70) and physical work capacity (r = 0.64) (from a maximal cycle ergometer test), significant correlation with FEV\textsubscript{1}, % predicted (r = 0.75) when only patients with lung disease were included in analysis</td>
</tr>
<tr>
<td>Study</td>
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</tr>
<tr>
<td>Guimans et al. 1996</td>
<td>6-minute walk</td>
<td>reliability: 23 children with CF (mean age 11.1 +/- 2.2 years)</td>
<td>no significant difference between 2 distances reached (p=0.59), strong correlation between the 2 distances for each individual (r = 0.90)</td>
<td>significant correlation between distance and VO$_2$max (r = 0.76) and maximum workload (r = 0.76) (from maximal cycle ergometer test), no significant correlation between distance and FEV$_1$ % predicted (r = 0.45)</td>
</tr>
<tr>
<td>Butland et al. 1982</td>
<td>2-, 6-, and 12-minute</td>
<td>reliability: 13 adults with COPD (mean age 51 +/- 14 years)</td>
<td>mean distances were 137 (+/-46), 141 (+/-43), 146 (+/-41) and 147 (+/-40), 2 practice walks are needed because of an initial training effect</td>
<td>significant correlation between the 2- and 6-minute (r = 0.892), 6- and 12-minute (r = 0.955) and the 2- and 12-minute (r = 0.864)</td>
</tr>
<tr>
<td>McGavin et al. 1976</td>
<td>12-minute walk and VO$_2$max (maximal cycle ergometer test)</td>
<td>35 adults with chronic bronchitis (age 40 to 70 years)</td>
<td>excellent (r = 0.97 between 2 attempts in individual patients, but distance walked on 2nd test was significantly greater p &lt; 0.001)</td>
<td>significant but poor correlation with FVC (r = 0.406) and FEV$_1$ (r = 0.283); 29 of these patients also did a maximal cycle ergometer test - fair correlation between distance and VO$_2$max (r = 0.52), fair correlation between VO$_2$max and FVC (0.67) and FEV$_1$ (r = 0.65)</td>
</tr>
<tr>
<td>McGavin et al. 1978</td>
<td>12-minute walk</td>
<td>62 adults (mean age 55.22 to 75 years; 44 with COPD, 18 with radiological evidence of lung disease without airway obstruction)</td>
<td>in the 44 COPD patients: fair correlation between distance walked and FVC (r = 0.52) and FEV$_1$ (r = 0.44) (p &lt; 0.01)</td>
<td>poor to fair correlation with FEV$_1$ (litres) (r = 0.62) and FEV$_1$ (% predicted) (r = 0.49)</td>
</tr>
<tr>
<td>Dehuyzen et al. 1986</td>
<td>12-minute walk</td>
<td>50 adults with COPD (mean age 57.2 +/- 7.3 years)</td>
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Table 3: Summary of Studies on Maximal and Submaximal Exercise Tests

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<tr>
<td>Cahalin et al. 1995</td>
<td>6-minute walk</td>
<td>60 adults with lung disease (mean age 44 years)</td>
<td>excellent (ICC = 0.99)</td>
<td>distance walked was strongest independent predictor of VO_{2\text{max}} (r = 0.73); when pulmonary function test results (FEV\textsubscript{1}, FVC and DCO), age and weight were added, r increased to 0.83</td>
</tr>
<tr>
<td>Cahalin et al. 1996</td>
<td>6-minute walk</td>
<td>45 adults with heart failure (mean age 49 +/- 8 years)</td>
<td>excellent (ICC = 0.96) (repeated in 20 of these patients)</td>
<td>significant correlation between distance and VO_{2\text{max}} (r = 0.64)</td>
</tr>
<tr>
<td>Upton et al. 1988</td>
<td>2-minute walk</td>
<td>reliability: 12 children with CF (mean age 10, 5 to 15 years) responsiveness: 16 children with CF (mean age 12.5, 6 to 16 years)</td>
<td>mean coefficient of variation for each child on 4 walks was low - 2.6% (range 1.9 to 5.9%), no significant change when re-tested after 1 to 3 months, suggests no training effect</td>
<td>significant improvement in distance after treatment in hospital for chest infection (mean 83.3 (+/- 10.9) at admission versus 90.8 (+/- 11.2) at discharge, p &lt; 0.005)</td>
</tr>
<tr>
<td>Singh and Morgan 1994</td>
<td>Shuttle walk</td>
<td>10 adults with COPD (mean age 63.4 +/- 6.8 years)</td>
<td></td>
<td>after a 7 week pulmonary rehab program: significant improvement in Shuttle distance (mean 278 to 341 metres, p=0.05), moderate correlation between FEV\textsubscript{1} and increase in Shuttle distance (r = 0.62)</td>
</tr>
<tr>
<td>Singh et al. 1994</td>
<td>Shuttle walk</td>
<td>19 adults with COPD, 10 performed Shuttle with portable O\textsubscript{2} consumption meter (mean age 61 +/- 7 years)</td>
<td></td>
<td>Shuttle distance correlated significantly with VO_{2\text{max}} measured with modified Balke treadmill test (r = 0.88) and measured with a portable device during Shuttle test (r = 0.81); significant correlation between VO_{2\text{max}} measured with the treadmill test and with the Shuttle test (r = 0.86); poor correlation between Shuttle distance and FEV\textsubscript{1} (r = 0.36)</td>
</tr>
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### Table 3: Summary of Studies on Maximal and Submaximal Exercise Tests

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<tbody>
<tr>
<td>Singh et al. 1996</td>
<td>Shuttle walk</td>
<td>132 adults with COPD (mean age 62 +/- 10 years), 18 of whom did a 7 week control period</td>
<td>no significant change in distance after 7 week control period (192 +/- 138 metres at baseline versus 184 +/- 156 metres at end of control period)</td>
<td>significant improvement in distance after 7 week outpatient pulmonary rehab program (215 +/- 113 metres to 273 +/- 128 metres, p &lt; 0.001)</td>
</tr>
<tr>
<td>Howard et al. 1997</td>
<td>Shuttle walk</td>
<td>10 adults with CF (mean age 27 +/- 5 years)</td>
<td></td>
<td>Shuttle distance correlated significantly with FEV₁ before (r = 0.76) and after (r = 0.70) intavenous antibiotic treatment, no correlation between the changes in Shuttle distance and FEV₁ (r = 0.1)</td>
</tr>
<tr>
<td>Balfour-Lynn et al. 1996</td>
<td>3-minute step</td>
<td>19 children with CF (mean age 13.3 years, range 9 to 16 years)</td>
<td></td>
<td>3-minute step test significantly increased heart rate - mean change 41% versus 26% for the 6-minute walk test (p&lt;0.005); significantly increased breathlessness - mean change in Borg dyspnea score was 2.4 versus 0.8 for the 6-minute walk test (p&lt;0.0001); the decrease in oxygen saturation was similar -3.5% versus -3.7% for the 6-minute walk test (p = 0.67)</td>
</tr>
</tbody>
</table>

**Legend:**
- ICC = intraclass correlation coefficient
- p = level of significance
- r = Pearson's correlation coefficient
- VO₂max = maximal oxygen uptake
- Wmax = maximum exercise capacity
- > = greater than
- < = less than
1.7.5 Measures of Functioning and Disability in Cystic Fibrosis: Health-Related Quality of Life Measures

"Quality of life" (QOL) is a broad concept that consists of many factors including physical and emotional health, social relationships, mental self-perception, environmental and financial factors (Tullis and Guyatt, 1995; Patrick and Erickson, 1993). The concept of "health-related quality of life" was developed to be narrower than quality of life (Tullis and Guyatt, 1995; Patrick and Erickson, 1993). Health-related quality of life (HRQOL) excludes the factors of income, personal freedom and physical environment since they are not considered to be health-related (Tullis and Guyatt, 1995). The items in a HRQOL measure usually include physical function (i.e. everyday function and symptoms), social relationships, emotional health, life satisfaction and general well-being (Tullis and Guyatt, 1995). Patrick and Erickson defined HRQOL as the value assigned by individuals, groups or society to the duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment or policy. This definition of HRQOL covers five concepts (i.e. impairments, functional states, health perceptions, social opportunities, and death or duration of life) that combine the quality and quantity of life on a continuum (Patrick and Erickson, 1993). Patrick and Erickson defined these five concepts by domains, which are states, attitudes, behaviours, perceptions, activity and thought. Therefore, measures of HRQOL may help researchers gain insight into a patient's level of functioning, or conversely their level of disability.

Health-related quality of life measures can be classified by the range of populations to which they are applied and the range of concepts that they include (Patrick and Erickson, 1993). Health-related quality of life measures may be generic or specific (Tullis and Guyatt, 1995; Patrick and Erickson, 1993).
Generic HRQOL measures are designed for use in different types and severities of disease, with different interventions, and in different demographic and cultural groups (Patrick and Erickson, 1993). Generic HRQOL measures allow broad comparisons to be made amongst many different diseases, impairments, conditions, patients and populations, and they may summarize several concepts in a single index value or in a profile of interrelated scores (Patrick and Erickson, 1993). Utility measures are a type of generic HRQOL instrument, which are derived from economic and decision theory (Tullis and Guyatt, 1995). They reflect health status and the value of that health status to the patient (Tullis and Guyatt, 1995). Generic HRQOL measures may be less responsive to changes in specific conditions, populations, concepts or domains (Tullis and Guyatt, 1995).

Specific HRQOL measures are designed to evaluate specific patient populations, diagnostic groups, individual concepts or domains (Patrick and Erickson, 1993). Disease-specific measures are used with specific diseases or health conditions (e.g. COPD, CF), and they are often developed to detect minimally important change in HRQOL (Patrick and Erickson, 1993). Specific HRQOL measures can also be related to specific domains or populations (Patrick and Erickson, 1993). Domain-specific measures are designed to assess a specific condition or symptom (e.g. shortness of breath), or specific domain (e.g. emotional function) (Patrick and Erickson, 1993). Population-specific measures are designed to assess special populations, that are usually defined by age or a combination of age and medical condition (e.g. frail elderly) (Patrick and Erickson, 1993).

In 1995, Tullis and Guyatt commented that no criterion or “gold standard” exists for HRQOL measures. Several HRQOL measures have been tested or developed specifically for the CF population since this study was designed, and they will be discussed briefly. The measures that have been used most in CF practice and research include the Short-Form-36, the
Functional Status Index, the Quality of Well-being Scale and the Chronic Respiratory Questionnaire. These measures will be reviewed in detail. No one measure is yet considered the "gold standard".

1.7.5 a) Child Health Questionnaire

The Child Health Questionnaire (CHQ) has been validated for children with chronic illnesses, such as CF, between 5 and 18 years of age (Douglas et al., 1999). There are 12 scales that contain questions about the physical and psychosocial domains of health in children (McGarrahan et al., 1999). The CHQ has both parent and child forms that attempt to provide a picture of overall health and QOL from the parents' and/or patients' view (McGarrahan et al., 1999). The CHQ will not be discussed further as it was designed for use with children.

1.7.5 b) Short Form-36

Several authors have recently evaluated the Short Form-36 (SF-36) with the CF population (Webster and Malone, 2000; Britto et al., 1999; Epker and Matt Maddrey, 1999a, b; Gee et al., 1999a). The SF-36 is a generic HRQOL measure that has been used to measure change in physical and emotional functioning over time in a variety of patient populations. It is a 36-item, self-report measure that contains eight domains: physical functioning, role limitation due to physical problems/functioning, social functioning, bodily pain, general mental health, role limitation due to emotional problems, vitality and general health perceptions (Abbott et al., 1997).

Gee et al. (1999a) examined the validity of the SF-36 in 225 adults with CF. They found that the factor structures for the CF group were similar to the above eight domains. Cronbach alpha coefficients were above 0.80 for each domain, and item to same domain correlations were higher than item to unrelated domain correlations. Gee et al. (1999a) stated that the SF-36 had some ability to discriminate between levels of disease severity, but that it
was not as discriminating as the newly developed Cystic Fibrosis Quality of Life Questionnaire.

Epker and Matt Maddrey (1999a, b) administered the SF-36 to 70 adult CF patients (mean age 25.86 +/- 8.84, range 16 to 60 years, 39 males). They found that the CF patients had more extensive limitations in each domain than data from the general United States population, with each mean score falling at or below the 25th percentile (Epker and Matt Maddrey, 1999b). Female CF patients reported more limitations than male CF patients in all eight domains (Epker and Matt Maddrey, 1999b). Epker and Matt Maddrey (1999a) also tested the concurrent criterion validity of the SF-36 by comparing it to the patients' Shwachman scores. Shwachman scores (which indicate disease severity) were significantly but poorly correlated to the following domains of the SF-36, with less disease severity coinciding with better functioning: physical functioning ($r = 0.369$, $p = 0.002$), social functioning ($r = 0.284$, $p = 0.018$), general health perceptions ($r = 0.397$, $p = 0.001$), and overall physical well-being ($r = 0.350$, $p = 0.003$) (Epker and Matt Maddrey, 1999a). However, there were no significant correlations between disease severity (Shwachman scores) and the following domains of the SF-36: role limitations due to physical problems/functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality and overall emotional well-being (Epker and Matt Maddrey, 1999a). Epker and Matt Maddrey (1999a) concluded that patient's perceptions of their QOL, or how they are doing in many physical and/or psychosocial domains, is not necessarily a function of disease severity.

These findings are similar to what Britto et al. (1999) reported when they evaluated the combined total scores of the CHQ from 78 CF patients age 5 to 17 years and the SF-36 from 27 CF patients 18 years of age and older. Unfortunately, they did not provide actual correlation values, making interpretation difficult; however they did report that they used a p-value of
0.01. There was no significant correlation between physical or psychosocial QOL scores and FEV₁, 6-minute walk distance, or height or weight percentile. However, they found a strong negative effect of pulmonary exacerbation on physical and psychosocial QOL. Britto et al. could not determine whether the lack of correlation between FEV₁ and QOL was due to measure insensitivity or whether people with more severe lung disease perceive their QOL to be similar to those with better lung function. Britto et al. suggested that because of the strong negative correlation between QOL scores and exacerbations that it may be change in disease status rather than disease severity that determines QOL.

Webster and Malone (2000) found conflicting results when they examined the relationship between the SF-36, pulmonary function, nutritional status (body mass index or BMI) and functional status (6-minute walk test) in 32 adults with CF. They did not report the actual correlation values, making interpretation difficult; however they did report that they used a p-value of 0.05. There were significant relationships between FEV₁ and three domains of the SF-36: physical functioning, social functioning and general health perceptions; and between FVC and two domains of the SF-36: physical functioning and general health perceptions. The 6-minute walk test significantly correlated to six domains of the SF-36: physical functioning, role limitation due to physical problems/functioning, social functioning, role limitation due to emotional problems, vitality and general health perceptions. Finally, BMI was significantly related to four SF-36 domains: physical functioning, social functioning, vitality and general health perceptions. Regression analysis of physical functioning, social functioning and general health perceptions determined percent variance was 43%, 54% and 48% (respectively). Therefore, Webster and Malone concluded that there are significant relationships between the SF-36, pulmonary function, functional status and nutritional status in adults with CF, but that these measures are not good predictors of HRQOL.
Waterhouse et al. (1994) evaluated the responsiveness of the SF-36 in patients with COPD using effect sizes. The SF-36 was administered to 150 patients with COPD. It was readministered to 126 of these patients at six months, and 100 of these patients at 12 months. The authors reported that the effect sizes for patients who claimed their health had changed showed large statistically significant differences in some dimensions of the SF-36 (p < 0.05). No studies were found that examined the responsiveness of the SF-36 in the CF population.

1.7.5 c) Cystic Fibrosis Quality of Life Questionnaire

The Cystic Fibrosis Quality of Life Questionnaire (CFQOL) is a relatively new measure that contains 52 items in nine CF-specific domains (Gee et al., 1999b). The nine domains are: physical functioning, social functioning, treatment issues, chest symptoms, emotional responses, body image, interpersonal relationships, career concerns, and concerns for the future (Gee et al., 1999b). There are also two global HRQOL questions and two general questions on health perception (Gee et al., 1999b). Disease-specific questions were developed through patient interviews and feedback, consultation with multidisciplinary CF teams, and through review of existing HRQOL measures and literature (Gee et al., 1999b). One hundred and one patients completed the initial version and provided feedback regarding its structure and content (Gee et al., 1999b). Internal consistency was measured using Cronbach's alpha; all values were higher than 0.8 (Gee et al., 1999b). If any of these values were higher than 0.9, it may suggest that some items are redundant (Streiner and Norman, 1995). A second version of the CFQOL was created and it was administered to 225 adult CF patients (Gee et al., 1999b). Tests of internal consistency (Cronbach's alpha) and item to domain correlations were similar to the first analysis (Gee et al., 1999b). The authors stated that it has good test-retest reliability, good ability to discriminate between levels of disease severity, and that it was "sensitive to changes in health" (Gee et al., 1999b). They also reported concurrent validity
when compared with the SF-36 (Gee et al., 1999b). With respect to the CFQOL discriminating between levels of disease severity, Gee et al. (2000) later presented work that looked at the CFQOL in CF patients with different levels of disease severity: mild (FEV₁ ≥ 71%, n = 60), moderate (FEV₁ between 41 and 70%, n = 97), and severe (FEV₁ ≤ 40%, n = 66). The results suggested that there was a progressive deterioration in all nine domains of the CFQOL i.e. patients had more difficulties as disease severity worsened (Gee et al., 2000). Patients with all three levels of disease severity ranked the domains which bothered them from the most to the least as: concerns for the future, career issues, interpersonal relationships, body image, chest symptoms, treatment issues, physical functioning, emotional responses and social functioning (Gee et al., 2000). Quittner et al. (2000) examined the reliability and validity of the CFQOL using 207 CF patients (age range 14 to 53 years) from multiple CF centres. Test-retest reliability (n = 24) was moderate to good (r ranged from 0.47 to 0.85, p < 0.05) (Quittner et al., 2000). There were significant, but poor to moderate, correlations between CFQOL scores and FEV₁ % predicted (r ranged from 0.22 to 0.42, p < 0.05) and age (r ranged from -0.23 to -0.35) (Quittner et al., 2000). Correlation with the SF-36 was also significant but moderate (mean r = 0.43, p < 0.05) (Quittner et al., 2000). The CFQOL measure appears to be a promising outcome measure; however more studies are needed to establish and confirm its reliability and validity. No evidence of the responsiveness of the CFQOL was found in the literature.

1.7.5  d) A New CF-Specific Quality of Life Measure

In 1999, Tullis et al. developed a CF-specific quality of life measure for evaluative purposes. Items were generated from the responses of over 200 adolescents (age > 13 years) and adults with CF and health care professionals from Canada, the United States, England and Australia. A list of 118 items was created and categorized into the following domains: daily
activities, physical, emotional, social, vocational and treatment related issues. They conducted structured interviews with 75 adults with CF with varying degrees of lung disease to determine which items pertained to their quality of life and how important the items were on a five-point scale. The final items were selected using frequency importance products. The top three items were having a supportive family, having a supportive relationship with a spouse, and exposure to an airborne irritant. These items were discarded as they felt they would not be likely to change with a therapeutic intervention. The top physical items were cough, dyspnea and chest congestion. Results of reliability, validity and responsiveness testing have not been published to date.

1.7.5 e) The Functional Status Index

The Functional Status Index (FSI) was derived from the RAND Health Insurance Study (and the RAND Health Insurance study was partly derived from the QWB scale) (Tullis and Guyatt, 1995). The FSI has 12 items, 10 which were taken from the RAND Functional Limitation Battery and two which were added to improve sensitivity (Tullis and Guyatt, 1995). The FSI contains four categories: mobility, physical activity, social activity, and general limitations (Tullis and Guyatt, 1995). The total number of categories in which a limitation exists is the FSI score; therefore, possible scores range from zero to four (Shepherd et al., 1992). Higher FSI scores indicate worse health-related quality of life.

Shepherd et al. (1992) examined the validity of the FSI in patients with CF. Of the 37 adults with CF who completed the FSI, 51% had a limitation in at least one category of the FSI. Of the 46 healthy adults who participated, 9% had a limitation in at least one category. The mean FSI scores of the two groups were significantly different (1.3 for CF patients versus 0.13 for healthy subjects, p<0.001). However, there was no significant difference between the CF patients and the healthy group in the category of mobility. Shepherd et al. suggested that
the mobility category is less sensitive because mobility limitations are the least common as they represent more severe illness. In the CF patients, the FSI scores were moderately correlated with FVC ($r = -0.57$, $p = 0.001$). The ability of the FSI to predict mortality was also assessed by comparing patient outcomes five years after the FSI was administered. The FSI score was a significant predictor of survival ($p<0.001$); however, when PFTs and nutritional status were included in a multivariate analysis, it was no longer a significant predictor of survival.

In summary, there is some evidence of the validity of the FSI; however there is no literature on its reliability or responsiveness in CF patients.

1.7.5 f) The Quality of Well-being Scale

The Quality of Well-Being Scale (QWB) (Appendix 1) is a generic HRQOL measure that combines preference-weighted measures of symptoms and functioning to provide a numerical point-in-time expression of well-being (Kaplan et al., 1989). Written authorization was received to include the QWB as an appendix and for the National Library to make use of the thesis. A weighting exercise was conducted in the general population so that a value could be applied to the disutility associated with each limitation or symptom (i.e. it is a utility measure) (Tullis and Guyatt, 1995). The score ranges from zero (for death) to one (for asymptomatic optimal functioning), i.e. the more limitations or symptoms a person reports, the lower the utility of that person's life on the scale of zero to one (Tullis and Guyatt, 1995). It is administered by an interviewer and has three scales of function: mobility, physical activity and social activity (Kaplan et al., 1989). Patients are also asked to indicate the presence of symptoms or problems on a particular day, regardless of their intensity or duration, or of the underlying pathology (Kaplan et al., 1989). The QWB can be used to estimate the impact of treatment in terms of the years of life they produce, adjusted for reduced quality of life. This
concept is referred to as well-years or quality adjusted life years. (Orenstein and Kaplan, 1991). However, the minimally important difference in QWB scores in patients with CF is unknown (Tullis and Guyatt, 1995).

A self-administered version of the QWB was recently developed; however, it varies from the interviewer-administered version and little research has been published on it to date (Kaplan et al., 1997). This paper will only refer to the original interviewer-administered version of the QWB, available in paper or computerized format.

The test-retest reliability of the QWB has been assessed in the general population (Kaplan et al., 1997). Two hundred and eighteen adults who were relatively healthy and stable were tested twice with a one-month interval in between. The test-retest reliability was moderate (r = 0.60).

Clinically, the QWB appears to have face and content validity. It has been used in many studies with patients with various conditions such as CF, Autoimmune Deficiency Syndrome (AIDS) and arthritis (Kaplan et al., 1989), which attests to its face validity. It is a utility measure therefore it reflects both health status and the value of that health status to the patient (Tullis and Guyatt, 1995). It appears to tap into the concepts of functioning and disability. For example, it has questions related to impairment (problems in body function or structure e.g. headache, broken arm), activity (e.g. mobility, self-care) and participation (e.g. involvement in social relationships, community life, work, school).

Kaplan et al. (1984) assessed the validity of the QWB using 75 patients with COPD (28 males, mean age 64.8 +/- 7.9 years). After initial assessment, patients were randomly assigned to a control group or a behaviour modification group designed to increase adherence to an exercise program. The subjects were assessed 3, 6, 12 and 18 months later. There was a significant correlation between QWB scores and FEV$_1$ at the initial and three-month follow-up
assessments (r = 0.51 and 0.54 respectively, p<0.001), and a poor correlation between QWB scores and FVC at the initial and three-month follow-up (r = 0.34 and 0.35 respectively). The mean QWB score at baseline was 0.608 (+/- 0.08) (n = 66), and it was 0.603 (+/- 0.09) at the three-month follow-up (n = 67). These two scores were moderately correlated (r = 0.65); however it was not reported if this was a statistically significant change. The change in QWB scores was not significantly correlated with change in FEV₁ or FVC over a three-month period (r = 0.11 and 0.03 respectively). However, the change in QWB scores was significantly correlated with change in exercise tolerance (r = 0.40) and oxygen saturation (r = 0.28) over a three-month period, and with the change in FEV₁ (r = 0.63) over an 18-month period. These correlations were poor to moderate. Tullis and Guyatt (1995) suggested that these findings support the use of the QWB in CF patients because they experience similar symptoms.

Orenstein et al. (1989) conducted a study involving 44 CF patients whose age ranged from 7 to 36 years. The QWB scale was completed by a parent if the subject was younger than 10 years of age, and if the subject was between 10 and 14 years of age, the QWB was completed by the subject together with a parent. Subjects 14 years of age and older completed the QWB themselves. Fifteen patients also performed a maximal cycle ergometer test to measure their VO₂max. The hypotheses tested were that QWB scores would be better in patients with better lung function and exercise tolerance. There was a significant correlation between the QWB scores and FEV₁ (r = 0.5518, p<0.0001), and FEF₂₅-₇₅% (r = 0.4793, p<0.001). There was also a significant correlation between the QWB scores and VO₂max (r = 0.5778, p<0.01). The results of this study provided evidence for the validity of the QWB in CF patients.

Orenstein et al. (1990) conducted another study to examine the validity of the QWB. In this study, the QWB was completed with 28 CF patients before and after a two-week course of
oral antibiotic used to treat pulmonary exacerbations. The results indicated that most patients had improved pulmonary function and improved QWB scores after the two-week treatment. The mean change in FEV₁ % predicted was 6.5 (+/- 11.9, range -17.0 to 33.0). The mean change in QWB scores was 0.104 (+/- 0.122, range -0.201 to 0.290). There was a moderate correlation between the change in QWB scores and the change in % predicted FEV₁ (r = 0.40, p < 0.03) and % predicted FVC (r = 0.50, p < 0.01). There was also a moderate correlation between the change in QWB scores and the change in oxygen saturation (r = 0.40, p < 0.05). These correlations were all statistically significant; however, the change in QWB scores and change in FEF₂₅₋₇₅ did not correlate significantly (r = 0.026, p < 0.90). In summary, this study attempted to evaluate the validity of the QWB as a measure of HRQOL in CF patients. In another study, Orenstein and Kaplan (1991) indirectly reported on the validity of the QWB, as the scores improved in CF patients after they received a lung transplant.

In summary, there is some evidence that the Quality of Well-Being Scale is a valid measure of HRQOL in CF patients, and it has been used in other physiotherapy studies (Gaskin et al., 1998). However, research is needed to determine the responsiveness of the QWB Scale in patients with CF. The QWB may be a valuable secondary outcome measure in CF practice and research.

1.7.5 g) The Chronic Respiratory Questionnaire

The Chronic Respiratory Questionnaire or Chronic Respiratory Disease Index Questionnaire (CRQ) (Appendix 2) is a disease-specific HRQOL questionnaire designed to measure change in the HRQOL of patients with chronic lung disease over time (Guyatt et al., 1987). Written authorization was received to include the CRQ as an appendix and for the National Library to make use of the thesis. An interviewer administers the CRQ and the questions are divided into four areas or dimensions: dyspnoea, fatigue, emotional function and
mastery (Guyatt et al., 1987). The dimension of mastery refers to the extent to which an individual feels in control or is able to cope with their illness (Guyatt et al., 1987). Each dimension includes four to seven items, and each item is answered on a seven-point scale (Guyatt et al., 1987). The total CRQ score is equal to the sum of all of the CRQ dimension scores (Guyatt et al., 1987). The maximum score is 140 and it represents best functioning. Lower scores indicate worse HRQOL; 20 is the minimum score (Guyatt et al., 1987). The section on the assessment of dyspnea or shortness of breath is individualized (Guyatt et al., 1987). Subjects choose five activities that make them short of breath and that are relevant and meaningful in their daily life (Guyatt et al., 1987). Therefore, the CRQ is standardized but it is flexible enough to reflect what is meaningful to the individual. Table 4 summarizes the minimum and maximum values for the CRQ total score and for each dimension.

<table>
<thead>
<tr>
<th>Score</th>
<th>Minimum Score (worst function)</th>
<th>Maximum Score (best function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>20</td>
<td>140</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Emotional Function</td>
<td>7</td>
<td>49</td>
</tr>
<tr>
<td>Mastery</td>
<td>4</td>
<td>28</td>
</tr>
</tbody>
</table>

Lacasse et al. (1997) suggested a standard method of reporting CRQ scores. They suggested that the score of each domain be divided by the number of items in that domain, so that possible scores range from one to seven in all domains.

The internal consistency of the CRQ was assessed in a study involving 61 patients with COPD (Waterhouse et al., 1994). The results showed good internal consistency in the fatigue, emotional function and mastery dimensions (Cronbach's alpha 0.85, 0.84 and 0.80)
respectively) (Waterhouse et al., 1994). However, the internal consistency was lower in the dyspnea dimension (Cronbach's alpha 0.64) (Waterhouse et al., 1994). This was attributed to the individualization of this dimension (Waterhouse et al., 1994). Bradley et al. (1998a) administered the CRQ to 45 adults with CF (32 males, mean age 27 years). The fatigue, emotional function (excluding item 8) and mastery dimensions showed high internal consistency (Cronbach's alpha = 0.934, 0.880 and 0.850 respectively) (Bradley et al., 1998a). Bradley et al. (1998a) found that items 14 (fatigue), 15 (emotional function) and 6 (mastery) accounted for 64.5% of the total variance, while all items accounted for 78.2% of the total variance. Therefore, they suggested that each dimension could be reduced to one item and thus make the CRQ more convenient and time efficient to use in busy clinical settings (Bradley et al., 1998a).

The test-retest reliability of the CRQ has been assessed in two studies with COPD patients (Larson et al., 1993; Guyatt et al., 1987). The CRQ was administered to 25 patients with stable COPD a total of six times at two-week intervals (Guyatt et al., 1987). The mean scores for all four dimensions were similar at each administration (Guyatt et al., 1987). The coefficient of variation was 6% for the dyspnea dimension, 9% for fatigue and emotional function, and 12% for mastery (Guyatt et al., 1987). This study demonstrated that there was no significant change (either improvement or deterioration) in CRQ scores in stable COPD patients over a 12-week period (Guyatt et al., 1987). The second study administered the CRQ two times to 30 patients with stable COPD one-week apart (Larson et al., 1993). There were moderate to good correlations in all four dimensions of the CRQ (r was equal to 0.64 for fatigue, 0.68 for dyspnea, 0.73 for mastery, and 0.76 for emotional function) (Larson et al., 1993). Therefore, the CRQ has been shown to have moderate to good test-retest reliability.
Clinically, the CRQ appears to have face validity as a HRQOL measure for patients with chronic lung disease. It has been used in at least 32 clinical trials in patients with chronic lung diseases, attesting to its face validity (Lacasse et al., 1997; Larson et al., 1993). The CRQ also appears to have content validity as it was developed through an extensive process involving literature review, suggestions from health professionals and in-depth interviews with patients (Lacasse et al., 1997). It appears to tap into the main concepts of the ICIDH-2, i.e. functioning and disability (e.g. dyspnea with activity) and contextual factors (e.g. embarrassment, confidence).

Numerous studies have examined the validity of the CRQ in COPD patients (Bradley et al., 1998a, b; Larson et al., 1993; Guyatt et al., 1989b; Guyatt et al., 1987). Larson et al. (1993) found a moderate correlation between the dyspnea dimension and FEV₁ % predicted in 30 patients with stable COPD (r = 0.44). Guyatt et al. (1987) administered the CRQ to 13 patients with COPD whose physicians predicted that they would improve with a change in their treatment. The patients completed the CRQ before and two to six weeks after a change was made in their treatment (Guyatt et al., 1987). The authors reported that the scores on all four dimensions of the CRQ improved substantially, but that the patients' pulmonary function improved only slightly (Guyatt et al., 1987). The CRQ scores for all four dimensions were standardized on a 10-point scale (Guyatt et al., 1987). The improvements in the dimension scores were not stated, but they were depicted in a figure. From the figure, the dyspnea dimension appeared to improve from approximately 5.4 to 7.9, the fatigue dimension from approximately 6.5 to 8, the emotional function dimension from approximately 7.3 to 8, and the mastery dimension from approximately 6.3 to 8.5. Guyatt et al. (1987) admitted that they could not tell how much of this improvement was due to an effect of the intervention, and how much was due to a placebo effect (Guyatt et al., 1987).
Guyatt et al. (1987) also examined the validity of the CRQ using 28 COPD patients who entered a multidisciplinary inpatient respiratory rehabilitation program. The following measures were administered before the program began, two weeks post-discharge and serially during the next six months: the CRQ, FEV₁, the 6-minute walk test, the RAND Dyspnea Index, the RAND Quality of Life measure, and global ratings of dyspnea, fatigue, and emotional function from patients, patients’ relatives, a physician and a physiotherapist. The RAND Dyspnea Index places subjects into one of five levels according to whether they are short of breath on dressing, walking at their own pace on level ground, walking with others on level ground, and climbing stairs (Guyatt et al., 1989b). The RAND Quality of Life measure is a generic HRQOL measure with physical and emotional function dimensions (Guyatt et al., 1987). The authors reported that the scores on all four dimensions of the CRQ improved substantially (p<0.001). Guyatt et al. (1987) did not state the CRQ results, but they were depicted in a figure. From the figure, the dyspnea dimension appeared to improve from approximately 3.2 to 6.2, the fatigue dimension from approximately 4.8 to 6.6, the emotional function dimension from approximately 5.9 to 7.9, and the mastery dimension from approximately 5.8 to 8.2 (standardized to a 10-point scale). However, there was no significant change in the RAND Dyspnea Index (p = 0.28) or in the RAND Quality of Life measure (physical dimension p = 0.12, emotional dimension p = 0.06). Therefore, the authors concluded that the CRQ is more responsive than these two measures. There were moderate correlations between the change in CRQ scores and the change in other related measures. For example, changes in the dyspnea dimension were significantly correlated with changes in the 6-minute walk test (r = 0.46, p<0.05) and the patients’ global ratings of dyspnea, fatigue and emotional function (r = 0.37, 0.36 and 0.35 respectively, p<0.05). Changes in the fatigue dimension were significantly correlated with changes in the 6-minute walk test (r = 0.35,
p<0.05) and the patients' global ratings of dyspnea, fatigue and emotional function (r = 0.62, 0.42 and 0.36 respectively, p<0.05). There was also a significant correlation between changes in the emotional function dimension and changes in the patients' global rating of emotional function and dyspnea (r = 0.35 and 0.37 respectively, p<0.05). Therefore, the authors suggested that the CRQ is valid in patients with COPD, but that the results should be confirmed with further research.

Guyatt et al. (1989b) later did another study which involved 24 COPD patients enrolled in a randomized controlled drug trial. The following measures were used: the CRQ dyspnea score, the RAND Dyspnea Index, the Oxygen Cost Diagram (OCD), FEV₁, the 6-minute walk test, dyspnea reported after the 6-minute walk test (measured on a 10 centimeter visual analogue scale) and global ratings of change in dyspnea (measured on a seven-point Likert scale). The OCD is a 10 centimeter line with day-to-day activities placed along it in proportion to their required oxygen uptake (Guyatt et al., 1989b). Subjects are asked to mark the line to indicate the level of activity they can undertake without being limited by breathlessness (Guyatt et al., 1989b). Significant correlations were found between the change in CRQ dyspnea scores and change in FEV₁ (r = 0.55), 6-minute walk test (r = 0.52), dyspnea following the 6-minute walk test (r = 0.56), and global ratings of change in dyspnea (r = 0.84) (p<0.01). The correlations between the change in the RAND Dyspnea Index and the OCD were not as strong; correlation with change in FEV₁ r = 0.28 and 0.43 respectively, 6-minute walk test r = 0.31 and 0.37 respectively, dyspnea following the 6-minute walk test r = 0.28 and 0.34 respectively, and global ratings of change in dyspnea r = 0.49 and 0.58 respectively. The authors concluded that the CRQ dyspnea score is a more valid measure than the RAND Dyspnea Index and the OCD.
Bradley et al. (1998a) examined the validity of the CRQ with CF patients. As described earlier, the CRQ was administered to 45 adults with CF. The correlations of the fatigue, emotional function and dyspnea dimensions with FEV\textsubscript{1} % predicted were insignificant and poor (fatigue \( r = 0.009, p = 0.475 \); emotional function \( r = 0.0029, p = 0.426 \); dyspnea \( r = 0.245, p = 0.13 \)). However, there was a significant (but still poor) correlation between the mastery dimension and FEV\textsubscript{1} % predicted (\( r = 0.266, p = 0.041 \)).

Bradley et al. (1998b) also examined the validity of the CRQ in 12 adult CF patients completing inpatient intravenous antibiotic treatment for an acute pulmonary exacerbation (12 males, mean age 29, range 17 to 34 years). Patients were also required to complete the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a disease-specific measure that was developed to measure the HRQOL of people with COPD (Jones et al., 1991). It is a 76-item, self-administered questionnaire that consists of three dimensions: impact, activity and symptoms (Jones et al., 1991). The mean percentage change in the CRQ was 78\% for the dyspnea dimension, 77\% for the fatigue dimension, 30\% for the emotional function dimension, and 22\% for the mastery dimension. The mean percentage change in the SGRQ was less: -27\% for the impact dimension, -7\% for the activity dimension, and -15\% for the symptoms dimension. The correlations between the change in FEV\textsubscript{1} and the change in the CRQ dimension scores were poor to moderate; \( r = 0.37 \) for dyspnea, 0.50 for fatigue, 0.60 for emotional function, and 0.50 for mastery. The correlations between the change in FEV\textsubscript{1} and the change in the dimensions of the SGRQ were poor: \( r = -0.2 \) for impact, -0.14 for activity, and -0.11 for symptoms. Bradley et al. (1998b) concluded that the CRQ is a more valid measure than the SGRQ in adults with CF. They also concluded that changes in pulmonary function do not predict changes in HRQOL; both measures add different information to aid in the evaluation of interventions.
Waterhouse et al. (1994) examined the responsiveness of the CRQ using effect sizes. Sixty-eight adults with COPD completed the CRQ, and some or all of these patients completed it again 6 and 12 months later. The effect sizes for the patients who claimed their health had changed showed large statistically significant differences in some dimensions of the CRQ ($p < 0.05$).

In summary, the CRQ has been shown to be a reliable and valid measure of health-related quality of life in patients with COPD. Studies need to further examine the reliability, validity and responsiveness of the CRQ in CF patients.

1.7.6 Outcome Measures in Cystic Fibrosis: Concluding Remarks

The ICIDH-2 provided a conceptual framework with which to consider the outcome measures that are commonly used in CF practice and research. It is important to recognize that some measures (e.g. HRQOL measures) cross several concepts within the ICIDH-2 framework.

Pulmonary function tests ($FEV_1$ in particular) measure impairment and they are considered the best overall or “gold standard” outcome measure in CF practice and research. Chest radiograph scoring systems are less valid and sensitive to change in impairment over time, and sputum volume/weight are not reliable, valid or responsive outcome measures. Exercise tests, maximal and submaximal, can provide information regarding an individual’s degree of impairment and their prognosis. However, the responsiveness of maximal and submaximal exercise tests with CF patients is unclear. They can be costly in terms of time, assessor/subject burden, space, and in the case of maximal exercise tests, equipment.

Health-related quality of life measures can provide important reflections of the degree of functioning or disability an individual is experiencing. The WHO’s definition of health is “a
complete state of physical, mental, and social well-being and not merely absence of disease” (World Health Organization, 1976). The QWB, CRQ, FSI, CHQ, SF-36, CFQOL and the new measure by Tullis et al. (1999) are measures that attempt to provide useful information that is not just solely related to a single organ system or disease, such as PFTs. New or different treatment techniques can impact HRQOL; therefore it is important to try to assess this. Research that further validates generic and disease-specific HRQOL measures in patients with CF will help increase their use in practice and research.

The primary outcome measure chosen for this study was PFTs, specifically FEV₁, FVC and FEF₂₅₋₇₅% (% predicted and actual litres). In particular, the rate of change in % predicted FEV₁ in one year was examined and compared with the average annual rate of decline in CF patients. Pulmonary function tests provided insight into the impairment experienced by patients with CF; however there was also a desire to include measures that provide more insight into aspects of functioning and disability. Hence, two HRQOL measures were chosen as secondary outcome measures, specifically the QWB and the CRQ. Adherence to therapy was also chosen as a secondary outcome measure. This will be discussed further in Chapter 2.
2.0 METHODS

A randomized controlled trial was used to evaluate the effectiveness of the Flutter Device in comparison to the PEP Mask in the treatment of adults with Cystic Fibrosis. Adults enrolled in the study were randomized to treatment with the Flutter Device or the PEP Mask for a 13-month period. The study was run on an intention-to-treat basis.

2.1 SUBJECTS

2.1.1 Sampling and Recruitment

The average annual rate of decline in FEV$_1$ (% predicted) in CF patients is approximately -2% predicted per year (Davis et al., 1997). Therefore, a change or decline of (-) 4 % predicted per year was considered a minimally clinically important difference in pulmonary function. Using a two-tailed test with type 1 error of 0.05 and power of 80%, the sample size was calculated to be a minimum of 40 subjects per group in order to detect a statistically significant difference in the annual rate of decline in FEV$_1$ (% predicted). This estimation was done using a SD equal to 6.3 that was reported by L. Gaskin (personal communication, June 2001) for the PEP group in their study that compared the PEP Mask and CPT.

Subjects were recruited from the Adult Cystic Fibrosis Clinic at St. Michael’s Hospital in Toronto, Ontario. Patients were informed of the study through several means. A notice announcing the study was written in “News and Views”, a newsletter that is mailed to all patients who attend the clinic. Letters were mailed to eligible subjects to inform them of the study and invite them to learn more if interested, and phone calls were made to eligible subjects in follow-up to those letters. Eligible subjects were also approached in the clinic.
during their routine follow-up visits. Subject recruitment occurred between June 1998 and May 1999.

2.1.2 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were used:

Inclusion Criteria:

- 18 years of age or older
- baseline FEV$_1$ > 40% predicted
- no pulmonary exacerbation requiring hospitalization within one month of study entry
- no change in medications within one month of study entry
- written informed consent obtained
- willingness to attend five follow-up appointments over a 13-month period

Exclusion Criteria:

- absence of a daily cough or daily production of sputum

This exclusion criterion was set to exclude patients with extremely mild pulmonary disease. Patients who do not chronically produce sputum are not likely to respond to a physiotherapy treatment aimed at facilitating sputum clearance.

2.2 OUTCOME MEASURES

2.2.1 Primary Outcome Measures

The primary outcome measure in this study was the rate of change in pulmonary function as assessed by FEV$_1$ in actual (litres) and percent predicted values. Measures of FVC and FEF$_{25-75}$ (actual and percent predicted values) were also analyzed. Pulmonary function data was measured with spirometry testing (KoKo Spirometer, McArthur Medical Sales,
Fleisch Type Pneumotac) at every follow-up visit by an independent assessor, blinded to treatment group and time. All pulmonary function data was calculated as percent predicted values based on the standards developed by the American Thoracic Society Snowbird Workshop (1979). All subjects had their clinic appointment at approximately the same time of day from visit to visit in order to help limit the variability that can be seen in pulmonary function depending on time of day. Each subject was asked to perform their physiotherapy treatment once on the day of their follow-up appointment, prior to their visit and spirometry testing, if possible.

2.2.2 Secondary Outcome Measures

Secondary outcome measures included the QWB Scale and the CRQ. These were administered by a physiotherapist at the first follow-up visit post-recruitment and at every subsequent follow-up visit. The computerized version of the QWB was utilized. This program generated the total QWB score and all four domain scores (symptom/problem complex, physical, mobility and social scales) upon completion of the interview. The CRQ scores (total, dyspnea, fatigue, emotional function and mastery scores) were calculated manually. The scores were reported in the standard method suggested by Lacasse et al. (1997) i.e. the mean score was determined for each domain, which led to possible scores of one to seven on all domains.

Secondary outcome measures also included adherence to therapy. Attendance at scheduled clinic visits was monitored as one tactic for determining compliance since those who fail to attend their appointments rarely comply with any treatment regimen (King et al., 1983). Adherence was also monitored through a review of the subject’s daily diary by the physiotherapist during their clinic visits. Appendix 3 contains a sample of the daily diary. The diary required that the patient indicate each day whether they did therapy (yes or no), the
duration and frequency of the treatment session, and whether sputum was produced during the treatment session (yes or no). They were also asked to indicate whether they did any exercise (yes or no), for what length of time they exercised and whether or not they perspired (yes or no). This last question was included to get a sense of the intensity of their exercise session. Space was provided for patients to write subjective comments about their therapy and/or exercise. If patients failed to bring their diary to their follow-up visits, they were asked questions regarding their therapy and exercise by the physiotherapist.

Each subject’s adherence and exercise were rated for each follow-up period according to the following scales:

<table>
<thead>
<tr>
<th>Adherence Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 noncompliant</td>
<td>doing no physiotherapy (PT) at all</td>
</tr>
<tr>
<td>1 low compliance</td>
<td>doing PT 1 to 5 times/week</td>
</tr>
<tr>
<td>2 compliant</td>
<td>doing PT 6 times/week or more</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exercise Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 inactive</td>
<td>little to no activity outside daily activities</td>
</tr>
<tr>
<td>1 low activity</td>
<td>aerobic activity 3 or more times/week, not intense enough to sweat; or</td>
</tr>
<tr>
<td></td>
<td>aerobic activity 1 to 2 times/week, intense enough to sweat</td>
</tr>
<tr>
<td>2 active</td>
<td>aerobic activity 3 to 5 times/week, intense enough to sweat</td>
</tr>
</tbody>
</table>

The adherence scale is a modification of the scale used by Gaskin et al. (L. Gaskin, personal communication, 1998). The exercise scale was designed by the author for the purpose of this study.

2.2.3 Descriptive Data

Demographic information such as subject’s date of birth, weight, height and body mass index (BMI) was collected from the medical chart and documented on the data collection forms (Appendix 4). The number of hospital admissions per subject due to pulmonary exacerbation was recorded.
2.3 PROTOCOL

This research protocol was approved by The Wellesley Hospital Research Institute (research proposal # 443) and was subsequently grandfathered by the Research Ethics Board of St. Michael's Hospital. The study was explained to each subject and subjects were given an information form explaining the purpose of the study, what to expect, and the phone numbers of investigators (Appendix 5). Written informed consent was obtained from all subjects (Appendix 6).

Upon recruitment to the study, subjects were randomized to either the Flutter Device or the PEP Mask. An independent assistant used a random number table and placed either the word Flutter or PEP in sealed envelopes numbered 1 to 80. The envelopes were opened in sequence each time a subject was enrolled to determine whether he/she would be in the Flutter or PEP group.

2.3.1 Baseline Assessment and Patient Instruction

Baseline spirometry was done on the date of recruitment. Following randomization, each subject was provided with their device and taught how to perform the treatment technique correctly by a physiotherapist. Time was spent with each subject individually until he/she performed the technique properly and felt comfortable with it. Subjects were provided with a daily diary to record their therapy and exercise habits for the 13-month period.

2.3.1 a) Flutter Device Technique

Patients were instructed how to use the Flutter Device by a physiotherapist. The instructions provided by the manufacturer of the Flutter Device (Scandipharm) were followed and are outlined below:

Holding the Flutter in one hand, the patient inhales deeply and holds his/her breath for two to three seconds. Then he/she places the Flutter in their mouth and, keeping cheeks as stiff as possible, exhales through the Flutter Device. The degree of tilt of the Flutter Device is adjusted in order to maximize vibrations. The exhalation does not have to be forced. The
subject should perform between five and fifteen exhalations through the Flutter to mobilize the mucus. After the mucus is “loosened”, the patient increases the depth and speed of exhalation through the Flutter for one to three breaths to precipitate coughing and expectoration. This cycle is repeated until the patient feels “clear”, or for approximately twenty minutes.

Subjects were advised to use the Flutter Device two times per day for approximately 20 minutes per session, following any bronchodilator therapy they may take.

2.3.1 b) PEP Mask Technique

A physiotherapist used a manometer to select the appropriate resistor for each subject to achieve an expiratory pressure of 10 to 20 cm H2O during the middle part of expiration. The PEP Mask technique was taught as follows:

Sitting comfortably with his/her elbows supported on a table, the patient seals the mask over his/her mouth and nose and proceeds to breathe in and out ten to fifteen times. Exhalation should not be forced but does require some active work in order to breathe out through the resistor. After these ten to fifteen breaths through the PEP Mask, the patient removes it from his/her face, huffs, coughs and clears any secretions he/she is able to. This is followed by a period of relaxed, controlled breathing. The cycle is repeated approximately five to six times, and should take approximately twenty minutes to complete.

Subjects were advised to use the PEP Mask two times per day for approximately 20 minutes per session, following any bronchodilator therapy they may take.

Written instructions of both treatment techniques were provided in effort to further standardize the treatment. Instructions regarding the care and cleaning of their device were also provided (Appendix 7 and 8).

2.3.2 Follow-up Assessments

Subjects were asked to return to clinic one month post-recruitment to review their technique with a physiotherapist and ensure it was being done correctly. This provided a one-month “training period” with their treatment technique. At this visit spirometry was repeated, adherence was reviewed, and the QWB and the CRQ were administered.

Subsequent to the visit one month post-recruitment, subjects were asked to return for follow-up assessment every three-months; that is at the 4th, 7th, 10th, and 13th month post-
recruitment. A three-month interval was chosen because most patients are routinely followed every three months, where they undergo spirometry and consultation by a respirologist, nurse, physiotherapist and dietician. To summarize, subjects were asked to attend a total of five follow-up visits post-recruitment. Spirometry, the QWB and the CRQ were measured at each follow-up visit. Subjects were also ranked on the adherence and exercise scales at each follow-up visit (for the time since their last follow-up visit) based on their diary and/or subjective comments.

A Simplified Timeline of Assessments

<table>
<thead>
<tr>
<th>Recruitment randomized teaching spirometry</th>
<th>1st Visit technique checked spirometry QWB CRQ adherence exercise</th>
<th>2nd Visit spirometry QWB CRQ adherence exercise</th>
<th>3rd Visit spirometry QWB CRQ adherence exercise</th>
</tr>
</thead>
</table>

2.4 Cointervention and Contamination

Cointervention is defined as the performance of additional diagnostic or therapeutic acts on the experimental but not the control patients (Sackett et al., 1991). This results in an increase in the difference in clinical outcomes between the experimental and control groups (Sackett et al., 1991). Contamination occurs when the control patients accidentally receive the experimental treatment (Sackett et al., 1991). This causes a reduction in the difference in clinical outcomes between the experimental and control groups (Sackett et al., 1991). All attempts were made to minimize cointervention and contamination.

Exercise has a potential influence on the health and well-being of CF patients. All subjects were encouraged to remain as active as possible, and they were asked to record any change in their exercise habits in their daily diary. The advice routinely given to patients is that
they should participate in aerobic exercise for 20 to 40 minutes per session, a minimum of three times per week. No formal exercise programs were prescribed for subjects as part of the study.

Subjects were asked to do no other form of airway clearance other than that assigned to them for the duration of the study. Any change in their treatment routines was recorded. If a subject developed a pulmonary exacerbation requiring intravenous antibiotics at home or in the hospital at any time during the study, the physiotherapist and the patient may have decided to increase the amount of therapy they do daily and/or add conventional physiotherapy during their exacerbation. Subjects returned to their study treatment (the Flutter Device or PEP Mask) once they stabilized. If a patient was due for a follow-up visit at the time of an exacerbation requiring intravenous antibiotics, his/her follow-up visit was delayed and completed approximately one month post-completion of the intravenous antibiotics. This fit with the practice of the Adult CF Clinic at St. Michael's Hospital where patients are routinely reassessed approximately one month post-discharge from hospital after a pulmonary exacerbation.

2.5 DATA MANAGEMENT AND ANALYSIS

Descriptive statistics were analyzed using SPSS Version 10.0 (SPSS Inc., Chicago, Illinois). Independent samples t-tests were used for between groups comparisons. Gender was an exception; it was analyzed with a chi-square test in SigmaStat Version 2.03 (SPSS Inc., Chicago, Illinois). SigmaStat was used to perform linear regression to determine each individual’s slope or rate of decline in pulmonary function values by visit. These slopes were entered into SPSS and analyzed using independent t-tests. The data was also converted into Excel (Microsoft 97) and then into SAS Release 6.12. A biostatistician used SAS to perform
linear regression to determine each individual's slope or rate of decline in pulmonary function values by time (i.e. one year), and to test for differences between groups. Adherence and exercise habits were evaluated through review of subjects' diaries and comments made at follow-up visits. Chi-square tests (done in SigmaStat) were used to compare adherence and exercise between groups. The level of significance used in all of the statistical tests was 0.05. SigmaPlot Version 5 (SPSS Inc, Chicago, Illinois) was used to create graphs.
3.0 RESULTS

3.1 SAMPLE CHARACTERISTICS

Approximately 200 patients were identified as potential candidates for this study i.e. patients who attend the Adult Cystic Fibrosis Clinic at St. Michael's Hospital who were 18 years of age and older and who had an FEV₁ > 40 % predicted. Forty-three subjects met the additional inclusion and exclusion criteria and provided informed, written consent to participate in the study. One subject was omitted from all analyses because he stopped attending clinic after his 2nd follow-up visit. Thus, the final sample size was 42. The characteristics of the subjects at recruitment (baseline) are shown in Table 5. There was no significant difference between the Flutter and PEP groups at the time of recruitment.

Table 5

Subject Characteristics at Recruitment (Baseline)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Flutter Group</th>
<th>PEP Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>9 males, 12 females</td>
<td>15 males, 6 females</td>
<td>0.119</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (+/- 8.7)</td>
<td>28 (+/- 8.1)</td>
<td>0.378</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.5 (+/- 14.2)</td>
<td>68.5 (+/- 12.8)</td>
<td>0.334</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>22.6 (+/- 3.9)</td>
<td>23.1 (+/- 3.1)</td>
<td>0.629</td>
</tr>
<tr>
<td>FEV₁ (Litres)</td>
<td>2.24 (+/- 0.66)</td>
<td>2.51 (+/- 1.24)</td>
<td>0.462</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>68.67 (+/- 18.51)</td>
<td>65.95 (+/- 19.91)</td>
<td>0.593</td>
</tr>
<tr>
<td>FVC (Litres)</td>
<td>3.54 (+/- 1.08)</td>
<td>3.76 (+/- 1.13)</td>
<td>0.415</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>84.81 (+/- 20.52)</td>
<td>82.05 (+/- 17.88)</td>
<td>0.697</td>
</tr>
<tr>
<td>FEF₂₅₋₇⁵% (Litres)</td>
<td>1.26 (+/- 0.57)</td>
<td>1.27 (+/- 0.76)</td>
<td>0.967</td>
</tr>
<tr>
<td>FEF₂₅₋₇⁵% (% pred)</td>
<td>30.72 (+/- 13.60)</td>
<td>26.84 (+/- 15.17)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- standard deviation (SD))
Not all subjects attended every follow-up assessment despite best efforts to achieve 100% attendance. The sample size at each follow-up visit is presented in Table 6.

Table 6
Sample Size at Each Follow-Up Assessment

<table>
<thead>
<tr>
<th>Visit</th>
<th>Flutter Group</th>
<th>PEP Group</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>1st Visit</td>
<td>15</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>2nd Visit</td>
<td>15</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>3rd Visit</td>
<td>16</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>4th Visit</td>
<td>17</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>5th Visit</td>
<td>21</td>
<td>21</td>
<td>42</td>
</tr>
</tbody>
</table>

3.2 PRIMARY OUTCOME MEASURES

3.2.1 Mean Pulmonary Function Data at Each Follow-up Visit

There was no significant difference between the two groups in mean FEV\textsubscript{1}, FVC or FEF\textsubscript{25-75} % predicted at any visit using independent t-tests. These results are summarized in Table 7 and are depicted in Figures 1, 2 and 4 A). There was also no significant difference between the two groups in mean FEV\textsubscript{1}, FVC or FEF\textsubscript{25-75} in litres at any visit with the exception of FEV\textsubscript{1} (litres) at the 2\textsuperscript{nd} follow-up (\( p = 0.045 \)), using independent t-tests. These results are summarized in Table 7 and are depicted in Figures 3 A) and B) and 4 B).

The divergence between the Flutter and PEP groups in mean pulmonary function values at the 1\textsuperscript{st} and 2\textsuperscript{nd} follow-up visits can be explained by the subjects missing at these visits. Table 8 shows that the Flutter subjects missing at the 1\textsuperscript{st} and 2\textsuperscript{nd} follow-up visits had, on average, higher mean pulmonary function values at recruitment. Hence, their absence at the 1\textsuperscript{st} and 2\textsuperscript{nd}
follow-up visits likely led to lower group mean pulmonary function values. Table 9 shows that the PEP subjects missing at the 1st and 2nd follow-up visits had lower mean pulmonary function values at recruitment. The absence of these PEP subjects at the 1st and 2nd follow-up visits likely inflated the group mean pulmonary function values.

Data in Table 7 is presented as the mean (+/- standard deviation (SD), standard error (SE)). Data in Tables 8 and 9 is presented as the mean (+/- SD), range. All of the graphs displayed in the results contain the mean values of the outcome of interest, and error bars that indicate the standard error of the mean. Although the x-axis shows the visits to be at equal time intervals, visit one was one month post-recruitment (recruitment = visit 0), and the subsequent visits took place approximately every three months, the 5th visit being at the 13th month.
<table>
<thead>
<tr>
<th>Visit</th>
<th>Treatment Group (Total Sample Size)</th>
<th>n</th>
<th>mean FEV(_1) (% predicted)</th>
<th>n</th>
<th>mean FEV(_1) (litres)</th>
<th>n</th>
<th>mean FVC (% predicted)</th>
<th>n</th>
<th>mean FVC (litres)</th>
<th>n</th>
<th>mean FEF(_{25-75}) (% predicted)</th>
<th>n</th>
<th>mean FEF(_{25-75}) (litres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Flutter (21)</td>
<td>21</td>
<td>68.67 (+/- 18.51, 4.04)</td>
<td>21</td>
<td>2.24 (+/- .66, .14)</td>
<td>21</td>
<td>84.81 (+/- 20.52, 4.48)</td>
<td>21</td>
<td>3.54 (+/- 1.08, .24)</td>
<td>18</td>
<td>30.72 (+/- 13.60, 3.21)</td>
<td>18</td>
<td>1.26 (+/- .57, .13)</td>
</tr>
<tr>
<td></td>
<td>PEP (21)</td>
<td>21</td>
<td>65.57 (+/- 18.77, 4.10)</td>
<td>21</td>
<td>2.43 (+/- .97, .21)</td>
<td>21</td>
<td>82.43 (+/- 18.73, 4.09)</td>
<td>21</td>
<td>3.85 (+/- 1.29, .28)</td>
<td>19</td>
<td>26.64 (+/- 15.17, 3.48)</td>
<td>20</td>
<td>1.27 (+/- .76, .17)</td>
</tr>
<tr>
<td>1st Visit</td>
<td>Flutter (15)</td>
<td>14</td>
<td>61.36 (+/- 14.10, 3.77)</td>
<td>15</td>
<td>1.99 (+/- .82, .16)</td>
<td>14</td>
<td>78.21 (+/- 18.84, 5.04)</td>
<td>15</td>
<td>3.10 (+/- 1.05, .27)</td>
<td>13</td>
<td>24.38 (+/- .94, .24, 2.56)</td>
<td>13</td>
<td>1.00 (+/- .47, .13)</td>
</tr>
<tr>
<td></td>
<td>PEP (17)</td>
<td>17</td>
<td>68.00 (+/- 18.28, 4.43)</td>
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<td>2.55 (+/- .99, .24)</td>
<td>17</td>
<td>83.76 (+/- 18.83, 4.57)</td>
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<td>3.92 (+/- 1.32, .32)</td>
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<td>29.75 (+/- 15.26, 3.82)</td>
<td>16</td>
<td>1.26 (+/- .83, .21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.275</td>
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<td>p = 0.277</td>
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<td>p = 0.325</td>
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<tr>
<td>2nd Visit</td>
<td>Flutter (15)</td>
<td>15</td>
<td>61.60 (+/- 11.06, 2.88)</td>
<td>15</td>
<td>2.00 (+/- .48, .12)</td>
<td>15</td>
<td>78.20 (+/- 14.22, 3.67)</td>
<td>15</td>
<td>3.26 (+/- .83, .22)</td>
<td>12</td>
<td>23.93 (+/- .87, .26, 2.29)</td>
<td>18</td>
<td>.98 (+/- .37, .10)</td>
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<tr>
<td></td>
<td>PEP (18)</td>
<td>18</td>
<td>69.89 (+/- 17.62, 4.15)</td>
<td>18</td>
<td>2.56 (1.00, .24)</td>
<td>18</td>
<td>86.89 (+/- 19.82, 4.67)</td>
<td>18</td>
<td>3.96 (+/- 1.35, .32)</td>
<td>18</td>
<td>30.26 (+/- 14.37, 3.39)</td>
<td>18</td>
<td>1.38 (+/- .76, .18)</td>
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<tr>
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<td>p = 0.124</td>
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<td>p = 0.048</td>
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<td>p = 0.146</td>
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<td>p = 0.061</td>
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<tr>
<td>3rd Visit</td>
<td>Flutter (16)</td>
<td>16</td>
<td>67.25 (+/- 18.58, 4.14)</td>
<td>16</td>
<td>2.16 (+/- .62, .16)</td>
<td>16</td>
<td>84.44 (+/- 18.04, 4.51)</td>
<td>16</td>
<td>3.48 (+/- 1.00, .25)</td>
<td>12</td>
<td>25.06 (+/- 10.28, 2.97)</td>
<td>12</td>
<td>1.04 (+/- .46, .13)</td>
</tr>
<tr>
<td></td>
<td>PEP (19)</td>
<td>19</td>
<td>68.21 (+/- 19.60, 4.50)</td>
<td>19</td>
<td>2.43 (+/- 1.01, .23)</td>
<td>19</td>
<td>82.95 (+/- 19.91, 4.57)</td>
<td>19</td>
<td>3.78 (+/- 1.40, .32)</td>
<td>19</td>
<td>28.53 (+/- 15.51, 3.56)</td>
<td>19</td>
<td>1.27 (+/- .77, .18)</td>
</tr>
<tr>
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<td>p = 0.503</td>
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<td>p = 0.345</td>
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<tr>
<td>4th Visit</td>
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<td>65.06 (+/- 14.55, 3.53)</td>
<td>17</td>
<td>2.13 (+/- .85, .16)</td>
<td>17</td>
<td>82.18 (+/- 18.21, 3.93)</td>
<td>17</td>
<td>3.44 (+/- 1.03, .25)</td>
<td>17</td>
<td>26.65 (+/- 14.26, 3.48)</td>
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<td>65.00 (+/- 20.69, 5.02)</td>
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<td>2.43 (+/- 1.03, .25)</td>
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<td>81.18 (+/- 24.24, 5.86)</td>
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<td>3.84 (+/- 1.47, .36)</td>
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<td>27.12 (+/- 12.52, 3.04)</td>
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<td>1.25 (+/- .86, .17)</td>
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<td>p = 0.919</td>
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<td>p = 0.514</td>
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<tr>
<td>5th Visit</td>
<td>Flutter (21)</td>
<td>21</td>
<td>65.24 (+/- 18.07, 3.94)</td>
<td>21</td>
<td>2.10 (+/- .61, .13)</td>
<td>21</td>
<td>80.19 (+/- 18.33, 4.00)</td>
<td>21</td>
<td>3.32 (+/- .96, .21)</td>
<td>19</td>
<td>27.79 (+/- 17.49, 4.01)</td>
<td>19</td>
<td>1.13 (+/- .85, .15)</td>
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<tr>
<td></td>
<td>PEP (21)</td>
<td>21</td>
<td>61.52 (+/- 20.98, 4.58)</td>
<td>21</td>
<td>2.28 (+/- .97, .21)</td>
<td>21</td>
<td>77.57 (+/- 21.86, 4.73)</td>
<td>21</td>
<td>3.62 (+/- 1.33, .29)</td>
<td>20</td>
<td>24.40 (+/- 14.08, 3.15)</td>
<td>20</td>
<td>1.13 (+/- .70, .16)</td>
</tr>
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<td></td>
<td></td>
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<td>p = 0.542</td>
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<td>p = 0.517</td>
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<td>p = 0.675</td>
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<td>p = 0.508</td>
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<td>p = 0.988</td>
</tr>
</tbody>
</table>
### Table 8

**Summary of Flutter Subjects Missing Follow-up Visits**

<table>
<thead>
<tr>
<th>Visit</th>
<th>number of Flutter subjects missing</th>
<th>mean FEV₁ (% predicted) at baseline</th>
<th>mean FEV₁ (litres) at baseline</th>
<th>mean FVC (% predicted) at baseline</th>
<th>mean FVC (litres) at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Visit</td>
<td>6</td>
<td>79.8% (+/- 14.8), 62-99</td>
<td>2.62 (+/- 0.30), 2.24-2.88</td>
<td>98.5% (+/- 11.4), 87-115</td>
<td>4.21 (+/- 0.86), 3.48-5.29</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Visit</td>
<td>6</td>
<td>88% (+/- 11.1), 73-99</td>
<td>2.87 (+/- 0.58), 2.20-3.94</td>
<td>104.7% (+/- 10.5), 90-117</td>
<td>4.38 (+/- 1.09), 3.21-6.10</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Visit</td>
<td>5</td>
<td>69% (+/- 19.6), 61-100</td>
<td>2.31 (+/- 0.58), 1.40-2.86</td>
<td>82.2% (+/- 23.3), 52-114</td>
<td>3.56 (+/- 1.20), 1.91-5.21</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; Visit</td>
<td>4</td>
<td>80% (+/- 16.3), 61-99</td>
<td>2.48 (+/- 0.26), 2.24-2.74</td>
<td>91.8% (+/- 19.1), 69-115</td>
<td>3.61 (+/- 0.39), 3.25-4.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit</th>
<th>number of Flutter subjects missing</th>
<th>mean FEF&lt;sub&gt;25-75&lt;/sub&gt;% (% predicted) at baseline</th>
<th>mean FEF&lt;sub&gt;25-75&lt;/sub&gt; (litres) at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Visit</td>
<td>6</td>
<td>35.3% (+/- 15.1), 20-56</td>
<td>1.41 (+/- 0.51), 0.87-2.29</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Visit</td>
<td>6</td>
<td>41.7% (+/- 13.0), 20-56</td>
<td>1.72 (+/- 0.53), 0.87-2.29</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Visit</td>
<td>5</td>
<td>32.5% (+/- 10.8), 21-47</td>
<td>1.37 (+/- 0.35), 1.03-1.86</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; Visit</td>
<td>4</td>
<td>39% (+/- 9.8), 30-51</td>
<td>1.54 (+/- 0.29), 1.27-1.88</td>
</tr>
</tbody>
</table>
Table 9

Summary of PEP Subjects Missing Follow-up Visits

<table>
<thead>
<tr>
<th>Visit</th>
<th>number of PEP subjects missing</th>
<th>mean FEV₁ (% predicted) at baseline</th>
<th>mean FEV₁ (litres) at baseline</th>
<th>mean FVC (% predicted) at baseline</th>
<th>mean FVC (litres) at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Visit</td>
<td>4</td>
<td>60.5% (+/- 12.5), 49-77</td>
<td>2.26 (+/- 0.66), 1.73-3.10</td>
<td>80.5% (+/- 7.7), 76-92</td>
<td>3.83 (+/- 0.64), 3.29-4.75</td>
</tr>
<tr>
<td>2nd Visit</td>
<td>3</td>
<td>52.7% (+/- 9.1), 46-63</td>
<td>2.21 (+/- 0.77), 1.73-3.10</td>
<td>72% (+/- 8.7), 62-77</td>
<td>3.76 (+/- 0.87), 3.06-4.75</td>
</tr>
<tr>
<td>3rd Visit</td>
<td>2</td>
<td>54.5% (+/- 12.0), 46-63</td>
<td>2.45 (+/- 0.93), 1.79-3.10</td>
<td>69.5% (+/- 10.6), 62-77</td>
<td>3.91 (+/- 1.20), 3.06-4.75</td>
</tr>
<tr>
<td>4th Visit</td>
<td>4</td>
<td>62.8% (+/- 12.4), 49-79</td>
<td>2.19 (+/- 0.62), 1.73-3.10</td>
<td>80.8% (+/- 10.3), 73-96</td>
<td>3.58 (+/- 0.82), 2.97-4.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit</th>
<th>number of PEP subjects missing</th>
<th>mean FEF₂₅-₇₅% (% predicted) at baseline</th>
<th>mean FEF 25-75% (litres) at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Visit</td>
<td>4</td>
<td>24.8% (+/- 12.9), 14-40</td>
<td>1.09 (+/- 0.57), 0.57-1.64</td>
</tr>
<tr>
<td>2nd Visit</td>
<td>3</td>
<td>20.3% (+/- 9.3), 14-31</td>
<td>1.00 (+/- 0.56), 0.62-1.64</td>
</tr>
<tr>
<td>3rd Visit</td>
<td>2</td>
<td>23.5 (+/- 10.6), 16-31</td>
<td>1.20 (+/- 0.63), 0.75-1.64</td>
</tr>
<tr>
<td>4th Visit</td>
<td>4</td>
<td>24.8% (+/- 7.5), 14-31</td>
<td>1.11 (+/- 0.42), 0.62-1.64</td>
</tr>
</tbody>
</table>
Figure 1: Mean FEV₁ (% predicted) Over Time

There was no significant difference between the Flutter and PEP groups in mean FEV₁ (% predicted) at any visit.
There was no significant difference between the Flutter and PEP groups in mean FVC (% predicted) at any visit.
Figure 3: A) Mean FEV₁ (litres) and B) Mean FVC (litres) Over Time

There was no significant difference between the two groups in mean FEV₁ or mean FVC (litres) at any visit.
Figure 4: A) Mean FEF_{25-75\%} % predicted and B) Mean FEF_{25-75\%} litres Over Time

There was no significant difference between groups in mean FEF_{25-75\%} (% predicted or litres) at any visit.
3.2.2 Change in Pulmonary Function Data From Recruitment to Each Follow-up Visit

There were no significant differences between the two groups in the change in FEV₁, FVC or FEF₂₅₋₇₅% from recruitment to any follow-up visit using independent t-tests. However, not every subject attended every follow-up visit, so the mean values are not always based on the same subjects over time. Table 10 summarizes these results, and the changes are depicted in Figures 5, 6 and 7.
## Table 10
Change in Mean Pulmonary Function Data From Recruitment to Each Follow-up Visit

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FEV₁ (% pred) from recruitment to 1st follow-up</th>
<th>Change in FEV₁ (% pred) from recruitment to 2nd follow-up</th>
<th>Change in FEV₁ (% pred) from recruitment to 3rd follow-up</th>
<th>Change in FEV₁ (% pred) from recruitment to 4th follow-up</th>
<th>Change in FEV₁ (% pred) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-3.21 (+/- 10.39, 2.78)</td>
<td>0.67 (+/- 10.13, 2.62)</td>
<td>-1.31 (+/- 8.31, 2.08)</td>
<td>-0.94 (+/- 10.49, 2.54)</td>
<td>-3.43 (+/- 12.37, 2.70)</td>
</tr>
<tr>
<td>PEP</td>
<td>1.24 (+/- 6.38, 1.55)</td>
<td>2.17 (+/- 9.01, 2.12)</td>
<td>-0.53 (+/- 8.75, 2.01)</td>
<td>-1.24 (+/- 9.33, 2.26)</td>
<td>-4.05 (+/- 9.58, 2.09)</td>
</tr>
<tr>
<td></td>
<td>p = 0.154</td>
<td>p = 0.880</td>
<td>p = 0.788</td>
<td>p = 0.932</td>
<td>p = 0.857</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FEV₁ (litres) from recruitment to 1st follow-up</th>
<th>Change in FEV₁ (litres) from recruitment to 2nd follow-up</th>
<th>Change in FEV₁ (litres) from recruitment to 3rd follow-up</th>
<th>Change in FEV₁ (litres) from recruitment to 4th follow-up</th>
<th>Change in FEV₁ (litres) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-0.08 (+/- 0.27, 0.07)</td>
<td>0.01 (+/- 0.32, 0.08)</td>
<td>-0.08 (+/- 0.27, 0.07)</td>
<td>-0.05 (+/- 0.33, 0.08)</td>
<td>-0.14 (+/- 0.43, 0.08)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.08 (+/- 0.25, 0.06)</td>
<td>0.10 (+/- 0.30, 0.07)</td>
<td>-0.002 (+/- 0.34, 0.08)</td>
<td>-0.08 (+/- 0.32, 0.06)</td>
<td>-0.17 (+/- 0.36, 0.06)</td>
</tr>
<tr>
<td></td>
<td>p = 0.075</td>
<td>p = 0.445</td>
<td>p = 0.592</td>
<td>p = 0.658</td>
<td>p = 0.631</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FVC (%) from recruitment to 1st follow-up</th>
<th>Change in FVC (%) from recruitment to 2nd follow-up</th>
<th>Change in FVC (%) from recruitment to 3rd follow-up</th>
<th>Change in FVC (%) from recruitment to 4th follow-up</th>
<th>Change in FVC (%) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-2.07 (+/- 8.70, 2.32)</td>
<td>1.33 (+/- 11.00, 2.84)</td>
<td>-1.19 (+/- 7.87, 1.97)</td>
<td>-1.00 (+/- 8.94, 2.41)</td>
<td>-4.82 (+/- 11.57, 2.53)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.88 (+/- 11.41, 2.40)</td>
<td>2.72 (+/- 10.18, 2.40)</td>
<td>-0.84 (+/- 6.80, 1.56)</td>
<td>-1.65 (+/- 9.57, 2.32)</td>
<td>-4.86 (+/- 8.87, 1.94)</td>
</tr>
<tr>
<td></td>
<td>p = 0.277</td>
<td>p = 0.711</td>
<td>p = 0.891</td>
<td>p = 0.848</td>
<td>p = 0.648</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FVC (litres) from recruitment to 1st follow-up</th>
<th>Change in FVC (litres) from recruitment to 2nd follow-up</th>
<th>Change in FVC (litres) from recruitment to 3rd follow-up</th>
<th>Change in FVC (litres) from recruitment to 4th follow-up</th>
<th>Change in FVC (litres) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-0.12 (+/- 0.35, 0.09)</td>
<td>0.05 (+/- 0.45, 0.12)</td>
<td>-0.06 (+/- 0.33, 0.08)</td>
<td>-0.09 (+/- 0.36, 0.09)</td>
<td>-0.22 (+/- 0.50, 0.11)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.07 (+/- 0.28, 0.08)</td>
<td>0.13 (+/- 0.38, 0.08)</td>
<td>-0.06 (+/- 0.29, 0.07)</td>
<td>-0.07 (+/- 0.44, 0.11)</td>
<td>-0.23 (+/- 0.45, 0.10)</td>
</tr>
<tr>
<td></td>
<td>p = 0.084</td>
<td>p = 0.595</td>
<td>p = 0.800</td>
<td>p = 0.938</td>
<td>p = 0.972</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FEF₂₅₋₇₀ (%) (% pred) from recruitment to 1st follow-up</th>
<th>Change in FEF₂₅₋₇₀ (%) (% pred) from recruitment to 2nd follow-up</th>
<th>Change in FEF₂₅₋₇₀ (%) (%pred) from recruitment to 3rd follow-up</th>
<th>Change in FEF₂₅₋₇₀ (%) (% pred) from recruitment to 4th follow-up</th>
<th>Change in FEF₂₅₋₇₀ (%) (% pred) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-1.00 (+/- 8.93, 2.19)</td>
<td>0.50 (+/- 6.78, 1.90)</td>
<td>-3.18 (+/- 8.37, 1.92)</td>
<td>-0.36 (+/- 9.65, 2.63)</td>
<td>-0.58 (+/- 11.18, 2.79)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.86 (+/- 6.96, 1.86)</td>
<td>2.00 (+/- 6.23, 1.98)</td>
<td>-0.18 (+/- 8.04, 1.95)</td>
<td>-1.73 (+/- 8.07, 2.68)</td>
<td>-4.17 (+/- 8.12, 1.91)</td>
</tr>
<tr>
<td></td>
<td>p = 0.525</td>
<td>p = 0.555</td>
<td>p = 0.308</td>
<td>p = 0.663</td>
<td>p = 0.286</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in FEF₂₅₋₇₀ (litres) from recruitment to 1st follow-up</th>
<th>Change in FEF₂₅₋₇₀ (litres) from recruitment to 2nd follow-up</th>
<th>Change in FEF₂₅₋₇₀ (litres) from recruitment to 3rd follow-up</th>
<th>Change in FEF₂₅₋₇₀ (litres) from recruitment to 4th follow-up</th>
<th>Change in FEF₂₅₋₇₀ (litres) from recruitment to 5th follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-0.04 (+/- 0.30, 0.09)</td>
<td>0.02 (+/- 0.28, 0.08)</td>
<td>-0.15 (+/- 0.28, 0.08)</td>
<td>-0.02 (+/- 0.42, 0.11)</td>
<td>-0.03 (+/- 0.44, 0.11)</td>
</tr>
<tr>
<td>PEP</td>
<td>-0.13 (+/- 0.52, 0.13)</td>
<td>0.04 (+/- 0.37, 0.09)</td>
<td>-0.06 (+/- 0.38, 0.09)</td>
<td>-0.10 (+/- 0.33, 0.08)</td>
<td>-0.18 (+/- 0.32, 0.07)</td>
</tr>
<tr>
<td></td>
<td>p = 0.647</td>
<td>p = 0.684</td>
<td>p = 0.469</td>
<td>p = 0.535</td>
<td>p = 0.237</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
There was no significant difference between the Flutter and PEP groups in the change in mean FEV<sub>1</sub> (% predicted) from recruitment to any follow-up visit.
Figure 6: Change in A) Mean FVC (% predicted) and B) Mean FEF$_{25-75\%}$ (% predicted) From Recruitment

There was no significant difference between the Flutter and PEP groups in the change in mean FVC or FEF$_{25-75\%}$ (% predicted) from recruitment to any follow-up visit.
Figure 7: Change in Mean A) FEV₁, B) FVC and C) FEF₂₅₋₇₅% (litres) From Recruitment

There was no significant difference between the Flutter and PEP groups in the change in mean FEV₁, FVC or FEF₂₅₋₇₅% (litres) from recruitment to any follow-up visit.
3.2.3 Change in Individual's FEV₁ % predicted From One Visit to the Next

The change in each individual's FEV₁ % predicted from recruitment to visit 1, visit 1 to 2, 2 to 3, 3 to 4 and 4 to 5 is displayed in Table 11. It is evident that there is variability in the change in FEV₁ % predicted in an individual from one visit to the next. However, 9 subjects in the Flutter group and 11 subjects in the PEP group had a positive mean change in FEV₁ % predicted per visit.
## Table 11

Change in Individual's FEV\(_1\) % predicted From One Visit to the Next

<table>
<thead>
<tr>
<th>Subject</th>
<th>change visit 0 to 1</th>
<th>change visit 1 to 2</th>
<th>change visit 2 to 3</th>
<th>change visit 3 to 4</th>
<th>change visit 4 to 5</th>
<th>mean change per visit (+/- SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>004 Flutter</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>-7</td>
<td>6</td>
<td>2.80 (+/- 5.66)</td>
</tr>
<tr>
<td>005 Flutter</td>
<td>-10</td>
<td>14</td>
<td>.</td>
<td>.</td>
<td>-10</td>
<td>-2.00 (+/- 13.86)</td>
</tr>
<tr>
<td>007 Flutter</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>3</td>
<td>1</td>
<td>2.00 (+/- 1.41)</td>
</tr>
<tr>
<td>010 Flutter</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>4</td>
<td>4.00 (-)</td>
</tr>
<tr>
<td>013 Flutter</td>
<td>5</td>
<td>12</td>
<td>-7</td>
<td>-2</td>
<td>5</td>
<td>2.60 (+/- 7.30)</td>
</tr>
<tr>
<td>014 Flutter</td>
<td>-32</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>-32.00 (-)</td>
</tr>
<tr>
<td>015 Flutter</td>
<td>.</td>
<td>.</td>
<td>8</td>
<td>1</td>
<td>-7</td>
<td>0.00 (+/- 8.68)</td>
</tr>
<tr>
<td>017 Flutter</td>
<td>8</td>
<td>-14</td>
<td>4</td>
<td>-4</td>
<td>-5</td>
<td>-2.20 (+/- 8.56)</td>
</tr>
<tr>
<td>018 Flutter</td>
<td>-2</td>
<td>2</td>
<td>-2</td>
<td>-2</td>
<td>.</td>
<td>0.80 (+/- 4.38)</td>
</tr>
<tr>
<td>019 Flutter</td>
<td>-8</td>
<td>-8</td>
<td>.</td>
<td>.</td>
<td>3</td>
<td>-3.67 (+/- 5.86)</td>
</tr>
<tr>
<td>020 Flutter</td>
<td>0</td>
<td>2</td>
<td>-1</td>
<td>-1</td>
<td>4</td>
<td>0.60 (+/- 2.17)</td>
</tr>
<tr>
<td>021 Flutter</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>22</td>
<td>5.60 (+/- 9.29)</td>
</tr>
<tr>
<td>022 Flutter</td>
<td>.</td>
<td>.</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2.00 (+/- 1.00)</td>
</tr>
<tr>
<td>024 Flutter</td>
<td>-4</td>
<td>-2</td>
<td>2</td>
<td>5</td>
<td>-4</td>
<td>-0.60 (+/- 3.98)</td>
</tr>
<tr>
<td>026 Flutter</td>
<td>9</td>
<td>-2</td>
<td>4</td>
<td>-6</td>
<td>3</td>
<td>1.60 (+/- 5.77)</td>
</tr>
<tr>
<td>033 Flutter</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
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</tr>
<tr>
<td>035 Flutter</td>
<td>-8</td>
<td>-8</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>-5.00 (+/- 0.00)</td>
</tr>
<tr>
<td>036 Flutter</td>
<td>-6</td>
<td>.</td>
<td>.</td>
<td>-2</td>
<td>3</td>
<td>-1.67 (+/- 4.51)</td>
</tr>
<tr>
<td>037 Flutter</td>
<td>-7</td>
<td>.</td>
<td>.</td>
<td>-3</td>
<td>9</td>
<td>-0.33 (+/- 8.33)</td>
</tr>
<tr>
<td>042 Flutter</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>043 Flutter</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>001 PEP</td>
<td>-5</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
<td>-8</td>
<td>-3.00 (+/- 2.35)</td>
</tr>
<tr>
<td>002 PEP</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>003 PEP</td>
<td>-3</td>
<td>-5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1.20 (+/- 2.78)</td>
</tr>
<tr>
<td>005 PEP</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>-3</td>
<td>5</td>
<td>2.60 (+/- 3.51)</td>
</tr>
<tr>
<td>008 PEP</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1.60 (+/- 1.14)</td>
</tr>
<tr>
<td>009 PEP</td>
<td>0</td>
<td>1</td>
<td>-6</td>
<td>19</td>
<td>-11</td>
<td>0.80 (+/- 11.37)</td>
</tr>
<tr>
<td>011 PEP</td>
<td>.</td>
<td>.</td>
<td>-10</td>
<td>3</td>
<td>-2</td>
<td>-3.00 (+/- 6.56)</td>
</tr>
<tr>
<td>012 PEP</td>
<td>15</td>
<td>-2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>3.40 (+/- 8.73)</td>
</tr>
<tr>
<td>018 PEP</td>
<td>-3</td>
<td>7</td>
<td>-12</td>
<td>4</td>
<td>-3</td>
<td>-1.40 (+/- 7.37)</td>
</tr>
<tr>
<td>023 PEP</td>
<td>0</td>
<td>-7</td>
<td>-11</td>
<td>12</td>
<td>-4</td>
<td>-2.00 (+/- 8.80)</td>
</tr>
<tr>
<td>027 PEP</td>
<td>-2</td>
<td>-4</td>
<td>6</td>
<td>.</td>
<td>.</td>
<td>0.00 (+/- 5.26)</td>
</tr>
<tr>
<td>028 PEP</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>.</td>
<td>.</td>
<td>6.00 (+/- 1.00)</td>
</tr>
<tr>
<td>029 PEP</td>
<td>11</td>
<td>0</td>
<td>4</td>
<td>-2</td>
<td>15</td>
<td>5.60 (+/- 7.23)</td>
</tr>
<tr>
<td>030 PEP</td>
<td>3</td>
<td>-3</td>
<td>21</td>
<td>-18</td>
<td>5</td>
<td>2.00 (+/- 13.42)</td>
</tr>
<tr>
<td>031 PEP</td>
<td>2</td>
<td>-3</td>
<td>10</td>
<td>-9</td>
<td>3</td>
<td>0.80 (+/- 7.06)</td>
</tr>
<tr>
<td>032 PEP</td>
<td>6</td>
<td>-19</td>
<td>11</td>
<td>-2</td>
<td>5</td>
<td>0.20 (+/- 11.89)</td>
</tr>
<tr>
<td>034 PEP</td>
<td>-2</td>
<td>-1</td>
<td>8</td>
<td>-7</td>
<td>8</td>
<td>1.20 (+/- 8.81)</td>
</tr>
<tr>
<td>038 PEP</td>
<td>.</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>.</td>
<td>5.30 (+/- 2.52)</td>
</tr>
<tr>
<td>039 PEP</td>
<td>-13</td>
<td>-3</td>
<td>-8</td>
<td>11</td>
<td>1</td>
<td>-2.00 (+/- 8.89)</td>
</tr>
<tr>
<td>040 PEP</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>041 PEP</td>
<td>2</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>-2</td>
<td>0.00 (+/- 2.83)</td>
</tr>
</tbody>
</table>
3.2.4 Estimate of the Annual Change in Pulmonary Function Data

Each individual's change in pulmonary function from recruitment to final follow-up was divided by their time from recruitment to final follow-up. This provided an estimate of the annual change in their pulmonary function. The mean estimated annual change in pulmonary function for the Flutter and PEP groups are found in Table 12. There was no significant difference between the two groups.

Table 12
Mean Estimated Annual Change in Pulmonary Function Data

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Annual change in FEV₁ (% predicted)</th>
<th>Annual change in FRC (lres)</th>
<th>Annual change in FVC (% predicted)</th>
<th>Annual change in FVC (lres)</th>
<th>Annual change in FEF₂⁰percent (%) predicted</th>
<th>Annual change in FEF₂⁰percent (lres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-2.72 (± 10.75, 2.35)</td>
<td>-0.11 (± 0.37, 0.08)</td>
<td>-3.53 (± 2.73, 2.13)</td>
<td>-0.17 (± 0.41, 0.08)</td>
<td>-0.08 (± 0.38, 2.35)</td>
<td>-0.03 (± 0.97, 0.08)</td>
</tr>
<tr>
<td>PEP</td>
<td>-0.53 (± 8.28, 1.81)</td>
<td>-0.14 (± 0.32, 0.07)</td>
<td>-4.28 (± 7.75, 1.68)</td>
<td>-0.20 (± 0.40, 0.08)</td>
<td>-3.54 (± 7.07, 1.87)</td>
<td>-0.15 (± 0.28, 0.08)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.748</td>
<td>0.748</td>
<td>0.741</td>
<td>0.776</td>
<td>0.300</td>
<td>0.294</td>
</tr>
</tbody>
</table>

Data is presented as mean (±/ SD, SE)

3.2.5 Slope of Pulmonary Function Data

The slope or annual rate of decline of the pulmonary function data was estimated or determined in several ways:

Linear regression was used to determine the slope for each subject by visit. There was no significant difference between the mean slope (by visit) of the Flutter and PEP groups. The mean slopes of the pulmonary function data by visit are summarized in Table 13.

Table 13
Slope of Pulmonary Function Data (by visit)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Slope of FEV₁ (% pred)</th>
<th>Slope of FEV₁ (lres)</th>
<th>Slope of FVC (% pred)</th>
<th>Slope of FVC (lres)</th>
<th>Slope of FEF₂⁰percent (% pred)</th>
<th>Slope of FEF₂⁰percent (lres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>-0.46 (± 2.08, 0.45)</td>
<td>-0.02 (± 0.08, 0.02)</td>
<td>-0.71 (± 2.04, 0.44)</td>
<td>-0.03 (± 0.08, 0.02)</td>
<td>-0.24 (± 2.35, 0.52)</td>
<td>-0.009 (± 0.08, 0.02)</td>
</tr>
<tr>
<td>PEP</td>
<td>-0.04 (± 2.00, 0.46)</td>
<td>-0.04 (± 0.07, 0.02)</td>
<td>-0.97 (± 1.98, 0.43)</td>
<td>-0.05 (± 0.08, 0.02)</td>
<td>-0.73 (± 1.51, 0.34)</td>
<td>-0.03 (± 0.08, 0.01)</td>
</tr>
<tr>
<td>p-value</td>
<td>p = 0.594</td>
<td>p = 0.509</td>
<td>p = 0.673</td>
<td>p = 0.659</td>
<td>p = 0.441</td>
<td>p = 0.365</td>
</tr>
</tbody>
</table>

Data is presented as mean (±/ SD, SE)
Subsequently, each individual's slope (by visit) was multiplied by four to obtain an estimate of the slope per year i.e. there was one follow-up visit approximately every three months, multiplied by four to get approximately 12 months. No significant difference was found between the two groups in the mean estimated slope per year (Table 14).

**Table 14**

Estimated Slope of Pulmonary Function Data (for one year)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Slope of FEV1 (% pred)</th>
<th>Slope of FEV1 (time)</th>
<th>Slope of FVC (% pred)</th>
<th>Slope of FVC (time)</th>
<th>Slope of RFEF25-75% (% pred)</th>
<th>Slope of RFEF25-75% (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutair</td>
<td>-1.97 (+/-.83, 1.02)</td>
<td>-0.06 (+/-.30, 0.07)</td>
<td>-2.86 (+/-.81, 1.78)</td>
<td>-0.14 (+/-.03, 0.09)</td>
<td>-0.97 (+/-.98, 2.18)</td>
<td>-0.04 (+/-.37, 0.09)</td>
</tr>
<tr>
<td>FEP</td>
<td>-3.35 (+/-.81, 1.75)</td>
<td>-0.14 (+/-.38, 0.08)</td>
<td>-3.50 (+/-.79, 1.71)</td>
<td>-0.06 (+/-.03, 0.09)</td>
<td>-2.91 (+/-.65, 1.38)</td>
<td>-0.12 (+/-.03, 0.05)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.584</td>
<td>0.509</td>
<td>0.673</td>
<td>0.669</td>
<td>0.441</td>
<td>0.396</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

Finally, the pulmonary function data was also analyzed by a biostatistician using linear regression to calculate each subject's slope by actual time (i.e. one year). This is the most appropriate method of determining the slopes. No significant difference was found between the two groups in the mean slope or annual rate of decline in pulmonary function. This data is presented in Table 15.

**Table 15**

Slope of Pulmonary Function Data (for one year)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Slope of FEV1 (% pred)</th>
<th>Slope of FEV1 (time)</th>
<th>Slope of FVC (% pred)</th>
<th>Slope of FVC (time)</th>
<th>Slope of RFEF25-75% (% pred)</th>
<th>Slope of RFEF25-75% (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutair</td>
<td>-1.97 (+/-.81, 1.78)</td>
<td>-0.09 (+/-.43, 0.09)</td>
<td>-3.04 (+/-.79, 1.79)</td>
<td>-0.13 (+/-.03, 0.09)</td>
<td>-2.09 (+/-.40, 1.79)</td>
<td>-0.08 (+/-.03, 0.09)</td>
</tr>
<tr>
<td>FEP</td>
<td>-4.19 (+/-.84, 1.75)</td>
<td>-0.16 (+/-.03, 0.09)</td>
<td>-4.69 (+/-.79, 1.79)</td>
<td>-0.03 (+/-.03, 0.09)</td>
<td>-3.05 (+/-.62, 1.39)</td>
<td>-0.11 (+/-.02, 0.09)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.394</td>
<td>0.233</td>
<td>0.681</td>
<td>0.345</td>
<td>0.709</td>
<td>0.722</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
3.3 SECONDARY OUTCOME MEASURES

3.3.1 Quality of Well-Being Scale

There was no significant difference between the Flutter and PEP groups in mean QWB total score at any follow-up visit. This data is summarized in Table 16. The mean slope of the Flutter group for the QWB total score was -0.001 (+/- 0.01). This was not significantly different from the mean slope of the PEP group which was -0.006 (+/- 0.02) (p = 0.295).

Table 16
Summary of Mean Total QWB Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>0.69 (+/- 0.07, 0.02)</td>
<td>0.68 (+/- 0.08, 0.02)</td>
<td>0.67 (+/- 0.07, 0.02)</td>
<td>0.68 (+/- 0.06, 0.01)</td>
<td>0.67 (+/- 0.07, 0.02)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.72 (+/- 0.06, 0.02)</td>
<td>0.67 (+/- 0.06, 0.02)</td>
<td>0.66 (+/- 0.05, 0.01)</td>
<td>0.68 (+/- 0.07, 0.02)</td>
<td>0.65 (+/- 0.11, 0.03)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.274</td>
<td>0.621</td>
<td>0.37</td>
<td>0.753</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

The mean score of the symptom or problem domain of the QWB did not differ significantly between the two groups at any follow-up visit (Table 17). The mean slope of this domain in the Flutter group was 0.001 (+/- 0.01), and it was 0.004 (+/- 0.01) in the PEP group. These mean slopes were not significantly different (p = 0.476).

Table 17
Summary of Mean QWB Symptom/Problem Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>0.27 (+/- 0.06, 0.01)</td>
<td>0.28 (+/- 0.03, 0.01)</td>
<td>0.29 (+/- 0.04, 0.01)</td>
<td>0.28 (+/- 0.02, 0.01)</td>
<td>0.29 (+/- 0.03, 0.01)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.28 (+/- 0.07, 0.02)</td>
<td>0.28 (+/- 0.03, 0.01)</td>
<td>0.28 (+/- 0.02, 0.01)</td>
<td>0.28 (+/- 0.03, 0.01)</td>
<td>0.27 (+/- 0.07, 0.02)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.534</td>
<td>0.632</td>
<td>0.675</td>
<td>0.658</td>
<td>0.295</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
The data of the QWB mobility dimension is presented in Table 18. There was no significant difference between the two groups in the mean mobility scores at any follow-up visit. There was also no significant difference in the mean slopes of the mobility dimension (p = 0.544). The mean slope of the Flutter group was 0.001 (+/- 0.00), and the mean slope of the PEP group was 0.000 (+/- 0.00).

Table 18

Summary of Mean QWB Mobility Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>0.005 (+/- 0.01, 0.03)</td>
<td>0.004 (+/- 0.02, 0.00)</td>
<td>0.001 (+/- 0.01, 0.00)</td>
<td>0.000 (+/- 0.01, 0.00)</td>
<td>0.008 (+/- 0.01, 0.00)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.004 (+/- 0.02, 0.00)</td>
<td>0.004 (+/- 0.02, 0.00)</td>
<td>0.003 (+/- 0.01, 0.00)</td>
<td>0.000 (+/- 0.00, 0.00)</td>
<td>0.003 (+/- 0.01, 0.00)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.815</td>
<td>0.925</td>
<td>0.637</td>
<td>0.333</td>
<td>0.710</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

The mean scores of the physical dimension did not differ significantly at any follow-up visit (Table 19). The mean slope of this dimension was 0.001 (+/- 0.01) for the Flutter group and 0.001 (+/- 0.00) for the PEP group. The difference between the two groups in the mean slope of the physical dimension was not significant (p = 0.869).

Table 19

Summary of Mean QWB Physical Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>0.017 (+/- 0.02, 0.01)</td>
<td>0.013 (+/- 0.02, 0.01)</td>
<td>0.016 (+/- 0.02, 0.01)</td>
<td>0.010 (+/- 0.02, 0.00)</td>
<td>0.002 (+/- 0.03, 0.05)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.006 (+/- 0.02, 0.00)</td>
<td>0.019 (+/- 0.03, 0.01)</td>
<td>0.009 (+/- 0.02, 0.01)</td>
<td>0.014 (+/- 0.02, 0.01)</td>
<td>0.014 (+/- 0.02, 0.01)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.147</td>
<td>0.468</td>
<td>0.342</td>
<td>0.581</td>
<td>0.360</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
The fourth dimension of the QWB is the social dimension. The mean social scores were not significantly different at any follow-up visit (Table 20). Similarly, the slopes of the Flutter and PEP groups for the social dimension were not significantly different (p = 0.088). The slopes of the Flutter and PEP groups were -0.001 (+/- 0.01) and 0.003 (+/- 0.01), respectively.

**Table 20**

Summary of Mean QWB Social Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (5 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>0.020 (+/- 0.03, 0.01)</td>
<td>0.023 (+/- 0.03, 0.01)</td>
<td>0.026 (+/- 0.03, 0.01)</td>
<td>0.024 (+/- 0.03, 0.01)</td>
<td>0.016 (+/- 0.02, 0.01)</td>
</tr>
<tr>
<td>PEP</td>
<td>0.014 (+/- 0.03, 0.01)</td>
<td>0.024 (+/- 0.03, 0.01)</td>
<td>0.017 (+/- 0.03, 0.01)</td>
<td>0.025 (+/- 0.03, 0.01)</td>
<td>0.027 (+/- 0.03, 0.01)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.584</td>
<td>0.934</td>
<td>0.362</td>
<td>0.026</td>
<td>0.202</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

Finally, there was no significant difference between the Flutter and PEP groups in the change in QWB total and dimension scores from the first to the final follow-up visit (Table 21).

**Table 21**

Change in QWB Scores from the First Follow-up Visit to the Final Assessment

<table>
<thead>
<tr>
<th>Change from 1st to final follow-up visit</th>
<th>Flutter</th>
<th>PEP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QWB total score</td>
<td>-0.017 (+/- 0.07, 0.02)</td>
<td>-0.072 (+/- 0.12, 0.03)</td>
<td>0.135</td>
</tr>
<tr>
<td>Symptom/problem</td>
<td>0.013 (+/- 0.06, 0.01)</td>
<td>0.008 (+/- 0.11, 0.03)</td>
<td>0.888</td>
</tr>
<tr>
<td>Mobility Score</td>
<td>0.002 (+/- 0.02, 0.00)</td>
<td>0.000 (+/- 0.02, 0.01)</td>
<td>0.762</td>
</tr>
<tr>
<td>Physical Score</td>
<td>0.004 (+/- 0.03, 0.01)</td>
<td>0.006 (+/- 0.01, 0.00)</td>
<td>0.796</td>
</tr>
<tr>
<td>Social Score</td>
<td>-0.001 (+/- 0.03, 0.01)</td>
<td>0.014 (+/- 0.02, 0.01)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
Figure 8 depicts the mean QWB total scores over time, while Figure 9 depicts the mean QWB dimension scores over time. Please note that Figures 9 B, C and D have a different scale than Figures 8 and 9 A. This was done to ensure that the data was legible. The error bars indicate the standard error of the mean.

Figure 8: Mean Total QWB Score Over Time

There was no significant difference between the Flutter and PEP groups in the mean total QWB score at any follow-up visit, nor between the mean slopes of the two groups (p = 0.295).
Figure 9: Mean QWB Dimension Scores Over Time (A-D)

There was no significant difference in mean scores at any follow-up visit or in the slopes (p-values for mean slopes: A) Symptom/Problem p = 0.476, B) Physical p = 0.869, C) Mobility p = 0.544, and D) Social Score p = 0.088).
3.3.2 Chronic Respiratory Questionnaire

The mean total CRQ score of the Flutter and PEP groups did not differ significantly at any follow-up visit (Table 22). The mean slope of the total CRQ score for the Flutter and PEP groups was 0.07 (+/- 1.00, 0.22) and 0.06 (+/- 0.86, 0.19) respectively. There was no statistical difference between the mean slopes of the two groups (p = 0.980).

Table 22
Summary of Mean Total CRQ Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Follow-up (1 month post-recruitment)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Follow-up (3 months post-recruitment)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Follow-up (6 months post-recruitment)</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Follow-up (9 months post-recruitment)</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>19.34 (+/- 3.02, 0.76)</td>
<td>18.68 (+/- 4.02, 1.07)</td>
<td>18.67 (+/- 3.72, 0.99)</td>
<td>19.82 (+/- 2.90, 0.73)</td>
<td>19.12 (+/- 3.97, 0.89)</td>
</tr>
<tr>
<td>PEP</td>
<td>20.35 (+/- 2.76, 0.87)</td>
<td>18.40 (+/- 4.25, 1.10)</td>
<td>20.01 (+/- 5.25, 1.24)</td>
<td>18.82 (+/- 5.43, 1.32)</td>
<td>20.03 (+/- 4.50, 1.01)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.326</td>
<td>0.410</td>
<td>0.423</td>
<td>0.501</td>
<td>0.501</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

There was no significant difference between the Flutter and PEP groups with respect to mean CRQ dyspnea scores at any follow-up visit (Table 23). The mean slope of the dyspnea dimension was 0.16 (+/- 0.33, 0.07) for the Flutter group and 0.07 (+/- 0.38, 0.09) for the PEP group. There was no statistical difference between these mean slopes (p = 0.462).

Table 23
Summary of Mean CRQ Dyspnea Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Follow-up (1 month post-recruitment)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Follow-up (3 months post-recruitment)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Follow-up (6 months post-recruitment)</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Follow-up (9 months post-recruitment)</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>4.02 (+/- 1.28, 0.32)</td>
<td>4.28 (+/- 1.14, 0.31)</td>
<td>4.03 (+/- 1.24, 0.33)</td>
<td>4.56 (+/- 1.23, 0.28)</td>
<td>4.35 (+/- 1.08, 0.24)</td>
</tr>
<tr>
<td>PEP</td>
<td>4.30 (+/- 0.97, 0.24)</td>
<td>4.15 (+/- 1.47, 0.38)</td>
<td>4.56 (+/- 1.39, 0.33)</td>
<td>4.37 (+/- 1.73, 0.42)</td>
<td>4.47 (+/- 1.43, 0.32)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.48</td>
<td>0.799</td>
<td>0.278</td>
<td>0.708</td>
<td>0.784</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
The mean CRQ fatigue dimension scores are presented in Table 24. There was no significant difference in the mean fatigue score of the Flutter and PEP groups at any follow-up visit. The mean slope of the fatigue dimension was 0.03 (+/- 0.40, 0.09) for the Flutter group, and -0.02 (+/- 0.31, 0.07) for the PEP group. This was not statistically significant (p = 0.674).

Table 24
Summary of Mean CRQ Fatigue Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>4.20 (+/- 1.19, 0.35)</td>
<td>4.38 (+/- 1.49, 0.40)</td>
<td>4.04 (+/- 1.42, 0.38)</td>
<td>4.14 (+/- 0.98, 0.25)</td>
<td>4.06 (+/- 1.45, 0.32)</td>
</tr>
<tr>
<td>PEP</td>
<td>4.91 (+/- 1.11, 0.27)</td>
<td>4.02 (1.67, 0.42)</td>
<td>4.39 (+/- 1.87, 0.44)</td>
<td>3.94 (+/- 1.81, 0.44)</td>
<td>4.49 (1.44, 0.32)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.088</td>
<td>0.543</td>
<td>0.562</td>
<td>0.695</td>
<td>0.358</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)

There was no significant difference in the mean scores for the emotional function dimension at any follow-up visit (Table 25). There was also no significant difference between the Flutter and PEP groups in the mean slope of the emotional function dimension (p = 0.354). The mean slope was -0.03 (0.40, 0.09) for the Flutter group and 0.08 (+/- 0.35, 0.08) for the PEP group.

Table 25
Summary of Mean CRQ Emotional Function Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>5.23 (+/- 0.69, 0.17)</td>
<td>5.16 (+/- 1.07, 0.26)</td>
<td>4.97 (+/- 1.26, 0.34)</td>
<td>5.02 (+/- 1.09, 0.27)</td>
<td>4.99 (+/- 1.16, 0.26)</td>
</tr>
<tr>
<td>PEP</td>
<td>4.98 (+/- 1.30, 0.32)</td>
<td>4.78 (+/- 1.50, 0.38)</td>
<td>5.10 (+/- 1.57, 0.37)</td>
<td>4.68 (+/- 1.43, 0.35)</td>
<td>5.37 (+/- 1.24, 0.28)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.454</td>
<td>0.431</td>
<td>0.788</td>
<td>0.452</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/- SD, SE)
The mean scores of the CRQ mastery dimension were also not significantly different at any follow-up visit. These scores are presented in Table 26. The mean slope of the mastery dimension was -0.05 (+/− 0.23, 0.05) for the Flutter group, and -0.07 (+/− 0.22, 0.05) for the PEP group. These were not significantly different (p = 0.715).

Table 26

Summary of Mean CRQ Mastery Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>1st Follow-up (1 month post-recruitment)</th>
<th>2nd Follow-up (3 months post-recruitment)</th>
<th>3rd Follow-up (6 months post-recruitment)</th>
<th>4th Follow-up (9 months post-recruitment)</th>
<th>5th Follow-up (12 months post-recruitment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutter</td>
<td>5.89 (+/− 0.87, 0.22)</td>
<td>5.88 (+/− 1.11, 0.30)</td>
<td>5.63 (+/− 0.88, 0.23)</td>
<td>5.69 (+/− 0.87, 0.22)</td>
<td>5.73 (+/− 1.15, 0.26)</td>
</tr>
<tr>
<td>PEP</td>
<td>6.18 (+/− 0.63, 0.15)</td>
<td>5.81 (+/− 0.80, 0.20)</td>
<td>5.96 (+/− 0.88, 0.21)</td>
<td>5.82 (+/− 1.10, 0.27)</td>
<td>5.71 (+/− 1.01, 0.23)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.284</td>
<td>0.86</td>
<td>0.296</td>
<td>0.848</td>
<td>0.971</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/− SD, SE)

Finally, there was no significant difference between the Flutter and PEP groups in the change in CRQ total and dimension scores from the first to the final follow-up visit (Table 27).

Table 27

Change in CRQ Scores from the First Follow-up Visit to the Final Assessment

<table>
<thead>
<tr>
<th>Change from 1st to final follow-up visit</th>
<th>Flutter</th>
<th>PEP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRQ total score</td>
<td>0.08 (+/− 2.97, 0.77)</td>
<td>0.36 (+/− 3.45, 0.83)</td>
<td>0.808</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>0.26 (+/− 1.46, 0.38)</td>
<td>0.31 (+/− 1.50, 0.36)</td>
<td>0.926</td>
</tr>
<tr>
<td>Fatigue score</td>
<td>-0.02 (+/− 0.77, 0.20)</td>
<td>-0.38 (+/− 1.30, 0.31)</td>
<td>0.335</td>
</tr>
<tr>
<td>Emotional function score</td>
<td>-0.09 (+/− 0.95, 0.25)</td>
<td>0.66 (+/− 1.36, 0.33)</td>
<td>0.085</td>
</tr>
<tr>
<td>Mastery score</td>
<td>-0.08 (+/− 0.86, 0.22)</td>
<td>-0.24 (+/− 0.78, 0.19)</td>
<td>0.604</td>
</tr>
</tbody>
</table>

Data is presented as mean (+/− SD, SE)
Figure 10 depicts the mean CRQ total scores over time, and Figure 11 depicts the mean CRQ dimension scores over time. The error bars indicate the standard error of the mean.

Figure 10: Mean Total CRQ Score Over Time

There was no significant difference between the Flutter and PEP groups in mean total CRQ score at any follow-up visit nor between the mean slopes of the two groups (p-value for mean slope: p = 0.980).
There was no significant difference in the mean CRQ dimension scores at any follow-up visit, nor between the mean slopes (p-values for mean slopes: A) dyspnea p = 0.462, B) fatigue p = 0.674, C) emotional function p = 0.354, D) mastery p = 0.715).
3.3.3 Adherence

Each subject's diary and subjective comments at follow-up visits were reviewed and each subject was classified according to the adherence scale described in the methods i.e. 0 noncompliant, 1 low compliance, or 2 good compliance. Chi-square analysis of this data revealed no significant difference between the Flutter and PEP groups in adherence throughout the study period. The results are summarized in Table 28.

Table 28

Summary of Adherence Analysis

<table>
<thead>
<tr>
<th>Adherence Scale</th>
<th>Visit 1 (1 Month follow-up)</th>
<th>Visit 2 (3 month follow-up)</th>
<th>Visit 3 (6 month follow-up)</th>
<th>Visit 4 (9 month follow-up)</th>
<th>Visit 5 (12 month follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 noncompliant</td>
<td>1 Flutter, 2 PEP</td>
<td>5 Flutter, 5 PEP</td>
<td>8 Flutter, 5 PEP</td>
<td>6 Flutter, 6 PEP</td>
<td>6 Flutter, 7 PEP</td>
</tr>
<tr>
<td>1 low compliance</td>
<td>10 Flutter, 7 PEP</td>
<td>6 Flutter, 5 PEP</td>
<td>2 Flutter, 6 PEP</td>
<td>3 Flutter, 6 PEP</td>
<td>3 Flutter, 4 PEP</td>
</tr>
<tr>
<td>2 good compliance</td>
<td>10 Flutter, 12 PEP</td>
<td>10 Flutter, 11 PEP</td>
<td>11 Flutter, 10 PEP</td>
<td>12 Flutter, 9 PEP</td>
<td>12 Flutter, 10 PEP</td>
</tr>
<tr>
<td>Chi-square</td>
<td>1.045</td>
<td>0.139</td>
<td>2.740</td>
<td>1.429</td>
<td>0.402</td>
</tr>
<tr>
<td>p-value</td>
<td>0.363</td>
<td>0.933</td>
<td>0.254</td>
<td>0.480</td>
<td>0.818</td>
</tr>
</tbody>
</table>

Figure 12 depicts the percentage of subjects in each group who were noncompliant with their therapy.
This study was run on an intention-to-treat basis. Patients were rated for their adherence to therapy even if they did not solely perform the assigned treatment. The subjects who strayed from their study routine are briefly described here, and Appendix 9 contains the comments or reasons these subjects gave for altering their treatment during the course of the study. Three subjects in the PEP group did not solely use the PEP Mask. One subject in the PEP group (001 PEP) reverted to CPT (her pre-study treatment) by the 2nd follow-up visit because she did not find the PEP Mask worked and she preferred CPT. Another PEP subject
(038 PEP) did not adhere to any therapy until approximately the 3rd follow-up visit when he started a combination of PEP Mask and CPT. A third subject in the PEP group (039 PEP) used CPT more than the PEP Mask throughout the study period (Appendix 9). Five subjects in the Flutter group used techniques other than the Flutter. One subject in the Flutter group (014 Flutter) used the Flutter for approximately one month before reverting to the PEP Mask (her pre-study treatment) (similar to contamination). By the final follow-up visit she was using a combination of PEP Mask and CPT (similar to conintervention). Another subject in the Flutter group (026 Flutter) reverted to CPT (his pre-study treatment) by the 2nd follow-up visit because he "didn't find the Flutter effective" (similar to contamination). A third patient in the Flutter group (015 Flutter) used the Flutter for the first month but then she became sick and started to use the Flutter approximately once per day and CPT approximately three times per day (similar to cointervention). She stated that she felt she had "not done her treatment if she only used the Flutter", and she was "not sure if this is because she has always used CPT". One patient in the Flutter group (018 Flutter) reported at her final follow-up visit that for the last two months of the study period she was using the Flutter at night and CPT in the morning (similar to conintervention). She found this routine suited her because "in the mornings when she feels lazy, CPT takes less energy", while "the Flutter takes more work". Finally, a fifth subject in the Flutter group who was expecting a baby (019 Flutter) reported at her 2nd follow-up visit that she was using a combination of Flutter and CPT (similar to cointervention); but by the final follow-up visit she was using the Flutter as a sole method of treatment again.

### 3.3.4 Exercise

Each subject's habitual level of exercise was estimated through review of their diary and summarized according to the exercise scale described in the methods i.e. 0 inactive, 1 low
activity, or 2 active. Chi-square analysis of this data revealed no significant difference in the exercise habits of the Flutter and PEP groups. The data is presented in Table 29.

Table 29

Summary of Analysis of Exercise Habits

<table>
<thead>
<tr>
<th>Exercise Scale</th>
<th>Visit 1 (1 month follow-up)</th>
<th>Visit 2 (3 month follow-up)</th>
<th>Visit 3 (6 month follow-up)</th>
<th>Visit 4 (9 month follow-up)</th>
<th>Visit 5 (12 month follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 inactive</td>
<td>14 Flutter, 7 PEP</td>
<td>14 Flutter, 8 PEP</td>
<td>14 Flutter, 8 PEP</td>
<td>12 Flutter, 9 PEP</td>
<td>13 Flutter, 7 PEP</td>
</tr>
<tr>
<td>1 low activity</td>
<td>4 Flutter, 10 PEP</td>
<td>6 Flutter, 11 PEP</td>
<td>4 Flutter, 10 PEP</td>
<td>6 Flutter, 8 PEP</td>
<td>6 Flutter, 9 PEP</td>
</tr>
<tr>
<td>2 active</td>
<td>3 Flutter, 4 PEP</td>
<td>1 Flutter, 2 PEP</td>
<td>3 Flutter, 3 PEP</td>
<td>3 Flutter, 4 PEP</td>
<td>2 Flutter, 5 PEP</td>
</tr>
<tr>
<td>Chi-square</td>
<td>5.048</td>
<td>3.440</td>
<td>4.208</td>
<td>0.857</td>
<td>3.856</td>
</tr>
<tr>
<td>p-value</td>
<td>0.080</td>
<td>0.179</td>
<td>0.122</td>
<td>0.851</td>
<td>0.158</td>
</tr>
</tbody>
</table>

3.3.5 Number of Hospital Admissions for Pulmonary Exacerbation

There were 14 hospitalizations in the Flutter group and 6 in the PEP group over the course of the study. Independent t-tests found no significant difference in the mean number of hospitalizations due to pulmonary exacerbation for individuals in the Flutter and PEP groups (mean 0.67 and 0.29 respectively, p = 0.168).

The next chapter summarizes and discusses the results.
4.0 DISCUSSION

Pulmonary disease is the primary cause of morbidity and mortality in individuals with CF (Davis et al., 1996; Ramsey, 1996). Chronic, persistent lung infection and inflammation lead to progressive airway obstruction and damage (Jankowski, 1987). This causes pulmonary function to decrease over time; however the rate at which it declines can vary (Davis et al., 1996).

Airway clearance techniques are nonpharmacologic treatments whose goal is to reduce airway obstruction, and thus help to maintain or improve pulmonary function and subsequently improve health-related quality of life. Some adults prefer independent and portable forms of physiotherapy, such as the Flutter Device or the PEP Mask.

The objective of this study was to evaluate the effectiveness of the Flutter Device in comparison to the PEP Mask in the treatment of adults with Cystic Fibrosis. The findings showed no significant difference between the mean slopes of FEV$_1$, FVC and FEF$_{25-75}$% in litres or % predicted values. Health-related quality of life was a secondary outcome that was measured with the QWB and the CRQ. There were no significant differences between the Flutter and PEP groups in the mean slopes of the QWB or CRQ total or dimension scores, or in the mean change in these scores from the beginning to the end of the study. Secondary outcome measures also included the evaluation of patient adherence to the Flutter Device and PEP Mask. Again, there was no significant difference between the Flutter and PEP groups in adherence. Finally, there was no significant difference in the mean number of hospitalizations for individuals in the Flutter and PEP groups. This study will contribute to the field of
rehabilitation in CF as it is the first study of its duration and size to evaluate the effectiveness of the Flutter Device in adults with CF. However, as will be discussed shortly, the findings of this study need to be further validated before a decision about the effectiveness of the Flutter Device can be made.

4.1 EFFECT ON PULMONARY FUNCTION

The primary outcome measure was the effect the Flutter Device and the PEP Mask had on pulmonary function over the study period, particularly FEV₁ % predicted. Although some individuals did not attend every follow-up visit, there was complete pulmonary function data for every subject at recruitment and at the final follow-up visit approximately 13 months post-recruitment. The pulmonary function data was analyzed in several ways with the consistent finding that there was no significant difference between the Flutter and PEP groups in the change or slope in any pulmonary function value over the study period.

The mean slope of FEV₁ % predicted was negative for both the Flutter and the PEP groups; however, as was illustrated in Table 11, nearly half of the Flutter and PEP groups (9 individuals in the Flutter group and 11 individuals in the PEP group) had a mean change in FEV₁ % predicted per visit that was positive. Therefore, some subjects did do well throughout the duration of the study, while others did not.

In this study the mean slope or annual rate of decline of FEV₁ % predicted was -1.97 (+/- 8.14) for the Flutter group and -4.16 (+/- 8.04) for the PEP group (p = 0.384). The average annual rate of decline in FEV₁ % predicted in CF patients is approximately -2%
predicted per year (Davis et al., 1997). Therefore, the Flutter group continued to decline at a rate just slightly less than average, while the PEP group declined at a rate greater than average. This difference was not statistically significant; however these trends favour the Flutter Device. A larger sample size or longer study duration would ensure that the lack of a significant difference was not simply the effect of low power.

Three other studies have recently evaluated the effects of the PEP Mask, PD and percussion and/or the Flutter Device on pulmonary function (McIlwaine et al., 2001, 1997; Gaskin et al., 1998). The results of this study are different than the findings of McIlwaine et al. (1997) who did a one-year trial comparing the PEP Mask to CPT in CF patients. They reported that the slope of FEV₁ % predicted was +5.98 (SE +/- 2.5) for the PEP Mask group and -2.28 (SE +/- 2.9) for the CPT group. Their study had a similar duration (one-year) and they attempted to control the contaminating effects of exercise by asking subjects to maintain their pre-study level of physical activity throughout the study period. However, there were several differences in methodology. McIlwaine et al. (1997) had a smaller sample size i.e. 40 subjects were recruited and 36 completed the study. The mean age for the PEP group was 10.4 years (range 6 to 17 years). They accepted patients with lower lung function, and did not appear to exclude patients with very mild disease (FEV₁ range 37 to 115 % predicted). Two subjects were withdrawn from each group secondary to nonattendance at clinic or noncompliance with their treatment. It was not reported whether the noncompliant subjects were in the PEP or CPT group. Noncompliance was defined as less than 85% adherence to twice daily physiotherapy over a one-month period. Only one subject was withdrawn from the current study because he stopped attending the CF Clinic at St. Michael's Hospital after his 2nd follow-up visit, and no one was withdrawn because of noncompliance. McIlwaine et al. (1997)
did not attempt to measure HRQOL with a standardized measure such as the QWB or the CRQ. They used a monthly questionnaire that asked patients about their physical activity level, impression of the physiotherapy technique, adverse reactions, how they were feeling, amount of cough and sputum, and a summary of reasons for compliance or noncompliance (McIlwaine et al., 1997). McIlwaine et al. (1997) concluded that the PEP Mask is superior to CPT in maintaining pulmonary function in patients with CF.

Gaskin et al. (1998) also compared the PEP Mask to CPT in CF patients in a two-year randomized controlled trial. Their results have been published in abstract form. Gaskin et al. used the same inclusion and exclusion criteria as the current study with the exception of minimum age. Their sample of 66 CF patients contained both adolescent and adult patients (mean age 21.6 years, range 11 to 45 years, 44 adults). The mean annual rate of decline of FEV$_1$ % predicted was -2.76 (+/- 6.3) in the PEP group and -2.11 (+/- 4.9) in the CPT group. There was no significant difference between these mean slopes. Five patients dropped out of the study (L. Gaskin, personal communication, June 2001). Four of these dropouts were randomized to CPT and they withdrew themselves right at the beginning of the study. These subjects continued to attend clinic allowing the authors to continue collection of their PFT data. The results described above included data from the five dropouts and also from patients who were "noncompliant" in order to test the "real life situation". A second analysis excluded the dropouts and noncompliant patients to test the "ideal situation". They found that the results were the same, that is, there was no statistically significant difference between the PEP and CPT groups. Furthermore, Gaskin et al. examined the rate of decline in FEV$_1$ % predicted in those subjects less than 19 years of age ($n = 22$) in order to make comparisons to the study by McIlwaine et al. (1997). Once again, they found no significant difference between the groups.
The slope of FEV₁ % predicted per year was -1.58 for the PEP group and -1.65 for the CPT group. The difference in the mean annual rate of decline in FEV₁ % predicted between the PEP groups in the study by Gaskin et al. and in the current study may be due to the inclusion of younger subjects in the study by Gaskin et al.. The mean annual rate of decline of FEV₁ % predicted of the adults in their sample (44 adults, age range 19 to 45 years) was not significantly different between the two groups: -3.74 for the PEP group and -2.54 for the CPT group (L. Gaskin, personal communication, June 2001). These results are comparable with the results of the current study that had a similar sample size (n = 42), and similar age range (18 to 49 years) and FEV₁ (> 40 % predicted) at baseline.

McIlwaine and colleagues (2001) also conducted a one-year randomized controlled trial to compare the PEP Mask to the Flutter Device in individuals with CF. Forty patients were recruited who used the PEP Mask as their routine form of airway clearance (age 7 to 17 years, 24 boys, FEV₁ 47 to 107 % predicted). Two patients were withdrawn from the PEP group because of noncompliance with treatment, and one was withdrawn because of nonattendance at clinic. Five patients in the Flutter group withdrew themselves from the study because they felt the Flutter was ineffective. The results for the 32 patients who completed the study showed that the mean annual rate of decline in FEV₁ was -10.95 % predicted (+/- 19.96) for the Flutter group and -1.24 % predicted (+/- 9.9) for the PEP group. This difference was not statistically significant (p = 0.08); however it appears to be clinically significant. Forced vital capacity decreased significantly more in the Flutter group (-8.62 +/- 15.5) than in the PEP group (+0.06 +/- 7.9) (p = 0.05). The level of compliance (recorded by patients with a diary) was reported to be very high with both the PEP and the Flutter. Differences in the sample and methodology of the study by McIlwaine et al. (2001) and this study may account for the differences in the
results. The age of the subjects was different. McIlwaine et al. (2001) used children and adolescents age 7 to 17 years, while the current study was conducted with adults age 18 to 49 years. McIlwaine et al. (2001) only recruited patients who were judged compliant with their physiotherapy in an attempt to control the effects of compliance on outcome. The definition of compliance/noncompliance and the treatment of "noncompliant" individuals was also quite different between the two studies. McIlwaine et al. (2001) used the same definition of noncompliance and the same subjective questionnaire as they did in their 1997 study on CPT versus PEP. They concluded that the Flutter Device was not as effective as the PEP Mask in maintaining pulmonary function.

In summary, there are differences between the results of studies on the effectiveness of the PEP Mask and the Flutter Device involving children versus adults with CF. There are several possible reasons for these differences. Firstly, children may have supervision or reinforcement from their parents/guardians to do their treatment every day at home, thus enhancing adherence and potentially influencing treatment effect. This is in contrast to adult patients (such as those in the current study), most of whom do not have regular supervision or encouragement at home to do their therapy on a daily basis. Secondly, age itself may influence the results. The annual rate of decline of FEV\(_1\) has been shown to correlate significantly with age; older patients with CF have a slower rate of decline than younger CF patients (Davis et al., 1997). Therefore, there may be more potential for improvement or change in children than in adults. As a result of chronic inflammation and infection, adults with CF may have more fixed damage to their lungs and less potential for reversibility with physiotherapy or other treatments.
4.2 EFFECT ON HEALTH-RELATED QUALITY OF LIFE

Two HRQOL measures, the QWB and the CRQ, were used as secondary outcome measures for this study. The Flutter Device and the PEP Mask are relatively new airway clearance techniques that are independent and portable. The QWB and the CRQ were used in effort to assess any impact they may have on the HRQOL, and level of functioning and disability of adults with CF.

The QWB scale is a utility measure that aims to measure overall HRQOL by generating a single score by adding the scores of three scales of function (mobility, physical activity and social activity) and symptoms/problems (Abbott et al., 1997). The QWB was chosen for this study because it has been validated in the CF population (Orenstein et al., 1990, 1989) and because it was used in a similar study by Gaskin et al. (1998) which compared CPT and the PEP Mask. The results of the study by Gaskin et al. (1998) were the same as those of the current study (i.e. the baseline QWB score was not significantly different between the PEP and CPT/Flutter groups, and there was no significant change seen in either group throughout the study). Further comparisons cannot be made because the actual scores (mean total and dimension scores) of the QWB from the study by Gaskin et al. (1998) have not been reported.

Two other studies were found that reported QWB scores (Orenstein et al., 1990; Kaplan et al., 1984). Briefly, Orenstein et al. (1990) reported the change in QWB total scores in 28 patients with CF (> 10 years old) after a two-week course of oral antibiotics to treat pulmonary exacerbation. The mean change in QWB total score was 0.104 (+/- 0.12) (Orenstein et al., 1990). The worst change was a decrease of 0.201, and the best change was an increase of 0.290 (Orenstein et al., 1990). Kaplan et al. (1984) conducted a study with 66 patients with
COPD (mean age 65 years) to assess the benefits of behavioural programs designed to increase adherence to an exercise program. The mean QWB total score was 0.608 (+/- 0.08) on initial assessment, and 0.603 (+/- 0.09) at the follow-up assessment (Orenstein et al., 1990). Neither study reported on whether these changes were significant (Orenstein et al., 1990; Kaplan et al., 1984). In the current study, there was no significant difference between the Flutter and PEP groups in the slopes of the total and dimension scores. As well, the mean change in the QWB total score from the beginning to the end of the study was not significantly different between the two groups (-0.017 +/- 0.07 for the Flutter group and -0.072 +/- 0.12 for the PEP group, p = 0.135). The degree of change appears to be very small, but it is difficult to interpret because the minimally important difference in QWB scores in patients with CF is unknown (Tullis and Guyatt, 1995).

The CRQ was chosen as an outcome measure for this study because it is a disease-specific HRQOL measure. The literature on the CRQ has focused on its reliability, validity and responsiveness in patients with COPD, and to a lesser extent in individuals with CF. No literature was found that reported on the actual results of the CRQ in a CF population. In this study, there was no significant difference between the Flutter and PEP groups in CRQ total or dimension scores at any follow-up visit, nor in the slopes of these scores. Lacasse et al. (1997) stated that the minimal important difference in CRQ score is 0.5 per domain, 1.0 represents moderate change, and changes greater than 1.5 represent large change. Applying this interpretation to the current study, the only dimension to show any evidence of a clinically important change from the beginning to the end of the study was the emotional function dimension in the PEP group (mean change 0.66). However, there was no significant difference
between the Flutter and PEP groups in the change in any score from the first follow-up visit to the end of the study.

The CRQ may not be valid or responsive to change in individuals with CF with moderate to mild lung disease. In the dyspnea dimension, subjects are asked to identify five activities of daily living that make them short of breath. Many subjects in this study were unable to list five activities. Guyatt suggested that if a patient has fewer than five activities, one should try to record a minimum of three activities (Background information and interviewing tips, 1986). However, there were still many subjects who were unable to list even three activities. There is no evidence that discusses this, or that indicates what effect this has on the validity of the CRQ in any population.

A CF-specific HRQOL measure may have been more sensitive and responsive to the changes experienced by CF patients. Researchers and clinicians must be aware that HRQOL measures ask how people feel and hence they are responsive to placebo effects (Guyatt et al., 1987). HRQOL measures are important to use in studies evaluating the effects of treatments on patients with CF and they can be used to complement the findings on the rate of change in pulmonary function.

4.3 EFFECT ON ADHERENCE

Patients with CF are asked to comply with many treatments throughout their daily lives. These treatments include medication, adequate nutrition, exercise and physiotherapy or airway clearance techniques. For many adults it is a daily battle to find time for all of these
treatments. Physiotherapy and exercise are typically the least adhered to treatments (Crossan et al., 1999). Most literature suggests that CF patient compliance rates range from 26 to 47% (Williams, 1994; Muszynski-Kwan et al., 1988; Passero et al., 1981). In 1994, a survey of 229 adult CF patients at the Wellesley Hospital in Toronto found that 30% of these patients were performing ineffective or no chest physiotherapy or exercise (Veress et al., 1994). Crossan et al. (1999) suggested that adherence is a continuum - from complete adherence to complete nonadherence, and that a person's position on this continuum is the result of a complex interaction of factors including psychological, health-related and lifestyle factors. Adherence may be improved if patients find the techniques effective, comfortable and convenient. Many adult CF patients find CPT cumbersome, inconvenient and uncomfortable. Therefore, alternative therapies such as the PEP Mask and the Flutter Device have been developed to offer patients a more attractive and hopefully equally or more effective form of airway clearance.

A roughly equal number of the subjects appeared to prefer the Flutter Device or the PEP Mask to their previous physiotherapy routine (Appendix 9). The results of this study showed that there was no significant difference between the PEP and Flutter groups with respect to adherence to treatment throughout the course of the study. For some subjects their level of adherence varied over the course of the study. This may be the result of many factors as described by Crossan et al. (1999). However, the level of noncompliance increased in both groups as the study progressed (Figure 23). Subjects may have been more compliant at the start because of initial enthusiasm and interest in learning a different form of treatment (new or different for most subjects). This enthusiasm may have worn off as the study progressed, hence compliance dropped and noncompliance rose. Reasons for not adhering to the Flutter Device or to the PEP Mask were similar (see Appendix 9). The most frequent reason given for
noncompliance in both groups was a lack of time to do the treatment e.g. "I don't have enough time" or "I'm too busy". The study was run on an intention-to-treat basis; therefore no subjects were withdrawn from the study due to noncompliance.

Similarly, no subject was withdrawn if he/she altered his/her treatment routine. Two subjects (one from each group) reverted to CPT (their pre-study treatment) because they preferred it. This introduced a bias similar in nature to contamination. Contamination occurs when control patients accidentally receive the experimental treatment (Sackett et al., 1991). As well, five subjects (one from the PEP Mask group, four from the Flutter group) changed to a combination of their study treatment and CPT. This bias is similar in nature to cointervention, that is, when additional therapeutic acts are performed on experimental but not control patients (Sackett et al., 1991). Note that contamination and cointervention occurred in both the Flutter and the PEP groups, hence their meanings are being used in a slightly different way. It was very difficult to control for these biases in this study, because the patients often alter their treatment as their health improves or deteriorates. A way to prevent cointervention is to blind both the patients and the clinicians to who is receiving which treatment (Sackett et al., 1991); however it was not possible to blind the subjects or the clinicians in this study.

It is difficult to make comparisons to other studies with respect to adherence because different definitions of compliance and noncompliance have been used in different studies. For example, as previously described, McIlwaine et al. (2001, 1997) used a stringent definition of noncompliance i.e. noncompliance was defined as less than 85% adherence to twice daily physiotherapy over a one-month period. Subjects who were noncompliant by this definition
were removed from the study (McIlwaine et al., 1997 and 2001). The results on compliance or adherence to therapy are then misleading, as only the compliant subjects are included in the results (e.g. the level of compliance was 95.6% in the PEP group and 93.85% in the Flutter group (McIlwaine et al., 2001)). This is in contrast to the adherence scale used in the current study where three levels of compliance were utilized in order to reflect a continuum of adherence (i.e. noncompliance was defined as doing no physiotherapy at all, low compliance was doing physiotherapy one to five times per week, and compliance was defined as doing physiotherapy six or more times per week). Subjects were scored on this adherence scale at every follow-up visit. A very small percentage of the adult CF patients who participated in the current study would satisfy McIlwaine et al.'s definition of compliance. If subjects were removed from the current study due to noncompliance as they were in the studies by McIlwaine et al. (2001, 1997), the sample size would have been extremely small. Based on clinical experience and previous research by Veress et al. (1994), the adherence of the sample in the current study is reflective of the population that attends the Adult CF Clinic at St. Michael's Hospital, Toronto.

4.4 EXERCISE AND THE NUMBER OF HOSPITAL ADMISSIONS

There was no significant difference in the exercise habits of the Flutter and PEP groups. Approximately 50% of the subjects involved in this study were inactive, which is higher than what was reported by Veress et al. in 1994 (i.e. 30% of 229 adult CF patients surveyed at the Wellesley Hospital in Toronto were performing ineffective or no chest physiotherapy or
exercise). Exercise did not appear to be a cointervention or to have an influence on the outcome of this study.

There were 14 hospitalizations in the Flutter group and six in the PEP group over the course of this study. This appears to be a clinically significant difference between the two groups, with considerably more costs incurred by the Flutter group. This trend favours the PEP Mask. However, there was no statistically significant difference in the mean number of hospital admissions for individuals in the Flutter or PEP groups (0.67 and 0.29 respectively, \( p = 0.168 \)). Unfortunately, information on the number of hospital admissions in a similar study by Gaskin et al. (1998) has not been reported. McIlwaine et al. (2001) found a significant difference in hospital admissions in their study comparing the Flutter Device and the PEP Mask (18 for the Flutter group versus 5 for the PEP group, \( p = 0.03 \)). In their study comparing the PEP Mask and CPT, McIlwaine et al. (1997) reported no significant difference between the PEP and CPT groups in the number of hospital admissions (13 for the PEP group, 11 for the CPT group). These studies had similar sample sizes and duration, and although the statistical significance of the findings varied, the actual number of hospital admissions during this study period does not appear to be abnormal.

4.5 LIMITATIONS OF THE CURRENT STUDY

The primary limitation of this study is power. The sample size was calculated to be a minimum of 40 subjects per group in order to detect a statistically significant difference in the annual rate of decline in FEV\(_1\) (% predicted), using a two-tailed test with type 1 error of 0.05 and power of 80%. This estimation was done using a SD equal to 6.3 that was reported by L.
Gaskin (personal communication, June 2001) for the PEP group in their study that compared the PEP Mask and CPT. A total of 42 subjects were recruited for this study, representing a recruitment rate of approximately 21%. Given the sample size (21 per group), type 1 error of 0.05, the SD of the PEP group (+- 8.04), and the difference between the mean slopes of FEV1 (% predicted) of the two groups (2.19), the power is low (0.137). This limits the ability to safely conclude that there really was no difference between the two groups.

A different sample size would have been estimated if data had been used from McIlwaine et al.'s 1997 study comparing the PEP Mask and CPT. They reported a SE of 2.5 (or SD = 15) for the PEP group; therefore, the sample size would have been calculated to be a minimum of 222 subjects per group. This standard deviation was not used in the sample size calculation of the current study because the subjects in McIlwaine et al.'s (1997) study were children/adolescents. Of interest, Davis et al. (1997) estimated that for a one-year study, with a type 1 error of 0.05 and power of 80%, it would take over 550 patients in each group to show that a treatment actually halts pulmonary decline (i.e. decline in FEV1 % predicted = 0). This may be unrealistic to obtain even with a multi-centred trial.

The reasons patients did not wish to participate in this study were varied and personal. Also, the program does draw patients from a wide geographical area; therefore not all potential subjects were willing/able to attend regular follow-up visits. The Adult CF Clinic at St. Michael's Hospital in Toronto is the largest adult CF clinic in North America. The current study recruited 42 subjects, and the study by Gaskin et al. (1998) recruited 44 adults. Therefore, it is unlikely that any more than 40 to 50 patients can be recruited from this CF Clinic in subsequent physiotherapy studies.
If the study duration were to remain one year, a multi-centred trial would be the only means of obtaining a sufficient sample size to detect a statistically or clinically important difference in FEV$_1$ (% predicted). There are approximately 3500 patients with CF in Canada (M. Corey, from Canadian CF Registry, personal communication, 2001). Approximately 1500 of these patients are 18 years of age or older, and approximately 1200 of these patients have an FEV$_1$ of greater than 40 % predicted (M. Corey, from Canadian CF Registry, personal communication, 2001). There are approximately 2000 CF patients under 18 years of age (M. Corey, from Canadian CF Registry, personal communication, 2001). Of these, approximately 1900 have an FEV$_1$ of greater than 40 % predicted (M. Corey, from Canadian CF Registry, personal communication, 2001). Therefore, there are enough adults (and children/adolescents) with CF in Canada to recruit a larger sample size. The recruitment rate in the current study was 21%; given this recruitment rate and the approximate pool of adult subjects available, potentially 252 subjects could be recruited. A national multi-centred trial of this size would ensure that the study is adequately powered to be able to detect a true treatment effect if one exists. Alternatively, a study of longer duration (e.g. two, three, four years) would require an increasingly smaller sample size to detect a treatment effect because the variability of the slope of FEV$_1$ decreases with time (Davis et al., 1997). It is because of the variability of FEV$_1$ over short periods of time that a study of short duration (e.g. a short-term cross-over trial, less than one year) would not be useful. The variability in an individual's FEV$_1$ over short-term periods was demonstrated in Table 11. It is the nature of the pulmonary disease in CF that there is a variable yet slow, persistent/chronic decline in pulmonary function over the long-term. For this reason, a multi-centred study a minimum of one-year duration is needed to obtain sufficient power.
There was not 100% attendance at every follow-up visit; hence there is not complete pulmonary function data at every follow-up visit for every subject. However, Davis et al. (1997) looked at the FEV₁ data of CF patients over a four-year period and found that increasing the number of data points collected in the course of their study had minimal impact on the calculated slope or the variability of the slope, and hence only a moderate impact on the number of patients needed to detect a treatment effect. In the current 13-month study, pulmonary function data was obtained for every subject at recruitment and at the final follow-up approximately 13 months post-recruitment. Regardless of the number of data points in between the first and final assessments, a larger sample size is still needed to detect a treatment effect in a 13-month study.

There was also not 100% acquisition of the QWB and CRQ data at every follow-up assessment for every subject. This is a limitation of this study, and unlike pulmonary function data, there is no literature on the effect the number of data points has on the slope of QWB or CRQ scores in CF patients. All attempts were made to administer the questionnaires while the patients waited in clinic to see the physician; however, some subjects left clinic prior to one or both of the questionnaires being administered. In one case, the CRQ (repeat administration) was completed over the phone - the response cards were faxed to the patient prior to the telephone interview in efforts to maintain its reliability and validity. This approach was not possible with other patients as they did not have access to a fax machine and without the possible responses in front of them, the CRQ would not be reliable. Furthermore, administration of the CRQ by phone has not been validated. The completion of the QWB and
the CRQ was also time sensitive i.e. they should have been conducted on the same day as the remainder of the follow-up (i.e. PFTs, etc.).

Diaries can provide researchers with information that they would like to observe but cannot, and they have been shown to be helpful where the recall of the subjects would not be accurate or detailed enough (Gibson, 1995; Jarrett, 2000). However, the use of diaries for data collection has a number of limitations. Some behaviours may be underreported if they are viewed as undesirable, and patients may modify their behaviour as a result of observing their own behaviour (Jarrett, 2000). Subjects may forget to complete the diary and then back-fill the missed days with less accuracy (Jarrett, 2000). Also, when subjects are asked to fill in a diary for a long time, "research fatigue" can set in and the subject may fill out the diary less completely (Jarrett, 2000). Structured diaries are recommended as they are faster for subjects to complete and they collect information that is more consistent in detail (Gibson, 1995).

Daily diaries were relied on in this study to collect information about compliance with therapy and exercise habits. The structured portion of the diary was designed to collect consistent detail regarding the frequency and duration of physiotherapy and exercise, and it was designed to be fast and easy for the subjects to complete. The unstructured portion of the diary allowed patients to record comments regarding their treatment. However, some of the limitations of diaries discussed above became apparent as the study progressed. It was difficult to get patients to comply with completing the diary daily and accurately, especially over the length of the study. Ideally, compliance should be measured in a more objective and standardized way. For example, each PEP Mask and Flutter Device used in the study would have an automatic counter that would record the frequency and duration of treatments. This
approach would eliminate the need for diaries to record treatment compliance, and it would help to reduce subject burden.

It was difficult to control the biases of cointervention and contamination, as patients with CF often make changes to their treatment as their health improves or deteriorates. There were subjects in both the Flutter and the PEP groups who strayed from performing strictly their study physiotherapy treatment. It is difficult to indicate what effect this had on the results of the study.

This study did not attempt to specifically measure patient satisfaction with the PEP Mask or the Flutter Device. Although a physiotherapist asked the subjects questions regarding their treatment and exercise at each follow-up visit and made notes of their comments, the questions and responses were not posed or recorded in a standardized manner. Each subject should have been asked standardized questions regarding adherence and satisfaction (or lack thereof) with therapy and exercise at every follow-up visit. Oermann et al. (2000) developed a survey for CF patients to measure satisfaction with physiotherapy techniques. It has 17 questions in the domains of efficacy, convenience, comfort and overall satisfaction. Oermann et al. (2000) found that the perceived importance of and compliance with physiotherapy increased linearly with disease severity, and that overall satisfaction was positively correlated with compliance. A standardized survey such as this would be useful to include as an outcome measure in future studies on physiotherapy in CF.

Another limitation of this study may be that the outcome measures did not include an exercise test. A maximal or submaximal exercise test may have provided useful information regarding any effect the Flutter Device and the PEP Mask have on aerobic capacity, and
possibly insight into patient's experience of activity limitation(s). An exercise test may also have provided a more objective picture of the extent of co-intervention due to exercise on pulmonary function.

4.6 FUTURE DIRECTIONS

With respect to clinical recommendations, based on the existing literature, it is not known whether one treatment (either the Flutter Device or the PEP Mask) is better than the other.

This study has demonstrated the need for further studies on the effect of the Flutter Device and the PEP Mask in the treatment of adults with CF. Recommendations for future research include the need for a national multi-centred study of a minimum of one-year duration in order to achieve greater power and more definitive results. Such a study may not be feasible; therefore more observational or cross-over studies should be done to further develop the body of evidence for or against these treatments in the CF population.

Recommendations also include a qualitative study to further examine the determinants of compliance or adherence to physiotherapy in adults with CF. Further evaluation should also be done of the physiologic effects of the Flutter Device and the PEP Mask on airway secretion clearance (e.g. with tracheobronchial clearance). This may be useful in determining or estimating which patients receive the greatest benefits from the treatments (e.g. patients with severe, moderate or mild lung disease, or patients who have a daily productive cough versus those who do not). It may also address the frequency that treatment should be done per day, as the current recommendations of therapy twice a day are not scientifically based.
A CF-specific HRQOL measure should be used in effort to gain more insight into issues specific to CF patients. A standardized survey on patient satisfaction with airway clearance techniques would also provide useful information.

This study raised questions regarding the significant differences seen in the results of studies on the Flutter Device and the PEP Mask involving children versus adults with CF. The reasons for these conflicting results should be further explored.

The effect of the Flutter Device and/or the PEP Mask should also be evaluated in patients with CF with severe pulmonary disease (i.e. FEV\(_1\) < 40 % predicted). It is unclear whether these patients can tolerate or perform these treatments adequately because they require effort. It is important to note that it would take a larger sample size to detect the effect of a treatment in patients with CF with severe pulmonary disease because the rate of decline in FEV\(_1\) (% predicted) is less in these patients (Davis et al, 1997). These patients have more fixed damage to their lungs; therefore there may be less potential for change with treatment.

As highlighted in the literature review on CPT, the Flutter Device and the PEP Mask, there are still other questions that need to be addressed with respect to the efficacy of these airway clearance techniques. For example, the effect of the Flutter Device or the PEP Mask in combination with exercise versus exercise alone, on pulmonary function and aerobic capacity, warrants evaluation. Cystic Fibrosis is a small population that is already over-studied; hence future studies should be large and long-term to ensure that the study is adequately powered to be able to detect a true treatment effect if one exists.
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APPENDIX 1

THE QUALITY OF WELL-BEING SCALE
QWB7 FUNCTION STATUS PROFILE CLASSIFICATION
AND QUALITY OF WELL-BEING SCALE ©

(Respondent/Proxy Questionnaire)

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USER'S PROJECT TITLE

1. Interviewer's ID

2. Respondent ID

3. Interview No.

4. Date (month/day/date)

5. Sex: M F (circle)

6. Age____________(Years)

7. Exact date of birth:

8. No. of Calls

9. Interview Length

10. Interview done on Respondent ()
Other Subject ()

Call Record. (Use the space for the Thumbnail Sketch to note any information that would be useful in locating the respondent.)

<table>
<thead>
<tr>
<th>Call Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of Week</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Result</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interviewer's Initials</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

INTRODUCTION
The next questions that I am going to ask are about (your/...) health situation in the past few days. We are interested in any and all health problems (you/...) may have had, even if they seem unimportant to you. In addition we need to know about each of the past several days and that is why we're asking about each one separately. Some of the questions may seem repetitive to you, but they are all different in some way. If you don't understand any question, please ask me to repeat it. If you feel you cannot answer a particular question, please say so, and I will move to the next question.

You may notice me checking my watch occasionally because I must record the time at certain points during the interview. I am not trying to rush you, so please take your time.

(Record time to nearest minute) ______AM/PM

Rev. 5/94 JPA
A. Symptom/Problem Complexes

For most of these questions, I'll be asking about the past 6 days, that is, from (day/date) through (day/date).

CPX1. First I would like to ask you about any health problems (you/...) might have had. Please look at this list one at a time and tell me the number of all the items that (you/...) had at any time during the past 6 days. Don't worry about how important or serious the problem was; if it was present at all in the last 6 days, please give me the number.

[IF NONE, X “CPX NONE” BOX. IF CPX GIVEN, ASK WHICH DAYS? AND CIRCLE CPX 0’S IN ANSWER COLUMNS. WHEN COMPLETED, GO TO CPX2.]

CPX2. Were there any health problems not on the list that (you/...) had at any time during the past 6 days?

[IF NONE, X “2 NONE” BOX. DESCRIBE 2 CPX ON COMMENT LINES. ASK WHICH DAYS? AND CIRCLE 2’S FOR DAYS OCCURRED. RECORD TIME. BEGIN MOB1.]

<table>
<thead>
<tr>
<th>CPX</th>
<th>CPX DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Loss of consciousness such as seizure (fits), fainting, or coma (out cold or knocked out)</td>
</tr>
<tr>
<td>3</td>
<td>Burn over large areas of face, body, arms, or legs</td>
</tr>
<tr>
<td>4</td>
<td>Pain, bleeding, itching, or discharge (drainage) from sexual organs -- does not include normal (monthly) menstrual bleeding</td>
</tr>
<tr>
<td>5</td>
<td>Trouble learning, remembering, or thinking clearly</td>
</tr>
<tr>
<td>6</td>
<td>Any combination of one or more hands, feet, arms, or legs either missing, deformed (crooked), paralyzed (unable to move), or broken -- includes wearing artificial limbs or braces</td>
</tr>
<tr>
<td>7</td>
<td>Pain, stiffness, weakness, numbness, or other discomfort in chest, stomach (including hernia or rupture), side, neck, back, hips, or in any joints of hands, feet, arms or legs</td>
</tr>
<tr>
<td>8</td>
<td>Pain, burning, bleeding, itching, or other difficulty with rectum, bowel movements, or urination (passing water)</td>
</tr>
<tr>
<td>9</td>
<td>Sick or upset stomach, vomiting or loose bowel movements, with or without fever, chill, or aching all over</td>
</tr>
<tr>
<td>10</td>
<td>General tiredness, weakness, or weight loss</td>
</tr>
<tr>
<td>11</td>
<td>Cough, wheezing, or shortness of breath with or without fever, chill, or aching all over</td>
</tr>
<tr>
<td>12</td>
<td>Spells of feeling upset, being depressed, or of crying</td>
</tr>
<tr>
<td>13</td>
<td>Headache, or dizziness, or ringing in ears, or spells of feeling hot, or nervous, or shaky</td>
</tr>
<tr>
<td>14</td>
<td>Pain in ear, tooth, jaw, throat, lips, tongue; missing or crooked permanent teeth -- includes wearing a hearing aid</td>
</tr>
<tr>
<td>18</td>
<td>Taking medication or staying on a prescribed diet for health reasons</td>
</tr>
<tr>
<td>20</td>
<td>Wore eyeglasses or contact lenses</td>
</tr>
<tr>
<td>21</td>
<td>Breathing snore or unpleasant air</td>
</tr>
<tr>
<td>24</td>
<td>Trouble sleeping</td>
</tr>
<tr>
<td>25</td>
<td>Intoxication</td>
</tr>
<tr>
<td>26</td>
<td>Problems with sexual interest or performance</td>
</tr>
<tr>
<td>27</td>
<td>Excessive worry or anxiety</td>
</tr>
</tbody>
</table>

TIME: ______ AM/PM
B. Mobility Scale

MOB1. On which of the past 6 days, if any, did (you/...) spend any part of a day or night as a bed patient in a hospital or similar health care facility?

[IF NONE, X "NONE BOX" AND GO TO MOB2. IF IN HOSPITAL OR SIMILAR FACILITY, X DAYS ON THE NUMBER LINE THAT APPLY. AND FOR EACH X DAY ASK:

MOB1A. What was the reason (you were/...was) in the hospital?

[RECORD RESPONSE. WHEN ALL DAYS ARE COVERED, GO TO MOBILITY CHECKPOINT.]

MOBILITY CHECKPOINT

REACTONDENT/OTHER SUBJECT: IF 16 OR OVER, ASK MOB2 (DRIVE CAR)
IF 15 OR UNDER, ASK MOB2E (RIDE)

MOB2. (Do you/Does...) now hold a valid driver's license?

[IF YES, ASK MOB2A.] [IF NO, ASK MOB2C.]

MOB2A. On which of the past 6 days, if any, did (you/...) drive a car?

[IF ALL, X "ALL BOX" AND BEGIN MOB3. IF NONE, X ALL DAYS ON THE NUMBER LINE. IF DROVE SOME BUT NOT ALL, CIRCLE DAYS DROVE. X REMAINING DAYS. FOR FIRST X DAY, ASK:

MOB2B. On (day/date) were there reasons related in any way to (your/...) health that (you/...) did not drive?

[RECORD RESPONSE. CIRCLE H OR O. ASK MOB2B FOR ALL X DAYS. BEGIN MOB3.]

MOB2C. What is the reason (you do/...does) not now have a valid driver's license?

[RECORD RESPONSE. IF HEALTH REASONS, CIRCLE H ALL DAYS AND BEGIN MOB3. IF NON-HEALTH REASONS, CIRCLE O ALL DAYS AND ASK:]

MOB2D. In addition to that reason, were there other reasons related in any way to (your/...) health that (you do/...does) not now have a driver's license?

[RECORD RESPONSE. CIRCLE H OR O FOR EACH DAY. BEGIN MOB3.]
MOB3. On which of the past 6 days, if any, did (you/...) use some form of public transportation, such as a bus, plane, train or trolley?

[IF NONE OR SOME: ON THE NUMBER LINE, CIRCLE DAYS USED, X DAYS DID NOT USE. FOR FIRST X DAY, ASK:]

MOB3A. On (day/date), were there reasons related in any way to (your/...’s) health that (you/...) did not use public transportation? [ASK:] What were those reasons?

[RECORD RESPONSE. CIRCLE H OR O. ASK MOB3A FOR EACH X DAY. IF O IS CIRCLED, BEGIN MOB3B. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN MOB3C. IF ALL 6 DAYS ARE CODED H, TURN TO PAC1.]

MOB3B. On (day/date), if (you/...) had taken public transportation, would (you/...) have used more help from someone else than usual for (your/...) age to do so?

[RECORD RESPONSE. CIRCLE U OR N. ASK MOB3B FOR EACH DAY O IS CIRCLED. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN MOB3C. IF ALL 6 DAYS ARE CODED H, U, OR N, GO TO PAC1.]

MOB3C. On (day/date), did (you/...) use more help from someone else than usual for (your/...) age in order to take public transportation?

[RECORD RESPONSE. CIRCLE U OR N. ASK MOB3C FOR ALL DAYS CIRCLED ON THE NUMBER LINE. IF ALL 6 DAYS ARE CODED H, U, OR N, BEGIN PAC1.]
C. Physical Activity Scale

PAC1. On which of the past 6 days, if any, did (you/...) spend most or all of the day in a wheelchair?

[IF NONE, X "NONE BOX" AND GO TO PAC2. IF SOME OR ALL, X DAYS IN WHEELCHAIR. FOR FIRST X DAY, ASK:]  

PAC1A. Did (you/...) move or control the movement of the wheelchair without help from someone else on (day/date)?

[CIRCLE M OR N. ASK PAC1A FOR ALL X DAYS. IF RESPONDENT OR OTHER SUBJECT IS CONFINED TO WHEELCHAIR ALL 6 DAYS OR PERMANENTLY, WRITE "INAP" (inappropriate) ON ALL FURTHER PAC SCALE QUESTIONS. GO TO PCL.]

PAC2. On which of the past 6 days, if any, did (you/...) spend most or all of the day in bed?

[IF NONE, X "NONE BOX" AND GO TO PAC3. IF SOME OR ALL, X DAYS IN BED. FOR FIRST X DAY, ASK:]  

PAC2A. On (day/date), were there reasons related in any way to (your/...) health that (you/...) stayed in bed? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE M OR O. ASK PAC2A FOR ALL X DAYS. GO TO PAC3.]

PAC3. On which of the past 6 days, if any, did (you/...) spend most or all of the day in any type of chair or couch?

[IF NONE, X "NONE BOX" AND GO TO PAC4. IF SOME OR ALL, X DAYS IN CHAIR OR COUCH. FOR FIRST X DAY, ASK:]  

PAC3A. On (day/date) were there reasons related in any way to (your/...) health that (you/...) stayed in a chair or couch? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE M OR O. ASK PAC3A FOR ALL X DAYS. GO TO PAC4.]

PAC4. On which of the past 6 days, if any, did (you/...) have trouble - or not try - to lift, stoop, bend over, or use stairs or inclines?

[IF NONE, X "NONE BOX" AND GO TO PAC5. IF SOME OR ALL, X DAYS LIMITED. FOR FIRST X DAY, ASK:]  

PAC4A. What was the reason (you were/...was) limited on (day/date)?

[RECORD RESPONSE. CIRCLE M OR O. ASK PAC4A FOR ALL X DAYS. GO TO PAC5.]
PAC5. On which of the past 6 days, if any, did (you/...) limp, or use a cane, crutches or walker?

[IF NONE, X "NONE BOX". GO TO PAC6. IF SOME OR ALL, X DAYS LIMITED. FOR FIRST X DAY, ASK:]

PAC5A. What was the reason (you were/...was) limited on (day/date)?

[RECORD RESPONSE. CIRCLE H OR O. ASK PAC5A FOR ALL X DAYS. GO TO PAC6.]

PAC6. On which of the past 6 days, if any, did (you/...) have any (other) physical limitation, or not try to walk as far or as fast as most persons (your/...) age are able?

[IF NONE, X "NONE BOX". GO TO INTERVIEWER CHECKPOINT BELOW. IF SOME OR ALL, X DAYS LIMITED AND FOR FIRST X DAY, ASK:]

PAC6A. What was the trouble or limitation on (day/date)?

[RECORD RESPONSE. CIRCLE H OR O. ASK PAC6A FOR ALL X DAYS. GO TO INTERVIEWER CHECKPOINT BELOW.]

INTERVIEWER CHECKPOINT: INTERVIEW DONE ON

RESPONDENT OR OTHER SUBJECT

AGE 65 OR OVER: ASK ROL1

AGE 18-64: TURN TO PAGE 8

UNDER 15 YEARS OLD: TURN TO PAGE 11

ROL1. At the present time, (are you/is...) primarily employed, unemployed, disabled, a homemaker, retired, a student, or what?

IF WORKING UNEMPLOYED ON STRIKE TEMPORARILY LAYED OFF DISABLED SICK LEAVE OTHER

ROL1A. Could you please describe the work (you/...) (now/usually/used to) do?

[RECORD RESPONSE. TURN TO PAGE 7.]

IF HOMEMAKER RETIRED STUDENT

ROL1B. At the present time, (are you/is ...) working 20 or more hours a week for pay?

[YES] [ASK ROL1A.] [NO] [HOMEMAKER. TURN TO PAGE 8]

[RETIRER. TURN TO PAGE 9]

[STUDENT. TURN TO PAGE 10.]
D. SOCIAL ACTIVITY SCALE FOR WORKERS

SAC1. On which, if any, of the past 6 days, including weekends, holidays and so on, did (you/...) work on a job at all?

[IF ALL, CIRCLE ALL DAYS ON THE NUMBER LINE. FOR FIRST X DAY, ASK:]

SAC1A. On (day/date) were there reasons related in any way to (your/...’s) health that (you/...) did not work on a job at all? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE H OR O. ASK SAC1A FOR EACH X DAY. IF O IS CIRCLED, BEGIN SAC1B. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL DAYS ARE CODED H, GO TO SAC2.]

SAC1B. If (you/...) had worked on a job on (day/date), would (you/...) have been limited in any way in the amount or kind of work done, such as using special working aids, not doing certain tasks, taking special rest periods, or working only part of the day?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1B FOR EACH DAY O IS CIRCLED. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL 6 DAYS ARE CODED H, L, OR N, GO TO SAC2.]

SAC1C. On (day/date), were (you/...) limited in any way in the amount or kind of work done, such as using special working aids, not doing certain tasks, taking special rest periods, or working only part of the day?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1C FOR ALL DAYS CIRCLED ON THE NUMBER LINE. IF ALL 6 DAYS ARE CODED H, L, OR N, GO TO SAC2.]
D. SOCIAL ACTIVITY SCALE FOR HOMEMAKER ROLE

SAC0. Is the reason (you/...) are not now working (more hours) for pay related in any way to (your/...) health?

[IIF YES, ASK:] [IF NO, CIRCLE O ON ALL DAYS AND ASK:]

SAC0A. What is the reason?

[RECORD RESPONSE. CIRCLE N OR O FOR ALL DAYS. ASK:]

SAC1. On which, if any, of the past 6 days, including weekends, holidays and so on, did (you/...) do any housework at all?

[IIF NONE OR SOME: ON THE NUMBER LINE, CIRCLE DAYS DID HOUSEWORK, X DAYS DID NOT DO HOUSEWORK. FOR FIRST X DAY, ASK:]

SAC1A. On (day/date) were there reasons related in any way to (your/...) health that (you/...) did no housework at all? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE N OR O. ASK SAC1A FOR EACH X DAY. IF O IS CIRCLED, BEGIN SAC1B. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL DAYS ARE CODED N, GO TO SAC2.]

SAC1B. If (you/...) had done housework on (day/date), would (you/...) have been limited in any way in the amount or kind of work done, such as not lifting small children, not cooking, washing or ironing, not doing heavy cleaning, or taking special rest periods?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1B FOR EACH DAY O IS CIRCLED. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL 6 DAYS ARE CODED N, L, OR N, GO TO SAC2.]

SAC1C. On (day/date), were (you/...) limited in any way in the amount or kind of housework, such as not lifting small children, not cooking, washing or ironing, not doing heavy cleaning, or taking special rest periods?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1C FOR ALL DAYS CIRCLED ON THE NUMBER LINE. IF ALL 6 DAYS ARE CODED N, L, OR N, GO TO SAC2.]
D.  SOCIAL ACTIVITY SCALE FOR RETIRED

SAC0. Is the reason (you/...) are not now working (more hours) for pay related in any way to (your/...) health?

[IF YES, ASK:]  

SAC0A. What are the reasons?

[RECORD RESPONSE. CIRCLE H OR O OR ALL DAYS. ASK:]  

SAC1. On which, if any of the past 6 days, including weekends, holidays and so on, did (you/...) do any kind of work activities at all, including not only a job, but also such activities as shopping, cooking, cleaning, or working in or around the house, yard or garden?

[IF NONE OR SOME: ON THE NUMBER LINE. CIRCLE WORK ACTIVITY DAYS, X DAYS DID NOT DO WORK ACTIVITIES. FOR FIRST X DAY, ASK:]  

SAC1A. On (day/date) were there reasons related in any way to (your/...’s) health that (you/...) did not do work activities? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE H OR O. ASK SAC1 A FOR EACH X DAY. IF O IS CIRCLED, BEGIN SAC1B. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL DAYS ARE CIRCLED H, GO TO SAC2.]  

SAC1B. If (you/...) had done work activities on (day/date), would (you/...) have been limited in any way in the amount or kind of work done, such as using special working aids, not doing certain tasks or strenuous work, taking special rest periods, or working only part of the day?

[RECORD RESPONSE. CIRCLE L OR H. ASK SAC1B FOR EACH DAY O IS CIRCLED. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE, BEGIN SAC1C. IF ALL 6 DAYS ARE CIRCLED H, L, OR N, GO TO SAC2.]  

SAC1C. On (day/date), were (you/...) limited in any way in the amount or kind of work activities, such as using special working aids, not doing certain tasks or strenuous work, taking special rest periods, or working only part of the day?

[RECORD RESPONSE. CIRCLE L OR H. ASK SAC1C FOR ALL DAYS CIRCLED ON THE NUMBER LINE. IF ALL 6 DAYS ARE CIRCLED H, L, OR N, GO TO SAC2.]
D. SOCIAL ACTIVITY SCALE FOR STUDENTS

SAC0. Is the reason (you/... ) are not now working (more hours) for pay related in any way to (your/...) health?

[IF YES, ASK:]

SAC0A. What are the reasons?

[RECORD RESPONSE. CIRCLE H OR O FOR ALL DAYS. ASK:]

SAC1. On which, if any, of the past 6 days, including weekends, holidays and so on, did (you/...) attend classes or do school activities at all?

[IF NONE OR SOME: ON THE NUMBER LINE, CIRCLE SCHOOLWORK DAYS. X DAYS DID NOT DO ALL SCHOOLWORK. FOR FIRST X DAY, ASK:]

SAC1A. On (day/date) were there reasons related in any way to (your/...) health that (you/...) did not (attend classes/ do school activities)? [WHETHER YES OR NO, ASK:] What were the reasons?

[RECORD RESPONSE. CIRCLE H OR O. ASK SAC1A FOR EACH X DAY. IF O IS CIRCLED. BEGIN SAC1B. IF CIRCLED DAYS REMAIN ON THE NUMER LINE. BEGIN SAC1C. IF ALL DAYS ARE CODED H. GO TO SAC2.]

SAC1B. If (you/...) had (attended classes/done school activities) on (day/date), would (you/...) have been limited in any way in the amount or kind of school activities, such as being excluded from certain courses, including gym or recess activities, attending a special school or classes, having special teaching or courses at home, or not carrying a full schedule?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1B FOR EACH DAY O IS CIRCLED. IF CIRCLED DAYS REMAIN ON THE NUMBER LINE. BEGIN SAC1C. IF ALL 6 DAYS ARE CODED L. OR N. GO TO SAC2.]

SAC1C. On (day/date), were (you/...) limited in any way in the amount or kind of school activities, such as being excluded from certain courses, including gym or recess activities, attending a special school or classes, having special teaching or courses at home, or not carrying a full schedule?

[RECORD RESPONSE. CIRCLE L OR N. ASK SAC1C FOR ALL DAYS CIRCLED ON THE NUMBER LINE. IF ALL 6 DAYS ARE CODED L. OR N. GO TO SAC2.]
### Social Activity Scale: Other & Self-Care

**OAC Card: Examples only (as usual for age)**

- Going shopping, handling personal business, and so on.
- Taking part in hobbies, games, play/entertainment, and so on.
- Visiting or meeting with friends, relatives, and so on.
- Taking part in community work, going to meetings, and so on.
- Attending movies, ballets, other entertainment, and so on.

**OAC Card: Did not do OR had MORE help than usual for others the same age**

- Did not do, or had MORE help than usual for others the same age.

**SPC Card: Examples only (as usual for age)**

- Attending movies, ballets, other entertainment, and so on.

**SPC Card: Did not do, or had MORE help than usual for others the same age**

1. Did not dress (tying shoes, buttons, coat, etc.).
2. Did not feed self (did not eat, received fluids by vein, etc.).
3. Did not use toilet (growing child, cleaning of toilet, including bed, etc.).
4. Did not take bath (growing child, or had help to take bath, all parts of body, etc.).
APPENDIX 2

THE CHRONIC RESPIRATORY QUESTIONNAIRE
CHRONIC RESPIRATORY INDEX QUESTIONNAIRE

First Administration, 7 Point Scale

INTERVIEWER FORM

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about how short of breath you have been, how tired you have been feeling and how your mood has been.

1. I would like you to think of the activities that you have done during the last 2 weeks that have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life. Please list as many activities as you can that you have done during the last 2 weeks that have made you feel short of breath.

[CIRCLE THE NUMBER ON THE ANSWER SHEET LIST ADJACENT TO EACH ACTIVITY MENTIONED. IF AN ACTIVITY MENTIONED IS NOT ON THE LIST, WRITE IT IN, IN THE RESPONDENT'S OWN WORDS, IN THE SPACE PROVIDED]

Can you think of any other activities you have done during the last 2 weeks that have made you feel short of breath?

[RECORD ADDITIONAL ITEMS]

2. I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 2 weeks. If you haven't done the activity during the last 2 weeks, just answer 'NO'. The activities are:

[READ ITEMS, OMITTING THOSE WHICH RESPONDENT HAS VOLUNTEERED SPONTANEOUSLY. PAUSE AFTER EACH ITEM TO GIVE RESPONDENT A CHANCE TO INDICATE WHETHER HE/SHE HAS BEEN SHORT OF BREATH WHILE PERFORMING THAT ACTIVITY DURING THE LAST WEEK. CIRCLE THE NUMBER ADJACENT TO APPROPRIATE ITEMS ON ANSWER SHEET]
1. BEING ANGRY OR UPSET
2. HAVING A BATH OR SHOWER
3. BENDING
4. CARRYING, SUCH AS CARRYING GROCERIES
5. DRESSING
6. EATING
7. GOING FOR A WALK
8. DOING YOUR HOUSEWORK
9. HURRYING
10. MAKING A BED
11. MOPPING OR SCRUBBING THE FLOOR
12. MOVING FURNITURE
13. PLAYING WITH CHILDREN OR GRANDCHILDREN
14. PLAYING SPORTS
15. REACHING OVER YOUR HEAD
16. RUNNING, SUCH AS FOR A BUS
17. SHOPPING
18. WHILE TRYING TO SLEEP
19. TALKING
20. VACUUMING
21. WALKING AROUND YOUR OWN HOME
22. WALKING UPHILL
23. WALKING UPSTAIRS
24. WALKING WITH OTHERS ON LEVEL GROUND
25. PREPARING MEALS

3.a) Of the items which you have listed, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH ALL ITEMS SPONTANEOUSLY VOLUNTEERED AND THOSE FROM THE LIST WHICH PATIENT MENTIONED]

Which of these items is most important to you in your day-to-day life?

[List item on response sheet]

b) Of the remaining items, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH REMAINING ITEMS]

Which of these items is most important to you in your day-to-day life?

[List item on response sheet]
c) Of the remaining items, which is most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

d) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

e) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

[FOR ALL SUBSEQUENT QUESTIONS, ENSURE RESPONDENT HAS APPROPRIATE RESPONSE CARD IN FRONT OF THEM BEFORE STARTING QUESTION]

4. I would now like you to describe how much shortness of breath you have experienced during the last 2 weeks while doing the five most important activities you have selected.

a) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3a] by choosing one of the following options from the card in front of you: [GREEN CARD]

1 EXREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

b) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3b] by choosing one of the following options from the card in front of you: [GREEN CARD]

1 EXREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH
c) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3c] by choosing one of the following options from the card in front of you: [GREEN CARD]

1. EXTREMELY SHORT OF BREATH
2. VERY SHORT OF BREATH
3. QUIET A BIT SHORT OF BREATH
4. MODERATE SHORTNESS OF BREATH
5. SOME SHORTNESS OF BREATH
6. A LITTLE SHORTNESS OF BREATH
7. NOT AT ALL SHORT OF BREATH

d) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3d] by choosing one of the following options from the card in front of you: [GREEN CARD]

1. EXTREMELY SHORT OF BREATH
2. VERY SHORT OF BREATH
3. QUIET A BIT SHORT OF BREATH
4. MODERATE SHORTNESS OF BREATH
5. SOME SHORTNESS OF BREATH
6. A LITTLE SHORTNESS OF BREATH
7. NOT AT ALL SHORT OF BREATH

e) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3e] by choosing one of the following options from the card in front of you: [GREEN CARD]

1. EXTREMELY SHORT OF BREATH
2. VERY SHORT OF BREATH
3. QUIET A BIT SHORT OF BREATH
4. MODERATE SHORTNESS OF BREATH
5. SOME SHORTNESS OF BREATH
6. A LITTLE SHORTNESS OF BREATH
7. NOT AT ALL SHORT OF BREATH

5. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
6. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you: [BLUE CARD]

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you: [ORANGE CARD]

1. Extremely tired
2. Very tired
3. Quite a bit of tiredness
4. Moderately tired
5. Somewhat tired
6. A little tired
7. Not at all tired

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you: [BLUE CARD]

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time
9. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you: [YELLOW CARD]

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you: [PINK CARD]

1. NO ENERGY AT ALL
2. A LITTLE ENERGY
3. SOME ENERGY
4. MODERATELY ENERGETIC
5. QUITE A BIT OF ENERGY
6. VERY ENERGETIC
7. FULL OF ENERGY

11. In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks? Please indicate how much of the time you felt upset, worried, or depressed during the past 2 weeks by choosing one of the following options from the card in front of you. [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
12. How often during the last 2 weeks did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you: [YELLOW CARD]

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME

13. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you: [YELLOW CARD]

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME

14. How often during the last 2 weeks have you felt low in energy? Please indicate how often during the last 2 weeks you have felt low in energy by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps? Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

16. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

17. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you: [GRAY CARD]

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2. GENERALLY DISSATISFIED, UNHAPPY
3. SOMEWHAT DISSATISFIED, UNHAPPY
4. GENERALLY SATISFIED, PLEASED
5. HAPPY MOST OF THE TIME
6. VERY HAPPY MOST OF THE TIME
7. EXTREMELY HAPPY, COULDN'T HAVE BEEN MORE SATISFIED OR PLEASED
18. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

19. In general, how often during the last 2 weeks have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense, or uptight by choosing one of the following options from the card in front of you: [BLUE CARD]

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
CRO RESPONSE SHEET

1. BEING ANGRY OR UPSET
2. HAVING A BATH OR SHOWER
3. BENDING
4. CARRYING, SUCH AS CARRYING GROCERIES
5. DRESSING
6. EATING
7. GOING FOR A WALK
8. DOING YOUR HOUSEWORK
9. MURMUR
10. MAKING A BED
11. MOPPIMG OR SCRUBBING THE FLOOR
12. MOVING FURNITURE
13. PLAYING WITH CHILDREN OR GRANDCHILDREN
14. PLAYING SPORTS
15. REACHING OVER YOUR HEAD
16. RUNNING, SUCH AS FOR A BUS
17. SHOPPING
18. WHILE TRYING TO SLEEP
19. TALKING
20. TACTURING
21. WALKING AROUND YOUR OWN HOME
22. WALKING UPHILL
23. WALKING UPSTAIRS
24. WALKING WITH OTHERS ON LEVEL GROUND
25. PREPARING MEALS

OTHER ACTIVITIES

________________________________________________________________________

________________________________________________________________________

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Activity 3a) ______________________________________________________________

Activity 3b) ______________________________________________________________

Activity 3c) ______________________________________________________________

Activity 3d) ______________________________________________________________

Activity 3e) ______________________________________________________________
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CRQ RESPONSE SHEET (cont’d)
APPENDIX 3

SAMPLE OF A DAILY DIARY (one month)
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APPENDIX 4

DATA COLLECTION FORMS
PHYSIOTHERAPY CYSTIC FIBROSIS STUDY
PEP MASK vs. FLUTTER DEVICE

PATIENT ELIGIBILITY CHECKLIST

Date:____________________

Inclusion Criteria (Please circle one)

1. Documented diagnosis of Cystic Fibrosis  yes  no
2. Baseline FEV$_1$ > 40% predicted  yes  no
3. No pulmonary exacerbation requiring hospitalization within one month of study entry  yes  no
4. No change in medications within one month of study entry  yes  no
5. Must have productive daily cough  yes  no
6. Age ≥ 18 years old  yes  no
7. Written informed consent obtained  yes  no

RANDOMIZATION  Date: ________________

____ PEP Mask

____ Flutter Device
**DEMOGRAPHICS**

Date of Birth: ________________  Age: ____  Male ____  Female ____

Telephone # the patient could easily be reached at: (   ) ________________

Address: ______________________________________________________________________________

Written consent obtained?  Yes ____  No ____  Date: ________________

**IMPORTANT DATES**

Randomization  Date: ________________

____ PEP Mask

____ Flutter Device

Teaching Date: ________________

Baseline Visit  (Initial visit after one month training period)  ________________

Three month follow-up  ________________

Six month follow-up  ________________

Nine month follow-up  ________________

Twelve month follow-up  ________________
**BASELINE VISIT** (after 1 month training period)

Date: ________________

I. A. Height ______

   Weight ______ kg

   BMI ______

B. **Chest Findings**

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<th>Location</th>
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C. **Spirometry Findings**

   Was physiotherapy done prior to testing?

   Yes ____   No ____   If yes, time: ______

   Has patient used bronchodilators within the last three hours?

   Yes ____   No ____   If yes, time: ______

   PFT Assessment time: _____________

**Results**

   FEV₁ _______ L _______ % predicted
   FVC _______ L _______ %
   FEF₂₅₋₇₅ _______ L _______ %

   Is FEV₁ result > 40% predicted? Yes ____ No _____

   If yes, proceed: if not, patient is ineligible.
D. **Arterial Blood Gases**
   Date Obtained: __________

   pH ______ pCO₂ ______ pO₂ ______ HCO₃ ______ O₂ Sat ______%

   on Room Air _____ or _____ O₂ ________ (state amount and route)

   If ABG not done, SpO₂ ______

E. **Quality of Well-Being Questionnaire**
   Date Obtained: __________

   If not done, state reason why: ________________________________________

   ________________________________________________________________

F. **Chronic Respiratory Disease Index Questionnaire**
   Date Obtained: __________

   If not done, state reason why: ________________________________________

   ________________________________________________________________

II. **PHYSIOTHERAPY HISTORY**

   Is routine physiotherapy done?
   Daily _____ Occasionally _____ Never _____

   If yes, state type: ______ postural drainage/percussion
   ______ ACB (FET)
   ______ PEP mask
   ______ autogenic drainage
   ______ routine exercise (aerobic)

   Frequency? __________________

   If never, reason why
   ______ do not see a need
   ______ too time consuming
   ______ not confident with technique used
   ______ no family/outside support
   ______ other ____________________________

III. History of pneumothorax? Yes ____ No ____

   If yes, date __________

   Location __________
FOLLOW-UP VISIT  _______ Month

Date: ________________

A.  Weight _____ kg
    BMI ________

B. Chest findings

<table>
<thead>
<tr>
<th>Breath Sounds</th>
<th>Present/Absent</th>
<th>Location</th>
</tr>
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<tbody>
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<td></td>
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<tr>
<td>Crackles</td>
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<tr>
<td>Wheezing</td>
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</tr>
</tbody>
</table>

C. Spirometry Findings

Was physio done prior to testing?  Yes ___  No ___  If yes, time: ______

Has patient used bronchodilators within last three hours?

Yes ___  No ___  If yes, time: ______

PFT Assessment Time: ________  (To be done at approximately same time each visit)

Results

- FEV₁ _______ L  ______% predicted
- FVC _______ L  ______%
- FEF_{25-75} _______ L  ______%

D. Arterial Blood Gases (To be done on last visit only)

Date Obtained: ________________

Results:  pH ____  pCO₂ ____  pO₂ ____  HCO₃ ____  O₂ Sat ____%

on Room Air _____ or  O₂ ______ (state amount and route)

If ABG not done, SpO₂ ______
E. **Quality of Well-Being Questionnaire done?** Yes ___ No ___

If no, reason why? ____________________________________________

F. **Chronic Respiratory Disease Index Questionnaire done?** Yes ___ No ___

If no, reason why? ____________________________________________

G. Has patient been hospitalized due to pulmonary exacerbation since last visit?

Yes ___ No ___ If yes, complete hospitalization record.

Has there been a change in medications since last visit?

Yes ___ No ___ If yes, update medication record.

Has patient been treated but not hospitalized for a pulmonary exacerbation since last visit?

Yes ___ No ___ If yes, please update medication record.

Is patient complying with study requirements?

Yes ___ No ___ If no, state reason: ________________________________

---

**Red Flags**

* Pneumothorax Yes ___ No ___

* A greater than 5% decline in their predicted FEV1 in one year

   yes ___ no ___
APPENDIX 5

INFORMATION FORM
"Effectiveness of the Flutter Device versus the PEP Mask in the Treatment of Adult Cystic Fibrosis"

Investigators: M. Ellen Newbold, Dr. D.E. Tullis, Brenda Ross

Purpose of Study:
As a result of Cystic Fibrosis, I am prone to recurrent lung infections because of abnormal mucus build up in my lungs. An important part of treatment of Cystic Fibrosis is physiotherapy, which consists of techniques designed to assist secretion clearance. This study will compare the effectiveness of two different airway clearance techniques over a thirteen-month period.

The two methods that are being studied are the Flutter Device and the PEP Mask. The Flutter Device is a relatively new device that is easy to learn and use, and it is meant to help clear mucus from the lungs. It is a pipe-like device that you hold in one hand and breathe out through. It causes a vibration in your chest, which loosens the mucus. It is used in a sitting position. The PEP Mask is also easy to learn and it is used in a sitting position. You seal it over your mouth and nose with two hands and breathe in and out through it. As you breathe out the mucus is loosened and moves up the airways so that you can cough it out. It is not known which technique is better, but this study will attempt to determine this by measuring their effect on lung function and general health.

What to Expect:
If I enter the study, I will be asked to perform one of these forms of airway clearance over the next thirteen months. A physiotherapist will randomly assign me to do either the Flutter or the PEP Mask, and will teach me how to do it. I will be asked to do my physiotherapy technique for twenty minutes, two times per day. I will record the treatment sessions in a daily diary, and even record the sessions I miss. The Flutter Device or the PEP Mask will be provided to me free of charge, and no further equipment is required. Both the Flutter Device and the PEP Mask are performed in a comfortable sitting position and should not result in any discomfort whatsoever.

When I first enroll in the study, a teaching session will add an extra half-hour to hour to this clinic visit. I will return to clinic one month after this teaching session to have my technique checked. After this, I will have to be seen in clinic every three months, which is the average/normal follow-up schedule. Completion of the questionnaires will add an additional thirty minutes to my next six clinic visits.

If I get a chest infection, I will call the clinic for assessment and medical advice. If I require admission to the hospital, I will be started on appropriate medications and the physiotherapist will advise me as to what physiotherapy I should be doing (this may include postural drainage and percussion/vibration). When I am better, I will start back on the physiotherapy routine I was doing at the time I became sick (either Flutter or PEP Mask), or with the routine otherwise advised by the physiotherapist.

If I have any questions, I may call: M. Ellen Newbold 416-864-6060 ext. 4127
Dr. Elizabeth Tullis 416-864-5409
ST. MICHAEL’S HOSPITAL, WELLESLEY CENTRAL SITE
ADULT CYSTIC FIBROSIS PROGRAM

“Effectiveness of the Flutter Device Versus the PEP Mask in the Treatment of Adult Cystic Fibrosis”

Consent Form

I have been asked to participate in a research study which will examine the effectiveness of two different types of physiotherapy, the Flutter Device and the PEP Mask. I am aware that there are no known risks associated with either of these two therapies and there are expected benefits. I acknowledge that this research study (described on the attached form) has been explained to me and that any questions I have asked have been answered to my satisfaction. I have been given a copy of the information form. If I have any further questions I may call Dr. Elizabeth Tullis (926-5046) or Ellen Newbold (Physiotherapist 926-5053 ext. 4253) at the Wellesley Central Site, St. Michael’s Hospital.

I have been assured that any information about myself learned during this study will be kept confidential and no information will be released or printed that would disclose personal identity without my permission.

I consent to take part in this study with the understanding that I may withdraw at any time. If I decide not to participate, even after signing this form, it will in no way effect the medical care that I or any member of my family will receive.

Name (print)                      Signature                      Date

Witness (print)                  Signature                      Date

I, the undersigned, have fully explained the relevant details of this study to the patient named above and believe that she/he has understood it.

Person obtaining consent (print)  Signature                      Date
APPENDIX 7

HOW TO USE YOUR NEW FLUTTER DEVICE

This Flutter Device is new and is only meant for your use. You shouldn't share it with other family members or friends. When the Flutter Device is used correctly, it can help keep your airways more clear of mucus. This will help decrease the number of infections you get and thereby decrease the amount of damage to your lungs. However, like any form of airway clearance, it will help the most if you use it regularly.

Use the Flutter Device within 1 hour after any bronchodilator therapy you take (e.g. Ventolin masks or puffers).

To use the Flutter Device, you should sit comfortably in a quiet area. Holding the Flutter in one hand, breathe in deeply and hold your breath for 2 to 3 seconds. Then place the Flutter in your mouth, keep your cheeks as stiff as possible, and breathe out reasonably fast, but not too forcefully through the Flutter. Do not empty your lungs completely, just breathe out to a comfortable point. Adjust the degree of tilt of the Flutter in order to maximize the vibrations in your chest. Do between 5 and 15 breaths out through the Flutter to get the mucus moving. After these 5 to 15 breaths, take a deeper breath in (fill your lungs completely) and blow out more quickly and forcefully through the Flutter. Do 1 to 3 of these breaths. This may cause you to cough and clear some secretions. After coughing, relax your breathing. When you feel relaxed and in control of your breathing, start the cycle again.

You should use the Flutter Device 2 times per day, for about 5 to 6 cycles or approximately 20 minutes per treatment. If you are more productive or need more rest in between cycles, you may spend more time doing the therapy.

Remember it is portable so you can take it with you to work, on holiday, etc. Also remember to fill out your diary every day.

You should clean your Flutter Device after each session to remove any moisture. Dismantle the pieces of the Flutter and rinse them with tap water, dry them with a clean towel and reassemble them. Every 2 days dismantle the pieces of the Flutter and wash them in warm water with a mild soap (e.g. dishwashing liquid). Do not use bleach or other chlorine compounds (e.g. detergents), as they are corrosive on the materials. Rinse and dry the parts and then reassemble them. At regular intervals, thoroughly disinfect your Flutter by soaking the pieces in a solution of 1 part vinegar and 3 parts tap water for 15 minutes. Rinse, dry and reassemble the pieces. It should not be dropped on a hard surface as it could break.

Bring your Flutter Device with you to each clinic visit so that we can check to see that everything is OK. In the meantime, if you have any questions about your Flutter Device or how to use it, call Ellen (Physiotherapist) at 416-864-6060 ext. 4127.
APPENDIX 8

HOW TO USE YOUR NEW PEP MASK

This PEP Mask is new and is only meant for your use. You shouldn't share it with other family members or friends.

PEP stands for Positive Expiratory Pressure. When it is used correctly, it can help keep your airways more clear of mucus. This will help decrease the number of infections you get and thereby decrease the amount of damage to your lungs. However, like any form of airway clearance, it will help the most if you use it regularly.

Use the PEP Mask within 1 hour after any bronchodilator therapy you take (e.g. Ventolin masks or puffers).

To use the PEP Mask, you should sit comfortably in a quiet area with your elbows supported on a table. Seal the mask tightly over your mouth and nose with 2 hands. Breathe in and out 10 to 15 times. Breathing out does require some muscle work because you are breathing out through a resistor (the coloured piece attached to the PEP Mask). After the 10 to 15 breaths through the PEP Mask remove it from your face, then huff and cough to clear secretions. Relax your breathing. When you feel relaxed and in control of your breathing, start the cycle again.

You should use the PEP Mask 2 times per day, for about 5 to 6 cycles or approximately 20 minutes per treatment. If you are more productive or need more rest in between cycles, you may spend more time doing the therapy.

Remember it is portable so you can take it with you to work, on holiday, etc. Also remember to fill out your diary every day.

You should clean your PEP Mask 1 to 2 times per week. Dismantle the pieces of the PEP Mask and wash them in lukewarm water with a mild soap (e.g. dishwashing liquid). Rinse the parts, allow them to air dry and then reassemble them. The Mask is made of natural rubber and should not be left in direct sunlight. You can occasionally lubricate the rubber collar with silicone oil, glycerin or lanolin to ensure that it doesn't deteriorate.

Bring your PEP Mask and all of the colored resistor pieces with you to clinic every time so that we can check to see that everything is OK. In the meantime, if you have any questions about your PEP Mask or how to use it, call Ellen (Physiotherapist) at 416-864-6060 ext. 4127.
APPENDIX 9

COLLECTION OF SUBJECTIVE COMMENTS REGARDING THERAPY AND OTHER IMPORTANT NOTES

FLUTTER GROUP

004 FLUTTER
Recruitment: used CPT occasionally, 1 to 2 times daily when congested
1st Visit: no comments
2nd Visit: as above
3rd Visit: as above
4th Visit: using Flutter regularly, doesn’t notice any direct or immediate improvement with it but PFTs are up
5th Visit: finds Flutter helps clear secretions if uses it for 5 to 10 minutes, finds no effect if uses it for <5 minutes; has not used it in the last month and a half since has been on holidays and travelling
Other Notes: diagnosed with CF-related Diabetes around the time of her 3rd visit; at 5th visit it was reported that Burkholderia cepacia was found in her most recent sputum sample

006 FLUTTER
Recruitment: never did any physiotherapy, did not see a need and was never told she needed to do any
1st Visit: no comments
2nd Visit: as above
3rd Visit: --
4th Visit: using Flutter 2 x/day for ~ 20 minutes/session
5th Visit: still using Flutter 2 x/day for 15 to 20 minutes/session, finds it loosens secretions, plans to continue using it

007 FLUTTER
Recruitment: had not used any physiotherapy in ~ 1 year, prior to that used CPT only when had a cold
1st Visit: lost Flutter within 1st month (given new one)
2nd Visit: --
3rd Visit: finds Flutter productive so uses it occasionally (~ once a week), but generally finds no time to use it
4th Visit: no comments
5th Visit: not using Flutter Device
Other Notes: at 1st visit pt. had lost his Flutter and was having problems with his seizure disorder – upset and fearful – refused PFTs and arterial blood gas (ABG); long time between 3rd and 4th visit because having marital problems, children involved, very upset

010 FLUTTER
Recruitment: never did any physiotherapy, did not see a need
1st Visit: --
2nd Visit: not using Flutter regularly because of time constraints, plays sports more
3rd Visit: --
4th Visit: not using Flutter at all because is too busy and plays sports
5th Visit: not using Flutter at all
013 FLUTTER
Recruitment: has done CPT in past (1 x/day up to 5 to 6 days/week) but not at all in past year, finds it too time consuming
1st Visit: using Flutter more often than has done CPT in past
2nd Visit: not using Flutter at all – no time, only taking inhaled medications (mask) ~ 1 x/week if that
(should be taking mask 1 to 2 x/day)
3rd Visit: not using Flutter, taking mask almost every day (1 x/day)
4th Visit: not using Flutter – no time
5th Visit: not using Flutter, feels she would use it if she gets sick, but when she feels well she struggles just trying to do masks 1-2 x/day (misses masks ~ 2 to 3 days/week)

014 FLUTTER
Recruitment: used PEP Mask ~ 1 x/week, not more frequently because did not see a need – exercising more and PFTs still good
1st Visit: no comments
2nd Visit: --
3rd Visit: used Flutter for ~ 1 month then changed back to PEP Mask, has been using it 1 to 2 x/day for ~ 10 to 15 minutes/session
4th Visit: --
5th Visit: now using a combination of PEP Mask and CPT – uses PEP Mask if she feels like she doesn’t need physiotherapy or if has less time (~ 10 minutes/session) – uses CPT if she feels a particular area is congested, this takes more time (percusses ~ 4 to 5 minutes/area)

015 FLUTTER
Recruitment: did CPT 3 x/day
1st Visit: --
2nd Visit: does CPT more than Flutter, became sick ~ 1 month after-recruitment – while sick (for ~ 7 weeks) stopped Flutter and only used CPT
3rd Visit: doing more CPT in last month than Flutter, out of habit of using Flutter but plans to start using it again
4th Visit: for about 2 to 3 weeks after 3rd visit used both Flutter and CPT daily, then switched to using Flutter ~ 1 x/week and CPT 3 x/day, feels like she has not done treatment if she only uses the Flutter
5th Visit: rarely uses Flutter, uses CPT 3 x/day, doesn’t feel she gets the same effect from the Flutter but states that she isn’t sure if its just because she has always used CPT

017 FLUTTER
Recruitment: occasionally uses CPT, finds it too time consuming
1st Visit: using Flutter daily
2nd Visit: as above
3rd Visit: --
4th Visit: no comments
5th Visit: as above

018 FLUTTER
Recruitment: did CPT 1 to 2 x/day
1st Visit: no comments
2nd Visit: as above
3rd Visit: finds the Flutter convenient
4th Visit: using Flutter at least 1 x/day for ~ 20 minutes/session
5th Visit: usually uses Flutter at night, for the last 2 months has been using CPT (with a mechanical percussor) in the morning because she finds this takes less energy and she feels lazy in the morning, finds the Flutter takes more work, plans to continue with this routine
019 FLUTTER
Recruitment: used the Flutter daily
1st Visit: recently stopped using the Flutter because of new morning nausea
2nd Visit: not using Flutter everyday, also using CPT
3rd Visit: -
4th Visit: using Flutter
5th Visit: using Flutter regularly – prefers to do it 1st thing in morning or not at all, doesn’t find it as helpful later in the day
Other Notes: patient was pregnant at time of recruitment, delivered baby ~ 1 month before her 3rd visit

020 FLUTTER
Recruitment: uses FET/ACB ~ 2 x/day, 7 days/week
1st Visit: no comments
2nd Visit: lost Flutter ~ 1 week ago hence missed treatment 1 week (given new one)
3rd Visit: uses it regularly for ~ 10 minutes/day with the exception of 2 to 2 1/2 weeks because he was too busy
4th Visit: using Flutter for ~ 15 minutes per day
5th Visit: as above, not sure if it is really helpful but has had no problems with it, plans to continue to use it

021 FLUTTER
Recruitment: did CPT once daily for ~ 30 minutes/session
1st Visit: no comments
2nd Visit: as above
3rd Visit: using Flutter 1 x/day, no time to use it 2 x/day
4th Visit: as above but plans to increase to using it 2 x/day now
5th Visit: using Flutter 1 x/day

022 FLUTTER
Recruitment: for last year has used CPT once daily (~ 15 minutes/session)
1st Visit: no comments
2nd Visit: as above
3rd Visit: as above
4th Visit: since last visit had been forgetting to do treatment (e.g. one month did it ~ 15 times) but doing it more regularly again now – once a day for ~ 30 minutes/session
5th Visit: using Flutter once a day for ~ 20 minutes/session, finds his cough is productive with it and plans to use it in the future
Other Notes: at 1st visit sputum was found to be positive for Mycobacterium avium complex (MAC) therefore started on 2 to 3 antibiotics (was on these throughout the duration of the study)

024 FLUTTER
Recruitment: did no physiotherapy, finds CPT uncomfortable and too time consuming
1st Visit: no comments
2nd Visit: as above
3rd Visit: as above
4th Visit: finds morning treatment is not as productive as evening treatment, last 5 minutes of 20 minute treatment session gets sputum moving
5th Visit: trying to use Flutter 3 x/day now although during the last 10 days has used it less because has felt discomfort/fullness due to pregnancy – coughing itself is less pleasant because of fullness and GER
Other Notes: was in 1st month of pregnancy at 3rd visit
026 FLUTTER
Recruitment: did CPT once daily, sometimes twice daily
1st Visit: no comments
2nd Visit: doing CPT as did not find Flutter effective at clearing secretions
3rd Visit: almost never uses the Flutter, does CPT 2 x/day
4th Visit: never uses the Flutter, doing CPT ~ 15 minutes/day, prefers CPT and exercise over the Flutter, finds he is less productive with the Flutter
5th Visit: still not using the Flutter — found it didn’t do anything, using CPT 2 x/day for ~ 10 minutes/session

033 FLUTTER
Recruitment: never did physiotherapy, did not see a need
1st Visit: finds Flutter works well, uses it 1 x/day for ~ 20 minutes
2nd Visit: no comments
3rd Visit: --
4th Visit: --
5th Visit: has not used Flutter for greater > or = 6 months

035 FLUTTER
Recruitment: never did physiotherapy, did not see a need
1st Visit: no comments
2nd Visit: as above
3rd Visit: tries to do Flutter regularly
4th Visit: --
5th Visit: uses Flutter ~ 1 to 2 x/week, when uses it notices breathing feels easier and that he coughs productively, plans to continue with it, wishes it wasn’t position dependent

036 FLUTTER
Recruitment: used CPT when sick
1st Visit: no comments
2nd Visit: --
3rd Visit: uses Flutter if has time (on a few days, off a few days), feels it helps her to clear secretions
4th Visit: uses Flutter more consistently, usually in the morning, occasionally in the evening
5th Visit: used Flutter 1 to 2 x/day for several weeks when was sick, but has not used it for the last 2 to 3 months, she does find it helps her to clear secretions but she is not sure why she can’t do it regularly

037 FLUTTER
Recruitment: did no physiotherapy
1st Visit: using Flutter ~ 1 x/day
2nd Visit: --
3rd Visit: used Flutter in 1st month, not again since then
4th Visit: not using Flutter at all, didn’t notice any change when he used it
5th Visit: not using Flutter at all, can’t find it

042 FLUTTER
Recruitment: never did any physiotherapy, recently diagnosed
1st Visit: --
2nd Visit: --
3rd Visit: not using Flutter, no time
4th Visit: --
5th Visit: not using Flutter, no time
043 FLUTTER
Recruitment: never did any physiotherapy, did not see a need, was never taught, recently diagnosed
1st Visit: --
2nd Visit: --
3rd Visit: has not used it for months (since soon after recruitment)
4th Visit: using Flutter 1 to 2 x/week for 5 to 10 minutes/session, plans to continue with this routine
5th Visit: using Flutter 1 to 2 x/month, plans to use it more when she gets sick/increased congestion

PEP MASK GROUP

001 PEP
Recruitment: used CPT 2 to 3 x/day for ~ 30 minutes/session
1st Visit: no comments
2nd Visit: not using the PEP at all, did not find it worked, prefers doing CPT (1 x/day)
3rd Visit: doing CPT 1 x/day
4th Visit: as above
5th Visit: doing CPT 2 x/day for ~ 15 minutes/session

002 PEP
Recruitment: did no physiotherapy
1st Visit: doing PEP 1 or 2 x/week
2nd Visit: --
3rd Visit: --
4th Visit: --
5th Visit: not doing any physiotherapy

003 PEP
Recruitment: did no regular physiotherapy, used CPT and/or ACB inconsistently, found it too time consuming, played more sports
1st Visit: happy with PEP Mask, finds it effective
2nd Visit: as above
3rd Visit: as above
4th Visit: going well with PEP, really likes it, feels better when uses it
5th Visit: still pleased with PEP Mask, really does like it, it is simple, finds it has a slight delayed effect – productive ~ 20 to 40 minutes post-treatment

005 PEP
Recruitment: did CPT ~ 2 x/week or less, found it awkward, inconvenient, noisy
1st Visit: really likes PEP (a lot more than CPT), finds it works well
2nd Visit: no comments
3rd Visit: as above
4th Visit: has used PEP less lately due to increase stress at home and workplace
5th Visit: uses PEP Mask 1 x/day when sick, when well uses it 2 to 3 x/week, finds it effective especially when he is more congested, may not find it any more effective than CPT but is much more likely to use it, it is more convenient, comfortable and quiet

008 PEP
Recruitment: used CPT 2 x/day, ~ 15 minutes/session
1st Visit: using PEP 2 x/day for ~ 10 to 15 minutes/session
2nd Visit: as above
3rd Visit: as above
4th Visit: using PEP 1 x/day for ~ 10 minutes
5th Visit: using PEP 2 x/day for ~ 10 minutes

009 PEP
Recruitment: did CPT when sick (several x/day), otherwise does not see a need to do it, does not find it enjoyable
1st Visit: using PEP 2 x/day
2nd Visit: as above
3rd Visit: as above
4th Visit: using PEP 2 x/day (~ 5 cycles/session), finds it helps with airway clearance
5th Visit: as above, likes it, plans to continue with it

011 PEP
Recruitment: never did PT because recently diagnosed
1st Visit: --
2nd Visit: has found it hard to do secondary to time
3rd Visit: no comments
4th Visit: uses PEP ~ 3 times/month, may try to use it more often
5th Visit: has not used PEP for ~ 4 months, still hard to find time

012 PEP
Recruitment: used ACB when congested, finds it time consuming, difficult if tired or in a hurry
1st Visit: using PEP 2 x/day, feeling a lot more clear, decreased cough at night
2nd Visit: as above
3rd Visit: as above
4th Visit: as above, going well, finds it helpful
5th Visit: using PEP 2 x/day for 15 to 20 minutes/session, finds it very helpful, wants to continue with it

016 PEP
Recruitment: never did physiotherapy, did not see a need
1st Visit: no comments
2nd Visit: finds PEP difficult if sinuses are congested and tender
3rd Visit: had sinus surgery therefore stopped using PEP for a while
4th Visit: using PEP 2 x/day for ~ 15 to 20 minutes/session, sinuses are better so it is easier to do treatment
5th Visit: as above, finds it helps to loosen secretions

023 PEP
Recruitment: used PEP therapy (TheraPEP) 1 x/day
1st Visit: using PEP 1 x/day
2nd Visit: as above
3rd Visit: as above
4th Visit: as above
5th Visit: using PEP 1 x/day in morning to help clear his chest out before day’s activities, if he doesn’t do it he coughs for the next hour, the mask gets rid of it (sputum) quicker

027 PEP
Recruitment: used PEP Mask a couple of times/month, did not see a need, lazy
1st Visit: using PEP 1 x/day, ~ 20 minutes
2nd Visit: no comments
3rd Visit: not using the PEP, ready to try it again 1 x/day
4th Visit: --
5th Visit: has not used PEP at all, finds coughing causes back pain

028 PEP
Recruitment: never did physiotherapy, did not see a need
1st Visit: using PEP 1 to 2 x/day, 3 to 6 x/week, ~ 20 minutes/session
2nd Visit: using PEP 4 to 5 x/week, motivated to use it once the study is over because she feels it is helping her
3rd Visit: PEP still helping to loosen secretions
4th Visit: --
5th Visit: hasn’t used PEP since sometime after 3rd visit, hard to find time since started new job

029 PEP
Recruitment: used CPT ~ 1 x/week if at all, did not see a need, does not like CPT
1st Visit: using PEP 1 to 2 x/day
2nd Visit: enjoys using PEP, very pleased with it, feels great
3rd Visit: continues to use PEP, more adherent to it than was with CPT
4th Visit: using PEP in am ~ 3 x/week, finds it helpful, can take more relaxed, deeper breaths, doesn’t have time to use it more often
5th Visit: hasn’t used PEP for ~ last 2 months because he is too busy working 2 jobs

030 PEP
Recruitment: never did physiotherapy, did not see a need
1st Visit: no comments
2nd Visit: as above
3rd Visit: started using PEP less before 2nd visit, now uses it < 1 x/week, partially because of time and partially because he just doesn’t use it
4th Visit: not using PEP at all, could make time for it but doesn’t get around to it
5th Visit: rarely uses PEP, prefers exercise

031 PEP
Recruitment: occasionally used ACB/FET
1st Visit: no comments
2nd Visit: as above
3rd Visit: stopped using PEP before 2nd visit because of time and didn’t notice a benefit or change with it
4th Visit: not using PEP at all
5th Visit: rarely uses PEP, prefers exercise

032 PEP
Recruitment: did CPT ~ 2 x/week, more often if sick
1st Visit: no comments
2nd Visit: as above
3rd Visit: as above
4th Visit: as above
5th Visit: prefers PEP Mask over mechanical percussor and PD, usually uses it 2 x/day for 15 to 20 minutes/session, usually would miss treatment only if too tired, plans to continue with it

034 PEP
Recruitment: never did physiotherapy, did not see a need
1st Visit: no comments
2nd Visit: uses PEP ~ every other day for ~ 10 minutes/session, helps to clear secretions but finds it tiring
3rd Visit: had been using PEP more often but recently using it ~ once per week on average, not using it more often because he feels down, procrastinates, tells himself "I’ll do it later"
4th Visit: had been using PEP ~ 1 x/day, missing it occasionally, but has not used it for ~ the last 2 weeks
5th Visit: had been using PEP ~ every other day, but has not used it for last 2 to 3 weeks, notices PEP
works when is sick and has increased congestion, when feels well and has little congestion the
PEP helps to loosen it

038 PEP
Recruitment: never did physiotherapy
1st Visit: did not attend 1st visit, reported that he “just doesn’t have the time, it is hard to keep up with
regular routine, started back with regular masks, next job is to do regular exercise, not doing the
PEP at all”
2nd Visit: not using PEP, no time
3rd Visit: using a combination of PEP and CPT, uses PEP on a “hit and miss” basis, gets help with CPT 2
x/week from home care, feels more productive with CPT but he questions if it is the time of day
the therapy is done, recently has had the flu and increased fatigue — “when I feel like this I don’t
do anything”
4th Visit: as above
5th Visit: continues with a combination of PEP and CPT, uses PEP ~ 2 to 3 x/week,
CPT with homecare 2 x/week and now wife also assisting with CPT almost every day

039 PEP
Recruitment: used CPT and/or FET daily
1st Visit: prefers CPT (mechanical percussion), generally feels better with percussion therefore stopped
using PEP for the most part
2nd Visit: uses a combination of PEP, CPT and FET, PEP Mask helps a bit but still feels congested, finds
that when he only does PEP it helps clear some secretions but by the end of the day it doesn’t
feel like he has done physiotherapy
3rd Visit: has only used PEP once or twice since the last visit, PEP feels “like a work out”, he feels “sort
of crappy afterwards”, CPT is easier and is more definite in terms of time, therefore he
continues with CPT, has no time to do anything else
4th Visit: using a combination of PEP and CPT, uses PEP more on weekends for ~ 30 minutes/session,
uses CPT on weekdays for ~ 25 minutes/session, finds CPT “more routine”
5th Visit: using PEP as needed for congestion ~ 2 x/week, having problems with percussion therefore has
relied more on PEP

040 PEP
Recruitment: never did physiotherapy
1st Visit: --
2nd Visit: --
3rd Visit: tried PEP at 1st, found it was productive but it bothered his sinuses, therefore not using it at all
really
4th Visit: --
5th Visit: started using PEP regularly after 3rd visit, using it once a day, 4 days/week on average, ~ 5
cycles/session, finds it helps to raise secretions, notices a difference with it

041 PEP
Recruitment: uses resistor portion of PEP Mask 2 x/day, ~ 10 minutes/session (mask portion broke long ago)
1st Visit: finds PEP helpful, using it 2 x/day, ~ 10 minutes/session
2nd Visit: --
3rd Visit: --
4th Visit: as per 1st visit
5th Visit: as above, finds PEP more effective after exercise