COMPARISON OF A HEATED HUMIDIFIER WITH A 
HEAT AND MOISTURE EXCHANGER FOR 
CONDITIONING THE GASES INSPIRED BY 
CHILDREN WITH TRACHEOSTOMIES.

DAVID MCNAMARA

A thesis submitted in partial fulfillment of the requirements for the Doctor of 
Philosophy (PhD) in Paediatrics, The University of Auckland, 2009.
Abstract

**Background:** Children with chronic tracheostomies should have the gases they inspire conditioned through warming and humidifying. The degree and most appropriate method of conditioning is debated.

**Methods:** Two randomised cross-over studies with partial observer-blinding were conducted comparing the use of a heated humidifier (HH) to a heat and moisture exchanger (HME) during sleep: a short-term study involving 20 hours of each treatment and a long-term study involving ten weeks of each treatment. The short-term study was conducted to investigate immediate treatment difference and the long-term study to investigate whether short-term differences translated into long-term differences in major clinical outcomes. At the time of assessment children in the short-term study were wearing the assigned treatment whereas in the long-term study all children were wearing the HME. Children were assessed in both studies for changes on clinical examination, airway secretion characteristics, airway inflammatory cytokine levels and occurrence of clinical events. Children in the long-term study also underwent mucociliary clearance (MCC) scans via inhaled radioaerosol. A parallel qualitative interview study was incorporated into the long-term study as well as assessment of parental and child quality of life.

**Results:** Fifteen children were enrolled in the short-term study. In this study children had improved clinical examination findings when treated with HH compared to HME for respiratory rate \( (p = 0.038) \), oxygen saturations \( (p = 0.012) \), retractions \( (p= 0.011) \), wheeze \( (p = 0.020) \) and summary examination score \( (p < 0.001) \). However, there was no difference in airway secretion characteristics, inflammatory cytokines or the frequency of required suctioning. Fourteen children were enrolled in the long-term study with two withdrawing prior to assessment. Fewer children in the long-term study had major clinical events \( (5 \text{ vs. } 12, p = \)
0.005) when treated with HH compared to HME with trends toward fewer experiencing acute respiratory admissions (1 vs. 5, p = 0.069) and chest infections (4 vs. 9, p = 0.061). No significant differences between treatments were observed for MCC scans, clinical examination, airway secretion characteristics, inflammatory cytokines or quality of life questionnaires. Interviews revealed how parents managed their child’s health and balanced the difficulties of using technology against the benefits of treatment.

**Conclusion:** The use of a HH compared to a HME resulted in short-term improvements in clinical examination findings and long-term improvements in the incidence of major clinical events.
Acknowledgements

I would like to thank my principal supervisor, Dr Cass Byrnes (Department of Paediatrics, The University of Auckland) who was involved with the planning, design, conduct and write-up of the research. She provided constant enthusiasm even when my own enthusiasm faltered and valuable editing and revisions for a stream of ethics applications and manuscripts. I would also like to thank Professor Innes Asher (Department of Paediatrics, The University of Auckland) who has been supportive throughout the design and conduct of the research and provided insightful comments on my writing. Mr Alistair Stewart (Biostatistician, School of Population Health, The University of Auckland) has also acted as a supervisor and provided much needed advice on the complexities of analysing cross-over studies. I am grateful for his patience in answering my repeated questions.

I am grateful to Cathy Douglas, Sheri Biscaldi and Shelley Broome (Respiratory Physiology, Starship Children's Hospital) for setting up the heated humidification circuits for the children and training parents in their use. Melody Trueman (previously Ward 26B nurse educator, Starship Children's Hospital) also provided ongoing training to staff and parents on tracheostomy cares and taught me how to perform tracheostomy suctioning. I am grateful to Mr Murali Mahadevan, Mr Colin Barber and Debby Sandow (Paediatric ENT Department, Starship Children's Hospital) for allowing me access for the research to their patients.

Special mentions to:

- Dr Annette Dickinson, formerly Auckland University of Technology and now Auckland City Hospital, kindly got me started on the path of qualitative research and guided me along the way
• Dr Jo Perry, Liggin's Institute, The University of Auckland, for answering my call for help and arranging the analysis of inflammatory cytokines.

• Gail Gillies, Nurse Manager, Children's Research Centre, Starship Children's Hospital for performing clinical examinations for the long-term study

• The Children's Research Centre, Starship Foundation, Starship Children's Hospital for allowing the use of their facilities for the long-term study assessments

• Dr Evangeline Daviskas, the Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, NSW, Australia, for advice on performing mucociliary clearance scans and on the collection of airway secretion samples

The research would not have been possible without generous financial support:

• The Joan Mary Reynolds Fellowship via Starship children's Hospital funded my salary for the first year of research

• Following this my salary was partly supported by a fellowship from the Foundation for Research, Science and Technology

• Fisher and Paykel Healthcare provided most of the remaining funding for my salary and the costs of the research. They also supplied heated humidifiers and hosing for use in the research

I am particularly grateful to the children and families who have taken part in the research. They have generously supplied their time and energy and allowed me insights into their lives.
Most of all I would like to thank my wife, Liz, who provided support throughout the research process and tolerated the impact on our family-life. She also provided much needed stern encouragement to enter the final phase of writing and completion without which the thesis would still be uncompleted.
Table of Contents

Abstract................................................................................................................................................ ii
Acknowledgements............................................................................................................................. iv
Table of Contents ............................................................................................................................. vii
List of Tables ...................................................................................................................................... xi
List of Figures.................................................................................................................................... xiv
List of Abbreviations......................................................................................................................... xvii
Chapter 1 Introduction ...................................................................................................................... 1
  1.1 Background to the Research ........................................................................................................ 1
  1.2 Terminology .................................................................................................................................. 7
  1.3 Aims of the Study ....................................................................................................................... 8
  1.4 Layout of Thesis ....................................................................................................................... 10
  1.5 Author’s Contribution ............................................................................................................. 11
  1.6 Ethics Approval ....................................................................................................................... 12
Chapter 2 Background and Review of the Literature .................................................................. 13
  2.1 History of Tracheostomy .......................................................................................................... 13
  2.2 Indications for Tracheostomy in Children .............................................................................. 16
  2.3 Complications of Tracheostomy ............................................................................................ 17
  2.4 The Airway and Respiratory Mucosa ..................................................................................... 22
    2.4.1 Structure and Function of the Airway................................................................................ 22
    2.4.2 Structure and Function of the Airway Mucosa: ............................................................... 23
    2.4.3 The Airway Surface Liquid ............................................................................................ 24
    2.4.4 The Mucus Layer ........................................................................................................... 25
    2.4.5 The Periciliary Layer .................................................................................................... 31
    2.4.6 The Ciliated Epithelium ............................................................................................... 34
  2.5 Relative and Absolute Humidity .............................................................................................. 36
  2.6 The Energy of Air and Moisture ............................................................................................... 37
  2.7 Physiology of Heat and Moisture Exchange in the Airway .................................................... 38
    2.7.1 Changes in the Isothermic Saturation Boundary (ISB) with Inhalation of Cold or Dry Air ........................................................................................................... 41
    2.7.2 Effects of Cold or Dry Air on Airway Blood Flow ......................................................... 42
    2.7.3 Effects of Cold or Dry Air On Surface Liquid Osmolarity ........................................... 44
  2.8 Respiratory Energy Exchange and Total Body Balance ......................................................... 48
8.2.3 In the fog vs Running smoothly ................................................................. 218
8.2.4 Living worried ........................................................................................... 219
8.2.5 Getting up in the night .............................................................................. 220
8.2.6 Frequent illness .......................................................................................... 220
8.2.7 Bearing the responsibility .......................................................................... 221
8.2.8 Management Strategies ........................................................................... 222
8.2.9 Constant checking (Monitoring) ................................................................. 223
8.2.10 Becoming the expert (Adapting & Learning) ............................................ 224
8.2.11 Family pulls together (Burden sharing) ................................................... 224
8.2.12 Electing to use preferred technology (Balancing) .................................... 225

8.3 Discussion and Comparison With The Literature .......................................... 227

Chapter 9 Discussion .......................................................................................... 238

9.1 Clinical outcomes from the short-term study ................................................. 238
9.2 Clinical outcomes from long-term study ....................................................... 240
9.3 Clearance of mucus from the airways ............................................................ 250
9.4 Inflammatory Cytokines ............................................................................... 254
9.5 Qualitative Interviews ................................................................................... 256
9.6 Summary of findings ..................................................................................... 258
9.7 Suggestions for future research ................................................................. 260
9.8 Clinical recommendations from the study ..................................................... 262
9.9 Conclusions .................................................................................................. 264

Chapter 10 Personal Reflections ................................................................. 266

References Cited in This Thesis ...................................................................... 269

APPENDIX A: Health-Related Quality of Life Questionnaire for Long-term Study ......................................................... 296

APPENDIX B: Clinical Examination Guide for Short-term and Long-term Studies ................................................................. 308

APPENDIX C: Overnight Event Record for Short-term Study ......................... 311
List of Tables

Table 2.1: Change in mortality due to the practice of prolonged intubation.

Table 2.2: Indications for tracheostomy in children presented in order of decreasing frequency.

Table 2.3: Complications of tracheostomy.

Table 2.4: Absolute Humidity of Air at Various Temperatures and 100% Relative Humidity.

Table 2.5: Differences in temperature and humidity of inspired air during nasal and oral breathing as measured at the oropharynx and trachea.

Table 3.1: Timing of assessments for short-term study.

Table 3.2: Timing of assessments for long-term study.

Table 4.1 Scoring criteria for clinical examination findings.

Table 4.2 Scoring criteria for assessing airway secretions following suctioning of the tracheostomy.

Table 4.3: Individual participant demographic details at enrolment for short-term study.

Table 4.4: Summary table showing participant’s demographic details at enrolment for short-term study.

Table 4.5: Significance tests for continuous variable examination findings for short-term study.

Table 4.6: Significance tests for categorical clinical examination findings for short-term study.

Table 4.7: Significance tests for categorical airway secretion assessment findings for short-term study.

Table 4.8: Comparison of overnight events.

Table 5.1: Original and revised questions for health visits domain for the Pediatric Tracheostomy Health Survey Index.

Table 5.2: Individual participant demographics at enrolment to long-term study.

Table 5.3: Summary table showing participant’s demographic details at enrolment to long-term study.

Table 5.4: Participants experiencing major clinical events during overnight treatment with HH or HME.

Table 5.5: Time-to-event data for major clinical events during treatment with HH or HME.
Table 5.6: Clinical examination findings for continuous variables for long-term study.

Table 5.7: Significance tests for clinical examination ordinal categorical for long-term study.

Table 5.8: Significance tests for airway secretion ordinal categorical findings for long-term study.

Table 5.9: Parents' health-related quality of life (HRQOL) SF36v2 data.

Table 5.10: Child's and parents' health-realted quality of life (HRQOL) data from Pediatric Tracheostomy Health Survey Index (PTHSI).

Table 5.11: Reliability statistics for Paediatric Tracheostomy Health Survey Index (PTHSI) measured from baseline results.

Table 5.12: Correlation between domains of Pediatric Tracheostomy Health Survey Index (PTHSI) and SF-36v2 t-scores measured from baseline results.

Table 5.13: Parents'retrospective recall of clinical events for treatment period or past eight weeks.

Table 6.1: Results from mucociliary clearance scans in three adult volunteers. Results expressed as a proportion of initial deposition.

Table 6.2: Results of mucociliary clearance scans in participants with repeated scans to assess repeatability performed during treatment with heated humidifier.

Table 6.3: Individual participant results for mucociliary clearance scans expressed as retention (proportion remaining of originally deposited activity).

Table 6.4: Results of mucociliary clearance scans expressed as retention (proportion remaining of originally deposited activity).

Table 7.1: Interleukin-8 (IL-8) levels in airway secretions for individual participants in short-term study.

Table 7.2: Interleukin-1beta (IL-1β) levels in airway secretions for individual participants in short-term study.

Table 7.3: Tumor necrosis factor-alpha (TNFα) levels in airway secretions for individual participants in short-term study.

Table 7.4: Inflammatory cytokines levels in airway secretions from children with tracheostomies in the short-term study.

Table 7.5: Inflammatory cytokine levels in airway secretions for individual participants in long-term study.

Table 7.6: Inflammatory cytokines levels in airway secretions from children with tracheostomies in the long-term study.
Table 7.7: Spearman correlation co-efficients for differing inflammatory cytokines from first period baseline values in short-term study.

Table 7.8: Spearman correlation co-efficients for inflammatory cytokines from baseline values in long-term study.

Table 8.1: Stages in grounded theory analysis as performed for this study.

Table 8.2: Original semi-structured interview questions which were subsequently progressively modified to sample incidents and concepts of interest (theoretical sampling).

Table 8.3: Participant demographics for qualitative interviews.
List of Figures

Figure 1.1: A – a tracheostomy tube. B – Child with tracheostomy tube in situ.

Figure 1.2: The heated humidifier set-up in one of the participant’s bedrooms.

Figure 1.3: Child with tracheostomy wearing the heated humidifier with tracheostomy mask over tracheostomy tube opening.

Figure 1.4: Portex Thermovent T heat and moisture exchanger (HME) partially disassembled to show roll of hydrophobic filter paper.

Figure 1.5: Heat and moisture exchanger (HME) attached to a tracheostomy tube.

Figure 1.6: Image of one of the study participants wearing the heat and moisture exchanger.

Figure 2.1: The structure of the airway mucosa.

Figure 2.2: Beating pattern of a cilium.

Figure 2.3: Cross-section of a cilium.

Figure 3.1: Study design for short-term study.

Figure 3.2: Study design for long-term Study.

Figure 4.1: Mean treatment differences for summary respiratory examination score.

Figure 4.2: Mean treatment differences for summary secretion score.

Figure 5.1: Diagram showing numbers of children eligible, enrolled and withdrawn and final treatment preference as stated by parents.

Figure 5.2: Numbers of participants experiencing events during overnight treatment with HH or HME.

Figure 5.3: End of study parental perceived effectiveness, convenience, overall satisfaction and treatment preference.

Figure 5.4: Difference between parents’ health-related quality of life (HRQOL) SF36v2 data standardised t-scores and national New Zealand norms.

Figure 5.5: Mean treatment differences for parents’ health-related quality of life (HRQOL) SF36v2 data t-scores.

Figure 5.6: Mean treatment differences for children’s and parents’ health-related quality of life (HRQOL) data from Paediatric Tracheostomy Health Survey Index (PTHSI).

Figure 5.7: Kaplan-Meier plot for outcome of all main clinical events.
Figure 5.8: Time-to-event plot all major clinical events.

Figure 5.9: Time-to-event plot for outcome of acute admission.

Figure 5.10: Time-to-event plot for outcome of acute respiratory admissions.

Figure 5.11: Time-to-event plot for outcome of chest infections.

Figure 5.12: Time-to-event plot for combined outcome of tracheostomy tube occlusions or emergency tracheostomy change.

Figure 5.13: Time-to-event plot for combined outcome of treatment failure or study withdrawal.

Figure 6.1: Cilia beat frequency measurements separated by specimen quality in samples from the upper tracheas of adult participants with tracheostomies.

Figure 6.2: Cilia beat frequency measurements in samples from the mid to lower tracheas of children with tracheostomies participating in long-term study.

Figure 6.3: Child in position to inhale radioaerosol from nebuliser for mucociliary clearance scan while sitting on caregiver's lap.

Figure 6.4: Plot of measured aerosol mass median diameter (MMD) with dotted lines indicating 10th and 90th centiles of droplet size. Obscuration is also plotted demonstrating a significant fall below 10% at flow rates of less than 5 L/min.

Figure 6.5: Division of right lung into central, intermediate and peripheral regions for calculation of "penetration index" and clearance from central region.

Figure 6.6: Child in restraining cradle during image acquisition.

Figure 6.7: Results from mucociliary clearance scans for three adult volunteers.

Figure 6.8: Mucociliary clearance scan imaged from one of the children in the pilot study.

Figure 6.9: Results from mucociliary clearance scans from three children in pilot study.

Figure 6.10: Mucociliary clearance scans from one of the children in the long-term study demonstrating clearance over two hours, particularly from central region.

Figure 6.11: Mucociliary clearance scan images from one of the participants in the long-term study showing probable retrograde flow of signal from the trachea into the central lung regions between the baseline and 30 minute scan images.

Figure 6.12: Retention at 60 minutes right central region for mucociliary clearance scans showing relationship of clearance to penetration index.

Figure 6.13: Mucociliary clearance scans from right central lung regions of study two participants showing effect of penetration index (PI) on retention.
Figure 7.1: Mean treatment differences for inflammatory cytokines for children in the short-term study.

Figure 7.2: Mean treatment differences for inflammatory cytokines for children in the long-term study.

Figure 8.1: Grounded theory of parents managing the child’s care.

Figure 9.1: Graph of number of children having tracheostomies inserted per year under the care of Starship Children's Hospital and number of children having tracheostomies decannulated, dying or turning 18 years old per year. Results derived from a database maintained by the Starship Children's Hospital ENT team.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>ASL</td>
<td>Airway surface liquid</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>Avidin-HRP</td>
<td>Avidin-Horseradish Peroxidase</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CBF</td>
<td>Cilia beat frequency</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance regulator</td>
</tr>
<tr>
<td>Cl'</td>
<td>Chloride</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest radiograph (x-ray)</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear Nose and Throat</td>
</tr>
<tr>
<td>ETT</td>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>GT</td>
<td>Grounded theory</td>
</tr>
<tr>
<td>H2O</td>
<td>Water</td>
</tr>
<tr>
<td>HCH</td>
<td>Hygroscopic condenser humidifier</td>
</tr>
<tr>
<td>HCH-HME</td>
<td>Hygroscopic condenser humidifier heat and moisture exchanger</td>
</tr>
<tr>
<td>HH</td>
<td>Heated humidifier</td>
</tr>
<tr>
<td>HME</td>
<td>Heat and moisture exchanger</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon-gamma</td>
</tr>
<tr>
<td>Ig</td>
<td>Immunoglobulin e.g. IgA or IgG</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin e.g. IL-8</td>
</tr>
<tr>
<td>ISB</td>
<td>Isothermic saturation boundary</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>L/min</td>
<td>Litres per minute</td>
</tr>
<tr>
<td>LRTI</td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>MCC</td>
<td>Mucociliary clearance</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>MMD</td>
<td>Mass median diameter</td>
</tr>
<tr>
<td>mSv</td>
<td>Millisieverts</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>Nm</td>
<td>Nanometres</td>
</tr>
<tr>
<td>PA</td>
<td>Posterior-anterior</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Partial pressure of oxygen in arterial blood</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-buffered saline</td>
</tr>
<tr>
<td>PCD</td>
<td>Primary ciliary dyskinesia</td>
</tr>
<tr>
<td>PCL</td>
<td>Periciliary liquid</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>PI</td>
<td>Penetration index</td>
</tr>
<tr>
<td>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>PID</td>
<td>Primary immune deficiency</td>
</tr>
<tr>
<td>PTHSI</td>
<td>Pediatric Tracheostomy Health Survey Index</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
</tbody>
</table>
SF36v2  Short Form-36 questionnaire version 2
TMV    Tracheal mucus velocity
TNFα   Tumor necrosis factor-alpha
μg     Microgram
μm     Micrometre
μL     Microlitre
UTP    Uridyl triphosphate
VAP    Ventilator associated pneumonia
vs.    Versus
Chapter 1 Introduction

1.1 Background to the Research

The upper airway plays an important role in the physical defences of the lung by filtering, humidifying and warming inspired gases before they reach the trachea. To protect the lungs inspired air is always conditioned by the normal upper and lower airway so that air reaching the alveoli is at body temperature and 100% relative humidity (1). This prevents drying out of the tissues, atelectasis and impaired gas exchange. The nose and oropharynx have a major role in this conditioning process (1, 2) with further conditioning continuing to occur in the lower airways.

A tracheostomy is an opening made anteriorly in the trachea to enable ventilation to occur directly via the lower airway. A tracheostomy tube is inserted through this opening to maintain a patent airway (Figure 1.1). This bypasses the upper airway resulting in ambient room air, which is relatively cool and dry, entering the trachea directly. This causes cooling and drying of the tracheal airway and mucosa, and may result in slowing of mucociliary clearance and airway inflammation [3].
Figure 1.1: A – a tracheostomy tube. B – Child with tracheostomy tube in situ (photo by permission of parents).
It is generally accepted that children breathing through tracheostomy tubes should have the gases that they inspire conditioned by warming and humidifying. The American Thoracic Society guidelines for care of a child with a chronic tracheostomy state that the “target for inspired gas temperature be 32˚ to 34˚ C and the target for inspired humidity be 36 to 40 mg H\textsubscript{2}O/L” (3). However, the means and the degree of conditioning of the inspired gases is debated. There are several techniques which provide conditioning of inspired gases for children spontaneously breathing through tracheostomy tubes:

- Aerosol nebulisers,
- Heated humidifiers (HHs)
- Heat and moisture exchangers (HMEs or “Swedish noses”)

Nebulisers produce a fine mist of droplets that are inhaled by the patient. These droplets are produced in a wide distribution of sizes with the larger droplets being deposited on equipment tubing, including the tracheostomy tube, and the smallest droplets remaining suspended in air within the patients lungs and exhaled. The remaining droplets, usually 1 to 10 micrometres (μm) in diameter, are deposited in the patient’s airway (4). As will be discussed in Chapter Two, aerosol nebulisers may deposit excessive moisture to the airways which is associated with potential adverse outcomes.

HHs function by delivering warm, moist air via a hose to the tracheostomy tube. The air is first conditioned by heating and then humidified by being blown over a hot water bath (Figure 1.2). The air will generally be at 100% relative humidity at this point. The conditioned air then travels up the hose and is delivered to the tracheostomy by a mask (Figure 1.3). HHs can be set to deliver any temperature of inspired gas and will deliver up to 100% relative humidity.
Figure 1.2: The heated humidifier set-up in one of the participant's bedrooms (photo courtesy of parents).

Figure 1.3: Child with tracheostomy wearing the heated humidifier with tracheostomy mask over tracheostomy tube opening (photo by permission of parents).
HMEs consist of a core of hydrophobic material inside a plastic housing (Figure 1.4). The hydrophobic material may be a simple piece of filter paper. The housing connects on to the tracheostomy (Figures 1.5 and 1.6) and inspired and expired gases pass through the housing and core material. A proportion of warmth and moisture in expired air is captured on the core material and is then available to warm and humidify the next inspired breath.

HME = Heat and moisture exchanger.

Figure 1.4: Portex Thermovent T heat and moisture exchanger (HME) partially disassembled to show roll of hydrophobic filter paper.
Figure 1.5: Heat and moisture exchanger (HME) attached to a tracheostomy tube.

Figure 1.6: Image of one of the study participants wearing the heat and moisture exchanger (photo by permission of parents).
In New Zealand, Starship Children's Hospital in Auckland is the major centre for children with tracheostomies. In this hospital the standard practice for conditioning of inspired gases for children breathing spontaneously through tracheostomy tubes has been to provide a HH during sleep and a HME for waking. The HHs were believed to be more effective at conditioning inspired gases while the HMEs enabled children to be more mobile. This practice developed after trialling a heated humidification system in two children, previously treated with HMEs, who had thick secretions, had difficulty maintaining oxygenation and had repeated hospital admissions for atelectasis and infection (5). These children were successfully treated with the HH asleep and the HME awake with improved outcomes - notably decreased admissions, improved chest radiograph appearances and improved health at home according to the caregivers. This practice was therefore adopted in 1999 for all children with tracheostomy tubes under the care of Starship Children's Hospital. However, this is not international practice and there are no previous randomised controlled trials to provide evidence to guide the selection of treatment. Many centres use HMEs alone as standard practice. In comparing these practices, each treatment has advantages and disadvantages with the use of HH being more expensive. It was my experience with these two children and the change of our hospital's practice that ultimately led me to undertake this research. The research presented here was conducted to compare the use of a HH to a HME overnight while using a HME during the day.

1.2 Terminology

In children, the opening made for the insertion of a tracheostomy tube is an incision or tracheotomy, as compared to the tracheostomy or mouth opening that is manufactured for adult patients. Once an artificial airway is inserted through the incision the airway is a stoma. The described procedure (6, 7) is to first moderately extend the neck by placing a sandbag or roll under the patient's shoulders. A horizontal skin crease incision is made and the subcutaneous tissue divided. The
strap muscles are exposed and retracted laterally and, if present, the thyroid isthmus is divided. Stay sutures are inserted on either side of the planned incision to maintain control of the stoma. A vertical incision is made through the trachea through the second, third and fourth tracheal rings. The endotracheal tube is partially withdrawn under direct vision and the tracheostomy tube inserted.

Although the surgical procedure is correctly termed a tracheotomy and the artificial airway that is inserted termed a tracheostomy tube, these airways are commonly referred to by hospital staff, equipment providers and the parents of the children as tracheostomies. Therefore, throughout this study I will use the term “tracheostomy” or “child with a tracheostomy” to refer to children who are spontaneously breathing through a tracheostomy tube. Similarly, I will employ the commonly used term “humidification” to refer to the process of conditioning inspired gases which is in effect composed of two processes; warming and humidifying.

1.3 Aims of the Study

The aim of this research was to examine the hypothesis that “Children breathing spontaneously via a tracheostomy tube will have improved outcomes if their inspired gases are conditioned via HH overnight and HME during the day as compared to via HME overnight and during the day”. We conducted two randomised controlled studies to examine this hypothesis. A short-term study was conducted to assess if there were any differences in outcomes when comparing the treatments over a 20-hour period. A long-term study was conducted to see if short-term benefits would translate into long-term improvements in clinical outcomes.

The principal hypotheses examined for this thesis were:
1. That children with tracheostomies will have fewer clinical events (chest infections, admissions to hospital, courses of antibiotics, and episodes of tracheostomy tube obstruction) when receiving humidification during sleep via a heated humidifier (HH) compared to via a heat and moisture exchanger (HME).

2. That children with tracheostomies will have a higher rate of mucociliary clearance when receiving humidification during sleep via a HH compared to via a HME.

In addition to the principal hypotheses, the following secondary hypotheses examined for this thesis were:

3. That children with tracheostomies will have improved airway mucus viscoelasticity when receiving humidification during sleep via a HH compared to via a HME. Ultimately, this hypothesis was unable to be tested due difficulties in communicating with and transporting samples to co-investigators in Canada.

4. That children with tracheostomies and their caregivers will have an improved quality of life (QOL) when receiving humidification during sleep via a HH compared to via a HME.

5. That children with tracheostomies will have less airway inflammation in terms of inflammatory cytokine levels in airway secretions when receiving humidification during sleep via a HH compared to via a HME.

6. That children with tracheostomies will have improved findings on clinical examination, including airway secretion characteristics (volume, colour and
thickness), when receiving humidification during sleep via a HH compared to via a HME.

Ciliary beat frequency measurements and bacterial culture of airway secretions were performed as additional explanatory measures for the above hypotheses. In addition, we performed qualitative interviews of parents in the long-term study. These interviews were performed to assess how parents behaved in choosing which humidification method they preferred to use.

1.4 Layout of Thesis

Chapter Two is the literature review which provides the scientific background for this research. Two clinical studies and one qualitative study were conducted for this thesis. The two clinical studies are designated the "short-term study" and the "long-term study". The two studies were conducted using a similar study design and measurement of similar (or identical) outcomes. The methods and results sections have been collated into chapters for each set of outcomes for ease of reading. Chapter Three describes the general study design and statistical methodologies of the studies conducted for this thesis. Chapter Four describes the methods and results for clinical outcomes such as clinical examination and clinical events in the short-term study and Chapter Five the clinical outcomes for the long-term study. Chapter Six describes the methods and results for measurement of mucociliary clearance. Chapter Seven describes the methods and results for the measurement of inflammatory cytokine levels in airway secretions. Chapter Eight describes the methods and results for qualitative interviews of parents participating in the study. Chapter Nine comprises the discussion and translation of what the results mean in the context of the care of these children. Chapter Ten is a personal reflection on my experiences of conducting this research and how it has shaped my clinical practice.
1.5 Author’s Contribution

I designed the study and selected the outcomes measured in this study. I recruited most of the participants for this study and conducted the clinical examinations for these participants and collected airway secretion samples. I am grateful to Dr Mirjana Jaksic, Department of Paediatrics, The University of Auckland who completed recruitment and assessment over the final six months of the study while I was absent undergoing further relevant training in Australia. For the long-term study I recruited all fourteen participants, and Dr Jaksic performed the final assessment on one participant. For the short-term study I recruited and assessed nine of the fifteen participants, and Dr Jaksic recruited and assessed six participants. I selected the nebuliser, flow rates and equipment used to perform the mucociliary clearance scans. I also performed the nebulisation for the scans performed on participants. I am grateful to Dr Michael Rutland, Department of Nuclear Medicine, Auckland City Hospital for advising on selection of a colloid molecule, for supervising the conduct of the scans and for performing the measurements on the images. The measurement of cilia beat frequency was conducted kindly by Dr Cass Byrnes who is a supervisor for this thesis. I am grateful to Kimi Himiora who performed measurements for inflammatory cytokine levels in airway secretions under the supervision of Dr Jo Perry, Liggin's Institute, The University of Auckland. I am also grateful to Dr Annette Dickinson, Auckland City Hospital, for conducting the initial two qualitative interviews and providing advice during data analysis. I conducted all data analysis for these interviews. All statistical analyses were performed by me, including the design of the analysis and selection of methods, with advice on the selection of appropriate statistical tests and on statistical software coding from Mr Alistair Stewart.
1.6 Ethics Approval

All studies conducted for this thesis were approved by the local ethics committee and registered with the Australian New Zealand Clinical Trials Registry (ACTR). Studies involving mucociliary clearance scans were also approved by the National Radiation Laboratory. Parents gave written informed consent for their children to be involved in all the studies. None of the children were cognitively mature enough or competent to give their own consent.

- The pilot mucociliary clearance study had Auckland Regional Ethics Committee number AKX/04/0/109
- The pilot cilia beat frequency study had Auckland Regional Ethics Committee number AKX/04/02/026
- The short-term study had Auckland Regional Ethics Committee number AKX/04/223 and ACTR number ACTRN12605000263695
- The long-term study had Northern Region Ethics Committee number NTY/05/08/062 and ACTR number ACTRN12605000673640
Chapter 2 Background and Review of the Literature

In this chapter I will describe the literature that forms the background and justification for the research conducted for this thesis. Firstly, I will describe the history and epidemiology of tracheostomy in children. Secondly, I will describe the structure and function of the airway mucosa and the roles of the different layers of the mucosa. Thirdly, I will describe the effects of intubation and tracheostomy on airway function and the effects of inhaling inadequately conditioned gases on mucociliary clearance in the airway. Lastly, I describe the animal and human studies that have been conducted to assess the effects of humidity and moisture on individuals who are intubated or who have tracheostomies in situ.

2.1 History of Tracheostomy

The tracheostomy is one of the oldest described surgical procedures. Tracheostomies have been found portrayed on ancient Egyptian tablets dating back to 3600BC and in ancient Hindu writings (8). The procedure was revived in the 16th century, but prior to the 1800s only 50 life-saving tracheostomies had been described in the literature (9). In 1799, George Washington died from upper airway obstruction secondary to bacterial epiglottitis, his physicians unwilling to perform on him what was at that time an experimental operation (10). However, by 1891, 23,941 tracheostomies had been described (9). Early indications were for upper airway obstruction, particularly related to infections such as diphtheria (9). Trendelenburg reported the use of tracheostomy during major operations of the jaw and mouth in 1873 (9) and in 1932 Wilson reported the use of tracheostomy in paralytic poliomyelitis (8). The widespread use of tracheostomy for bulbar palsy related to poliomyelitis from the 1930s to the 1950s led to acceptance of the procedure for the treatment of respiratory failure of any cause (9).
The early tracheostomy tubes were made of silver or stainless steel (8). These tubes did not conform well to the airway and had a high rate of adverse events such as granuloma formation, tracheal wall erosion and tube occlusion against the tracheal wall (8). Modern tracheostomy tubes are made from synthetic materials and are shaped to conform to the trachea.

In children, tracheostomy was initially performed for upper airway obstruction due to infection, primarily diphtheria. This indication decreased from the 1940s with the commencement of the antibiotic era. During the 1950s the indications for tracheostomy in children extended to include bulbar palsy from poliomyelitis (9). During the 1950s and 1960s tracheostomy was common for epiglottitis and laryngotracheitis. The acceptance of prolonged endotracheal intubation in the 1960s and 1970s led to a reduction in the use of tracheostomy for this indication and, indeed, a reduction in tracheostomy insertion overall (6). Prolonged endotracheal intubation was made possible by the change in composition of the tube to polyvinyl chloride, at that time a novel material. This enabled intubation with far less trauma than the previously used silver or vulcanite rubber tubes and, due to the inert nature of polyvinyl chloride, less tissue reaction than the highly reactive vulcanite tubes (11). Subsequently, improved outcomes and survival of premature infants led to an increase in the number of young infants undergoing tracheostomy for iatrogenically acquired subglottic stenosis and bronchopulmonary dysplasia (7, 12). Recently tracheostomies have been performed more widely for airway obstruction secondary to neurological conditions (13-15).

Prior to the 1960s tracheostomy in children was often an emergency procedure performed on children in extreme respiratory distress (11). The procedure was not carried out in ideal circumstances and resulted in a high rate of complications. In 1960 Allen pioneered the use of prolonged intubation with polyvinyl chloride
endotracheal tubes for laryngotracheitis and epiglottitis and the use of intubation to stabilise the airway prior to emergency tracheostomy (11). This resulted in a dramatic reduction in overall mortality (Table 2.1). Importantly, the authors reported that the practice of endotracheal intubation to stabilise the airway prior to tracheostomy eliminated the mortality due to the procedure itself. The authors also identified subglottic stenosis as a complication of prolonged intubation. This complication has now become a major indication for tracheostomy in recent years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Admissions for “croup”</th>
<th>Tracheostomies</th>
<th>Deaths</th>
<th>Overall Mortality due to “croup”</th>
<th>Percentage of mortality due to tracheostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-1960</td>
<td>1829</td>
<td>59</td>
<td>18</td>
<td>1%</td>
<td>30%</td>
</tr>
<tr>
<td>1960-64</td>
<td>940</td>
<td>52</td>
<td>8</td>
<td>0.8%*</td>
<td>0</td>
</tr>
<tr>
<td>1960-61</td>
<td>231</td>
<td>18</td>
<td>2</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>1961-62</td>
<td>218</td>
<td>18</td>
<td>6</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>1962-64</td>
<td>591</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*There were a total of 10 deaths, all due to underlying poisoning, sepsis, injury or congenital syndrome.

Table 2.1: Change in mortality due to the practice of prolonged intubation. Redrawn from Allen TH and Steven M. BJA 1965;37:566-573 (11).

The ratio of tracheostomies performed for upper airway obstruction compared to lower airway disorders has become reversed in recent years, previously being approximately 90:10 and now being 20:80 (9). Potential reasons for the change include immunisation against diphtheria, poliomyelitis and *Haemophilus influenzae* type B, the development of effective medicines to treat infection and inflammation of the upper airway and the use of prolonged endotracheal intubation in the Paediatric Intensive Care Unit (PICU). As the epidemiology and non-surgical management of respiratory disease has evolved, the indications for tracheostomy have continued to change. The age of the children undergoing the procedure has also dramatically changed, as will be discussed in the next section (6, 7, 12).
2.2 Indications for Tracheostomy in Children

The current indication for tracheostomy is for patients with respiratory insufficiency requiring an artificial airway and where an endotracheal tube is inappropriate. This usually occurs in patients who will have a prolonged requirement for the artificial airway. Infants and children requiring tracheostomy can be divided into two groups; those with upper airway obstruction and those needing prolonged ventilation or lower airway toilet for other reasons. The indications for tracheostomy are summarised in Table 2.2.

<table>
<thead>
<tr>
<th>Upper Airway Obstruction</th>
<th>Prolonged Ventilation or Bronchial Toilet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subglottic Stenosis</td>
<td>Prematurity or Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Craniofacial syndromes</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Haemangioma</td>
<td>Neurological or Neuromuscular Impairment</td>
</tr>
<tr>
<td>Laryngo-tracheomalacia</td>
<td>- Cerebral Palsy</td>
</tr>
<tr>
<td>Vocal fold web or palsy</td>
<td>- Hypoxic ischaemic encephalopathy</td>
</tr>
<tr>
<td>Lymphangioma</td>
<td>- Spinal Muscular Atrophy</td>
</tr>
<tr>
<td>Laryngeal Cyst</td>
<td>- Spina bifida</td>
</tr>
<tr>
<td>Laryngeal papilloma</td>
<td>- Central Hypoventilation Syndrome</td>
</tr>
<tr>
<td>Tracheal stenosis or compression</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Laryngeal or tracheal trauma</td>
<td>Tracheo-oesophageal fistula</td>
</tr>
<tr>
<td></td>
<td>Burns</td>
</tr>
<tr>
<td></td>
<td>Other chronic pulmonary disease</td>
</tr>
</tbody>
</table>

Table 2.2: Indications for tracheostomy in children (7, 13) presented in order of decreasing frequency.

As the indications for tracheostomy have changed the age of children undergoing the procedure has also changed (6, 7, 12). Prior to the 1970s most tracheostomies were performed in older children with acute upper airway obstruction due to infection (7).
An increased proportion, 32-60%, are now performed on infants under one year of age (6, 7, 12-14, 16-20) and about a third are now undertaken in infants less than three months of age (7).

The average time to decannulation (removal of the tracheostomy tube) has increased from 2-6 months in the 1970s to 1-3 years in more recent studies (6, 7, 12-14, 18). The majority of tracheostomies now remain inserted for over 2 years (12). Children with neurological impairment and infants with acquired subglottic stenosis due to prolonged intubation require a longer duration of tracheostomy compared to those with acute disorders and those undergoing surgery for craniofacial abnormalities (7, 13). Overall, 22-78% of children are successfully decannulated (6, 12, 13, 16), but only 12.5% of those with neurological impairment are similarly successfully reversed (13).

### 2.3 Complications of Tracheostomy

Both the procedure and maintaining a tracheostomy in children is more difficult than in adults with a higher mortality and complication rate (7), especially in preterm infants (21). Children requiring tracheostomy have a high overall mortality rate of 7.8-22%, with most deaths due to their underlying condition (12-14, 17, 18). The mortality rate due to complications of the tracheostomy itself is 1.8-3.6% (12, 13, 18). The most common problem is granuloma formation either in the trachea or externally at the stoma site, which is almost universal and may not be regarded as a complication unless it causes difficulties (7, 12, 13). The overall complication rate in children is 31-56% (6, 7, 13, 14, 18) with infants having the highest complication rate of 63-70% (6, 7, 12).
Early complications (11.2 – 14%) | Late complications (34 - 44.8%)
--- | ---
Tube obstruction | Excessive granulation – trachea or stoma
Accidental decannulation | Tracheocutaneous fistula
Infection | Tube obstruction
Pneumothorax/Pneumomediastinum | Accidental decannulation
Pneumonia | Pneumonia
Emphysema | Tracheomalacia
Haemorrhage | Tracheal stenosis

Table 2.3: Complications of tracheostomy (7, 12).

As well as physical complications to the individual child, families caring for children with tracheostomies may suffer adverse psychosocial outcomes. Children with tracheostomies are often included with “medically fragile” or “technology-dependent children” in studies employing qualitative research methodologies or studies employing measures of stress, life satisfaction, quality of life (QOL) or health-related quality of life (HRQOL). Studies employing qualitative methodologies are discussed in detail in the discussion section of Chapter 9 which contains our own qualitative interview study. In this section I will discuss findings from quantitative survey and questionnaire studies.

Teague et al (22) found moderate levels of stress and frequent non-reimbursement of financial costs in a study of 73 technology-dependent children. This may be a particular burden in the USA for some families who do not have private medical insurance and do not qualify for Medicare support. Similarly, Leonard et al (23) found
that 59% of 57 mothers of medically fragile children reported symptoms of distress severe enough to require psychiatric evaluation. Higher stressors and lower family well-being compared to families of healthy controls were also reported in a study of 85 technology-dependent children (24). Theyen et al (25) reported reduced household income in a study of 70 families of technology-dependent children. Several studies have reported social isolation or disruption to family life as a result of caring for a technology-dependent child (26, 27). Likewise, studies of caregivers of adults on home ventilation have found that the social and support circle diminishes with time resulting in increasing loneliness and isolation (28, 29). Despite the high levels of stress, high levels of parent-satisfaction have also been reported in studies of technology-dependent children (30).

Caring for a medically fragile child was also found to negatively affect the physical health of caregivers, with more physical symptoms reported when there was a higher financial burden in a study of 48 families (26). Having support from home health aides rather than professional nurses also had a greater negative psychosocial impact on the families. Similarly, studies of adults on home ventilation have reported that professional home carers are often unreliable or inadequately skilled, placing more stress on caregivers (28, 29). Meltzer and Mindell (31) found higher levels of sleep disruption and fatigue in caregivers of children on home ventilation than parents caring for children with other chronic illnesses. Undisturbed sleep was found to mediate the effects of fatigue on depressive symptoms which has implications for the emotional health of parents of children with tracheostomies.

Several studies have specifically surveyed caregivers of children with tracheostomies. Caring for a child with a tracheostomy was found to be more stressful than caring for children with other chronic illnesses in a study of 50 children with tracheostomies and gastrostomies (27). This may be due to decreased feelings
of coping compared to other illnesses as constant attention needs to be given to managing the airway (24, 27). Hartnick et al (32) found that the burden of caring for a child with a tracheostomy affected parental emotional and mental well-being in a study of 154 families in the US. The Hartnick study utilised the Pediatric Tracheostomy Health Survey Instrument (PTHSI), which is the same instrument we ultimately used in our study, and found correlations between the domain of caregiver burden and financial costs and also the child’s overall physical impairment. Caregivers of children with additional major health problems experienced a significantly greater burden. Hopkins et al (33) used the PTHSI to measure HRQOL of 26 caregivers caring for children with tracheotomies in the UK and found surprisingly that only 27% rated the child’s HRQOL as “fair” or “poor”. However, half of the caregivers reported interrupted sleep “often” or “all of the time” and a majority reported decreased household incomes and inadequate carer support. Cohen et al reported lower QOL in families of children undergoing tracheostomy as compared to other surgery for airway obstruction (34).

Some parallels can be drawn from the literature regarding other home respiratory supports. The literature on home oxygen therapy in infants suggests that while this therapy is well accepted by families (35), there is still a negative impact on QOL (36). Families experience difficulty getting babysitters, social isolation, and fear of the equipment (35, 36). This effect disappears on cessation of home oxygen therapy and is not found in age and disease matched controls (36). Having an extra piece of equipment in the home, such as the mechanical HH we planned to use in the current research study, may similarly have a negative impact on QOL for families.

The above studies generally discuss the caregivers’ rather than the child’s well-being or QOL, due to the difficulty of administering questionnaires to young and/or disabled children. The effect of a tracheostomy on the child’s well-being may be inferred from
studies in adults on home mechanical ventilation where surprisingly high overall satisfaction levels are reported that are little different from healthy controls (37-41) with most patients stating that they would undergo this treatment again (29, 41). However, most studies have indicated a preference for non-invasive ventilation (NIV) via a nasal mask rather than ventilation via a tracheostomy (37-39) and reported a greater burden on caregivers with tracheostomy (29).

Long-term follow-up of children with tracheostomies indicates high rates of mortality, poor growth, persistent respiratory symptoms and long-term developmental cognitive and physical delay (42, 43). Many of these poor outcomes are due to the underlying conditions in children who have multiple disabilities and require tracheostomy for inability to control secretions. These outcomes are different for children who have isolated airway abnormalities. However, even when children with underlying mental retardation are excluded, persistent speech and communication problems are found (44, 45).

In summary, caring for a child with a tracheostomy has a negative effect on parental well-being which appears to be greater than other chronic diseases with significant levels of burden, stress, sleep disruption, additional financial costs, reduced income, social isolation, and inadequate support. Children with tracheostomies appear to have a good level of QOL although they may suffer from multiple associated disabilities. Long-term there are high rates of mortality and morbidity which are related to the underlying condition. These effects on QOL lead us to test the hypothesis that children with tracheostomies and their caregivers will have an improved quality of life (QOL) when receiving humidification during sleep with a HH compared to a HME.
2.4 The Airway and Respiratory Mucosa

The respiratory mucosa plays an essential protective role in filtering, warming and humidifying the airways and the insertion of a tracheostomy bypasses the upper airway where much of the conditioning of inspired air occurs. This results in ambient air being delivered straight to the trachea which may have adverse effects. In this section I will discuss the role of the upper airways, the effects of inadequate humidification and the implications of these for the management of tracheostomies.

2.4.1 Structure and Function of the Airway

The airway delivers oxygen to the alveoli and transports away carbon dioxide. Air is conducted by laminar and turbulent flow in the large airways and by molecular diffusion in the smallest airways (46). The airway divides 20-25 times into progressively smaller conducting branches. This highly branching system presents a large surface area of over two square metres (47) to the ambient environment. In addition the alveoli have a total surface area of 70 square metres and are vulnerable to injury from particles, microbes, desiccation and excessive heat or cold. To protect the alveoli, the airways therefore also play a role in host defense by acting as a heat and moisture exchange system (48), conditioning inhaled air through filtering, warming, and humidification. The upper airway takes in air that is relatively cool and dry and conditions it so that by the time the air reaches the small airways it is at core body temperature and 100% relative humidity (49). The structure of the airway mucosa is important in this process; the airway surface liquid (ASL) acts as a large store of heat and moisture allowing the conditioning of airway gases even at extreme conditions, the mucosa rapidly transports water and electrolytes to balance changes in the ASL, and the vasculature replenishes lost energy and water.
2.4.2 Structure and Function of the Airway Mucosa:

In this section I will describe the structure of the airway mucosa in relation to heat and moisture exchange function of the airways.

Figure 2.1 shows the structure of the airway mucosa. Functionally, the respiratory mucosa may be viewed as comprising five components;

1. The mucus layer
2. The periciliary layer
3. The ciliated epithelium
4. The submucosal glands
5. The mucosal vasculature

![Figure 2.1: The structure of the airway mucosa.](image-url)
Figure 2.2: Beating pattern of a cilium. The effector stroke is applied by the outstretched cilium which touches the mucus layer and propels it forward. During the recovery stroke the cilium curves to move through the low viscosity periciliary liquid layer below the mucus layer.

2.4.3 The Airway Surface Liquid

The ASL is a thin layer of moisture lining the respiratory airway epithelium comprising two layers; a viscous gel or mucus layer and a thin liquid layer called the periciliary liquid layer (PCL). The mucus layer traps inhaled particles and microbes. The cilia of the epithelium beat the mucus continuously up to the pharynx where the mucus and the inhaled particles are swallowed. The tips of the outstretched cilia just reach the mucus layer (50). During an active stroke the cilia are outstretched and the tips of the cilia push the mucus layer along. During the recovery stroke the cilia are bent over and flow through the low resistance PCL and below the mucus layer. This is known as mucociliary clearance (MCC) or the mucociliary escalator. The PCL also prevents the mucus from adhering to the mucosal lining so it is more easily cleared and provides a shear plane for the clearance of mucus by coughing. The two layers are therefore essential to the efficient clearance of the mucus. Sputum is distinct from mucus or the ASL and is the product of airway secretions cleared by cough. Sputum
is comprised of the ASL as well as products of infection and inflammation and, in some disease states, may consist of more purulent material than mucus (51).

Given its thinness, the ASL has proven difficult to measure. In addition, the measuring devices themselves tend to stimulate the secretion of additional fluid or component secretions (52). The measured values for the depth of the ASL in \textit{in vitro} and \textit{in vivo} in human and animal models range from $<5 \, \mu m$ to $>100 \, \mu m$ (52-60), with the accepted range being 25 to 55 $\mu m$ for humans \textit{in vivo}.

As well as its mucociliary clearance function, the ASL also has a direct role in airway defence through the secretion of anti-microbial peptides and proteins; beta-defensins, lysozyme, lactoferrin, and secretory leukoproteinase inhibitor (61, 62). Albumin and immunoglobulin-A (IgA) are also secreted by the submucosal glands. The expression of proteins in the ASL can be modulated through the action of pro-inflammatory cytokines (63). These proteins are important in killing and/or inhibiting the growth of organisms landing on the airway surface.

\textbf{2.4.4 The Mucus Layer}

The mucus layer, or gel layer, is the outer layer of the mucosa that is in direct contact with airway gases and comes into first contact with inhaled particles or microbes. The mucus layer is a blanket that coats the epithelium and traps particles that are deposited on the surface. Large particles are trapped in the hairs of the nose or on the mucosa of the nasal turbinate while medium sized particles are deposited on the lower airway mucosa. Very small particles remain suspended in the air and travel to the alveoli where they are ultimately ingested by alveolar macrophages.

Mucus is referred to as a viscoelastic substance as it possesses both liquid properties (viscosity or resistance to flow) and solid properties (elasticity or stiffness)
In terms of its liquid properties, mucus is a non-Newtonian substance, that is the viscosity (resistance to flow) of mucus decreases with rates of deforming force, or shear, as compared with a Newtonian liquid such as water which has a constant viscosity irrespective of the rate of shear (64). The viscoelastic properties of mucus vary with mucus composition and are important in mucus' role in host defense.

It should be noted that the viscoelastic properties or rheology of mucus vary between the nano- or microrheologic scale and the macrorheologic or bulk scale (64). Particles, including proteins and viruses, that are smaller than the gaps or pores between mucin chains pass through mucus as if its viscosity were similar to water. Particles or viruses larger than these pores (approximately 100 - 200 nm) are affected by the bulk rheologic properties of mucus (65). All the following discussion will refer to the bulk of macrorheologic properties of mucus as the bulk clearance of mucus from the airways is the most relevant for this thesis.

The mucus layer is composed predominantly of water and salt in a gel formed by mucins. Mucins are high molecular weight glycoconjugated proteins composed of multiple repeating units forming long, tangled chains. Mucins bind to each other and other proteins through thiol, ionic and hydrophobic interactions (66) forming a tangled network which gives the mucus layer its viscosity and elasticity (67, 68) and traps inhaled particles (69). The tangled nature of mucins and their reversible linkages allows mucin bonds to be easily broken and reformed, unlike other cross-linked gels whose bonds are irreversibly torn by shear (70). This allows mucus to be easily thinned and cleared from proximal to peripheral airways by the rapidly shearing force of a cough and then for the mucin bonds to recoalesce so that the mucus does not run peripherally under the force of gravity. Other substances and proteins that contribute to the viscoelasticity of mucus include albumin (71), lysozyme (72), secretory IgA (73), lipids, deoxyribonucleic acid (DNA) and IgG (74).
concentration of many of these substances is increased in diseases such as cystic fibrosis, increasing mucus viscosity (64). The expression of a wide range of carbohydrate sequences on the mucin chain enables them to bind to any particle epitopes that land on the mucosal surface (75).

The production of mucins is controlled by mucin genes with twenty mucin genes identified to date of which eleven are expressed in airways (76, 77). Overexpression and abnormal expression of mucin genes by goblet cells have been found in airway diseases associated with increased mucus production such as asthma and chronic bronchitis (78, 79).

Mucus is produced from the goblet cells, Clara cells and submucus glands. Goblet cells are the principal secretory cells found in the cartilaginous airway epithelium and synthesise, store and secrete mucins. In the more distal airways the Clara cell becomes the principal secretory cell. Clara cells generally rapidly synthesise and secrete mucins usually without storing them. The submucus glands are comprised of ciliated ducts, collecting ducts, mucous tubules and serous acini. The serous cells of the serous acini secrete water, salts and antimicrobial peptide ions (80). The mucus cells secrete mucins which are stored in large secretory granules. Like goblet cells, submucus glands are more common in the large airways.

The release of mucus from the respiratory epithelium is triggered by a wide range of stimuli but particularly inflammation. For goblet cells, some stimuli act directly while others have been found to act through changes in pH which induces mucus secretion (81). Adenosine triphosphate (ATP) and uridyl triphosphate (UTP) have been found to be the strongest stimulus for mucus secretion from goblet cells, acting on a purinergic receptor (81-84). ATP is released in response to mechanical strain of the airway (85). Other stimuli for mucus secretion are irritant gases, pH < 4, pH > 9,
hypoosmolarity, histamine, antigen, inflammatory messengers and bacterial products (81). Autonomic nerve fibres are found in close association with goblet cells but these cells have not been found to be strongly responsive to vagal or adrenergic stimulation (81, 84). The submucus glands are densely innervated by the autonomic system and are strongly responsive in terms of mucus secretion to vagal stimulation but less so to adrenergic stimulation (86). Intracellular calcium and cyclic adenosine monophosphate (cAMP) have been found to be second messengers for the release of mucus from glands (81). Submucus glands have also been found to respond to a wide range of stimuli including cold, hyperosmolarity, histamine, antigen, bacterial products and inflammatory messengers (81).

The submucus glands also secrete liquid through the active secretion of chloride ions by the serous cells (87). Chloride is secreted via chloride channels in the apical cell membrane, one of these being the cystic fibrosis transmembrane conductance regulator (CFTR) which is a cAMP activated channel.

The mucus and its contents are cleared from the airway through MCC as described above. Mucus may also be cleared by cough when sudden episodes of high airflow move the mucus. The clearance of mucus by these mechanisms is dependent on the thickness (viscosity) and stiffness (elasticity) of the mucus.

The tips of the cilia just reach the mucus layer with the length of cilia ranging from 5-7 μm in the trachea to 2-3 μm in the smaller airways (50). For MCC to occur efficiently mucus must have both elastic properties so that it remains cohesive and viscous properties so that it can be moved like a liquid (88). Resistance is the amount of energy lost in moving an object. For mucus the resistance comprises the frictional resistance of the mucus to flow along the mucosal surface (the mechanical impedance) plus the energy lost by the cilia in beating through the mucus due to its
viscoelastic properties (fractional dissipation of energy). As mucus becomes more rigid more energy is lost in resistance to forward motion (the mechanical impedance increases).

During coughing, mucus is exposed to a high shear force and thereby becomes less viscous, enabling the mucus to be easily moved up the airway. After coughing the mucus is no longer exposed to this shear force and its viscosity returns to its previous level so that it does not run distally down the airway under the force of gravity. Clark et al (89) showed that if a viscoelastic fluid was made too thick or too thin then it was not effectively cleared by high airflow (a simulated cough). If the gel was too viscous then it was too thick or heavy to clear (i.e. the energy of the cough was unable to overcome the resistance of the mucus). If the gel was too thin then the energy of a cough would not be transferred to the gel and it would not be cleared. The viscoelastic properties of mucus seem to represent a compromise between MCC and cough clearance.

In respiratory disease the composition and nature of secreted mucus is changed. In infection the concentration of mucus glycoprotein is increased and there is an increase in the amount of sialylated and sulphated glycoprotein (90). In chronic airway disease mucus is oversecreted and both the viscosity and elasticity of mucus have been found to be abnormally high (91, 92). Oversecretion of mucus results in airway obstruction (93, 94). Cochrane et al (95) demonstrated that removing excess sputum from the airways improved airways conductance. Likewise, Chatila et al (96) showed that suctioning secretion from the airways of intubated patients reduced airway resistance.
As the viscoelastic properties of mucus depend on the amount of shear and the rate of deformation, viscoelasticity is measured using dynamic rather than static techniques. The viscosity of human mucus varies from $10^3$ to $10^4$ times that of water at low shear rates to a viscosity close to that of water at high shear rates such as those achieved with coughing (97). Dynamic viscoelasticity (rheology) may be measured by a cone and plate rheometer for larger samples. In this technique, the mucus sample is suspended between a cone and a flat plate. The plate is then oscillated at a known amplitude and rate and the torque applied to the cone by the mucus sample used to calculate the shear stress. This is a widely used test in industry for measuring the properties of gels and liquids and commercially manufactured machines which perform accurate measurements are available. A capillary viscometer may also be used which measures the velocity of mucus moving along a thin tube under a fixed pressure (98).

However, the above techniques are not suitable for samples in the microlitre range, as obtained in studies of airway mucus in children and small animals, and a magnetic microrheometer may be used for these smaller samples. (99, 100). In this process a small steel ball is positioned in a sample of mucus. The ball is then oscillated by a magnetic field at the approximate frequencies of beating cilia found in health (10 Hz) and disease (1 Hz) (101). This technique has the disadvantage that the sample may rapidly evaporate due to its small size. In addition, the mucus viscoelasticity curve has some hysteresis properties and it is not possible to know which part of the curve is being measured using this technique. More recently, Rubin and colleagues have been able to utilise the cone and plate technique for small samples by employing a plate precisely curved at $0.5^\circ$ rather than a flat plate (102). Small samples may also be measured for their cohesive properties by measuring spinnability with a filancometer which draw out the sample under tension into a thread and measures
the distance at which the mucus thread breaks (103). Mucus surface tension may be measured with relatively small samples as may "wettability" via the contact angle formed under a glass cover slip are also commonly measured with small samples (102). However, the relationship of these measurements to mucociliary and cough clearance is less clear than with measures of rheometry.

The properties of mucus may also be measured at the microrheologic scale measuring the transport of nanoparticles or beads through the mucus gel. These techniques can be applied to measuring the macrorheology of mucus through using beads larger than 300 nm (104). However, this technique applies shear at low levels and may not be able to measure viscous mucus like that found in disease states such as cystic fibrosis.

As the viscoelastic properties of mucus change with mucus composition, particularly the water composition we sought to test the hypothesis that children with tracheostomies will have improved airway mucus viscoelasticity when receiving humidification during sleep via a HH compared to via a HME.

2.4.4 The Periciliary Layer

The periciliary liquid layer (PCL) is a liquid layer lying between the respiratory epithelium and the mucus layer. The height of the PCL is 5-6 μm (105), the height of an outstretched cilium (50). The PCL provides a low resistance environment in which the cilia beat. The PCL is secreted by the serous and Clara cells of the respiratory mucosa. The depth of the PCL is affected by evaporation and condensation (106), by cellular secretion and absorption (107), and by active ion transport (108-110). Matsui et al (105) showed that the PCL is transported at the same rate as the mucus layer, thought to occur by friction transferring momentum from the mucus layer to the PCL.
The PCL therefore is a thin sheet of water continually migrating proximally to replace water lost by evaporation (111).

The fluid of the PCL is secreted via chloride ion transport from the mucus, serous, Clara and neuroendocrine cells of the bronchioles and by the submucus glands of the larger airways (112, 113). Water, sodium and other ions passively follow the chloride ions. The volume of ASL fluid is then regulated by a balance of secretory and absorptive processes in the ciliated columnar epithelial cells. It is not clear how epithelial cells sense and maintain the ASL volume (112). As the ASL is transported toward the larger airways, the total surface area of the airways decreases so absorption of PCL needs to take place. However, further secretion of fluid, ions and mucus also takes place in the larger airways. The secretory process is thought to be driven by the active secretion of chloride ions via the CFTR and calcium dependent chloride (Cl⁻) channels in response to adenosine nucleotides (114). Absorption of fluid is thought to be driven by the absorption of sodium (Na⁺) ions from the lumen into the cell across a sodium gradient maintained by a sodium-potassium ATPase on the cell’s basal surface. The absorption of sodium ions from the airway lumen occurs primarily through an amiloride-sensitive channel. Dehydration of the ASL may occur through excess activity of this channel or through decreased secretion via the CFTR channel (115). In addition to Na⁺ and Cl⁻ ions, the PCL contains bicarbonate and potassium ions in small concentrations. A wide range of proteins are also found in the PCL which can be modified by the action of inflammatory cytokines.

There are two theories with regard to the composition of the PCL, based on research into normal and cystic fibrosis (CF) airway mucus; the isotonic theory and the hypotonic theory. The isotonic theory is that the PCL is maintained in an isotonic state by the transport of ions and water crossing the epithelium to and from the PCL along the osmotic gradient. The hypotonic theory is that the epithelium is
impermeable to water and the PCL is maintained in a hypotonic state by the active transport of ions. The hypotonic theory is based on the presence of antimicrobial cationic polypeptides in the mucus and periciliary layer, which are more active in a hypotonic environment (62). It has also been found that cultured respiratory epithelia do not secrete the normal complement of proteins in the mucus (116). These proteins could act as osmoles in the PCL allowing the epithelium to maintain a low ionic environment.

Currently, there is more evidence to support the isotonic theory as the respiratory epithelium is only capable of maintaining a small osmotic gradient (52, 115). Early studies used filter paper to sample the airway surface liquid. These studies found a wide variety of ionic concentrations in the ASL in normal subjects (60, 117). The studies have been criticised because the technique itself causes irritation and the sample volumes obtained were larger than the total ASL volume. The ASL has been found to be isotonic in vivo using a non-invasive tracheal window in a mouse model (118), and in vitro in cultured human epithelium using a micropipette technique (52, 105). Other investigators have reported lower ionic concentrations (Na⁺ 45-90 mmol/L) using a coupled capillary sampling and conductivity detection technique in vivo in mice and rats (119, 120). However, using a filter paper technique Knowles et al (75) found a Na⁺ concentration of 110 mmol/L in nasal mucosa airway surface liquid and 80-85 mmol/L in tracheobronchial ASL. Using a nitrocellulose membrane sampling technique, Hull et al (121) found a tracheal ASL Na⁺ concentration of 80-85 mmol/L in normal subjects. Using a miniaturised solid-state electrode, Caldwell et al (122) measured ASL Cl⁻ concentrations of 117 mmol/L from the nasal cavities of human volunteers and showed similar results from the lower airways of animals. Vanthanouvong et al (123) used an x-ray microanalysis technique and determined concentrations of Na⁺ and Cl⁻ ions of 140-160 mmol/L from normal human nasal ASL. Jayaraman et al (118) measured Na⁺ of 115 mmol/L and Cl⁻ concentrations of
140 mmol/L in mice in vivo trachea using fluorescent probes. Thus the majority of studies show isotonic rather than hypotonic values.

2.4.5 The Ciliated Epithelium

The pseudostratified epithelial layer of the lower airway is composed chiefly of ciliated columnar cells, each cell having approximately 300 cilia on the apical surface (124). The cilia vary in length along the airways as previously mentioned, being 5-7 μm in the trachea and 2-3 μm in the distal airways of the intrapulmonary bronchi (50). Each cilium contains a scaffolding of nine peripheral doublet microtubules and two central microtubules in a “9 + 2” design (shown in Figure 2.3) which is evolutionarily well-preserved from single cell organisms to complex vertebrates (125, 126). The microtubule doublets are cross-linked by radial spokes to a sheath covering the central microtubule pair so that the bending and sliding of the microtubules generates the beating movement of the cilia (127, 128). Along each side of the microtubules are projections of dynein arranged as inner and outer arms (129, 130). The dynein is an ATPase and acts as the motor unit of the cilium: the dynein forms cross-bridges with the adjacent microtubules and by repeatedly attaching and detaching to successive tubulin subunits of the microtubule the dynein units cause the microtubules to bend and one member of the doublet pair to slide over the other. At the base of the cilium the peripheral doublets become triplets and form the basal body, which along with ciliary rootlets, anchors the cilium to the cell (131). A basal foot projects laterally from the basal body in the direction of the active stroke (132).
The cilia of the respiratory epithelium beat in co-ordinated waves to move the mucus toward the pharynx where the mucus is swallowed (126). As described above, cilia beat toward the pharynx in an effective stroke and then return through the periciliary layer in a recovery stroke (Figure 2.2). There is a pause at the end of the effective stroke (134). During the effective stroke, the outstretched cilia reach the mucus layer and propel it with claw-like projections on the cilia tip (135). During the recovery stroke the cilia are curved and inclined laterally so as not to cause retrograde movement of the mucus. In the normal human airway cilia beat at 12-15 Hz (136).

The cilia are co-ordinated to beat in metachronic waves, with each cilium being slightly out of phase with its neighbour (126). The metachronal rhythm is believed to be co-ordinated by hydrodynamic coupling and is limited to short distances so that metachronal waves occur in multiple small areas (126). The cilia beat frequency and the degree of co-ordination decrease as mucus viscosity increases (137).
The cilia beat frequency (CBF) is regulated by the autonomic nervous system and is mediated by intracellular calcium and cAMP (131). The CBF can be affected by a wide range of stimuli including environmental conditions, irritants and medications. CBF is increased by mechanical stimulation, acetylcholine, purines such as ATP, adrenergic stimulants, and aminophylline and is decreased by beta-blockers, anaesthetic agents, anti-cholinergics, and bacterial products (131). Inflammatory mediators have a range of positive and negative effects on the CBF (131). As inadequate humidification may result in inflammation, and differing humidification therapies may affect epithelia; temperature and CBF, we sought to measure CBF from participants in this study.

2.5 Relative and Absolute Humidity

To understand the mechanisms of heat and moisture exchange in the airway it is necessary to discuss some concepts relating to the moisture content of air, these being the relative and absolute humidity and the energy content of air and moisture.

Air may carry water as humidity in molecular form or in droplet form (aerosol). The amount of water carried in droplet or aerosol form is independent of air temperature. The amount of water that air can carry as humidity is directly proportional to the temperature of the air (2). The humidity of inspired gases can be expressed as relative or absolute humidity. The absolute humidity is the weight of water carried by air in molecular form and is expressed in milligrams of water per litre of air (mg/L). The relative humidity is the amount of water carried by the air relative to the maximum amount of water that air can carry at the current temperature and is expressed as a percentage. If air is at 100% relative humidity it is said to be saturated and no further water can be carried in molecular form. If the air cools the amount of humidity the air can carry falls and the air will lose water as condensation,
remaining at 100% relative humidity. Table 2.4 correlates the capacity of air to carry water (absolute humidity at 100% relative humidity) and air temperature.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Absolute Humidity (mg H₂O per litre of air) at 100% Relative Humidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>40</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 2.4: Absolute humidity of air at various temperatures and 100% relative humidity. From Irlbeck D. Resp Care Clin N Am 1998;4(2):189-198 (2).

2.6 The Energy of Air and Moisture

The amount of energy carried in air is proportional to the temperature of the air. The sensible heat of air is the amount of energy required to change the temperature of air by 1°C. This is the amount of energy given off as heat if air cools or the amount of energy required to warm the air by this amount. Water also has a sensible heat so that the total sensible energy of air is the sensible energy of the non-water gases plus the sensible energy of water. When a substance changes state, for instance from liquid to gas, the amount of energy involved is known as the latent heat of the substance. The latent heat of water is released as heat when humidity condenses or is required to vaporise water into humidity.

The total energy content of air is the sum of the sensible heat of the non-water gases plus the sensible and latent heats of the water carried as humidity. Therefore humid air has much higher energy content than dry air. Because the latent heat of water is higher than the sensible heat of water, the energy content of air may be considered as the sensible heat of the air and the latent heat of the water. Measurement of
tracheal airway temperature in the absence of moisture measurement has been found to inadequately measure energy losses, as it does not take into account changes in energy due to changes in state of moisture (138).

When air is inspired, the airways warm the air to core temperature, requiring energy, and provide moisture to create 100% humidity, requiring further energy to vaporise airway moisture. The amount of energy required, and therefore lost from the airways, is proportional to the change in air temperature plus the change in absolute humidity. This energy can be viewed as an “energy challenge” to the airway (4). If the inspired air is too hot then the air must be cooled, which is also an energy challenge to the airway. This challenge is distributed over a length of airway mucosa, from the airway opening to the point at which steady state is reached.

In a similar fashion, the water content of inspired air may be viewed as a “moisture challenge”. The airway must supply moisture to inspired air containing less than 44 mg H₂O/L (100% relative humidity at 37°C). Excess moisture in air, in the form of aerosol or condensate, is also a challenge to the airway and must be removed.

2.7 Physiology of Heat and Moisture Exchange in the Airway

The upper airways function as the main heat and moisture exchange system for inspired gases (48), taking in air that is cool and dry, and conditioning it so that air reaching the small airways has been conditioned to core body temperature and humidified to 100% relative humidity (139). During laminar flow only the air in direct contact with the mucosa is conditioned (2) and the remaining portion must acquire heat and moisture from the adjacent conditioned air. In turbulent flow the air mixes and the entirety of the inspired air comes into contact with the mucosa allowing more efficient conditioning (140). During normal respiration the conditioning process begins in the nasal passages. Air enters the nasal vestibule as laminar flow (2). The nasal
turbinates cause the flow to become turbulent (2) allowing all the portions of the air to mix and come into contact with the nasal mucosa. In mouth breathing the turbinates are bypassed and inspiration is with laminar flow only. In studies in humans, nasal breathing is 7-10% more efficient than mouth breathing in conditioning inspired air (1, 141). This is not just due to turbulent flow but also to changes in temperature and blood flow within the mucosa of the nasal turbinates (142). In a study of healthy subjects and patients with CF, Primiano et al (143) showed that ambient air at 24°C reaching the pharynx was warmed more during nasal breathing than during mouth breathing. In addition, the water content of the inspired gas was higher during nasal breathing (Table 2.5). Beyond the nasal airway, airflow returns to laminar flow. Dias et al (144) demonstrated that the larynx and cervical trachea also play an important role in conditioning inspired gases by collecting inspired tracheal gases from dogs with and without this section of the airway bypassed. They found that inspired gases were at a slightly higher temperature and at a higher absolute humidity when the larynx and cervical trachea were not bypassed by a tracheal tube.
<table>
<thead>
<tr>
<th>Site</th>
<th>Temperature (°C)</th>
<th>Relative Humidity (%)</th>
<th>Absolute Humidity (mg H₂O per litre of air)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Breathing</td>
<td>32-34</td>
<td>80-90</td>
<td>27-33</td>
</tr>
<tr>
<td>Mouth Breathing</td>
<td>21</td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td><strong>Trachea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Breathing</td>
<td>34</td>
<td>90</td>
<td>33</td>
</tr>
<tr>
<td>Mouth Breathing</td>
<td>31</td>
<td>80</td>
<td>25</td>
</tr>
</tbody>
</table>

**Table 2.5:** Differences in temperature and humidity of inspired air during nasal and oral breathing as measured at the oropharynx and trachea. From Primiano et al. [128, 132]

The point at which inhaled air is conditioned to core body temperature and 100% relative humidity is known as the *isothermic saturation boundary* (ISB) (145). Distal to the ISB, air is conditioned to core temperature and 100% relative humidity and no exchange of heat or moisture occurs. Proximal to the ISB is a gradient of steadily cooler and drier airways to the airway opening (145, 146). This gradient allows the airway to recapture some of the energy and moisture from exhaled air in a countercurrent mechanism (48, 142, 147-149). Sara and Currie (150) showed that air cooled from 37°C in the large airways to 32°C on exiting the nose or mouth in human adult subjects. The recaptured energy and moisture is then available for the next breath. Dery et al (145) performed measurements in patients undergoing anaesthesia and found a gradient of airway temperature from the distal to the proximal airways. This was confirmed by McFadden et al (146) in a study of six healthy volunteers breathing combinations of ambient room air and frigid air during quiet tidal breathing and maximal ventilation. They inferred that conditioning of inspired gases and the recovery of energy and moisture from expired air occurs over a length of the airway rather than in a limited location. The ASL is able to store a
relatively large amount of energy because of the high heat capacity of water (151). Combined with the low heat capacity of air, this allows the airways to condition inspired gases at extreme conditions without either freezing or suffering thermal injury.

Cole demonstrated in dogs and human volunteers that the energy and moisture to condition inspired gases come predominantly from the respiratory mucosa, with between a third and a half coming from the expired gases and the remainder being supplied to the mucosa by the vascular system (152). The vascular supply to the trachea, which performs the main work of airway conditioning below the level of the upper airway, is from the inferior and superior thyroid arteries, and the vascular supply to the bronchial airways to the level of the peripheral bronchioles is from the bronchial arterial circulation. The more distal airways and alveoli are supplied by the pulmonary arterial circulation.

This process of recapturing exhaled energy and moisture is not 100% efficient. Expired air is 32-34°C and contains 27-34 mg H₂O/L in studies in human subjects (143, 146) and thus energy and water are lost from the airways with every breath. In a 24 hour period the adult human respiratory tract normally loses 250-350 mL of water (2, 4) and 350-1512 calories of heat (2, 48). Even at extremes of temperature, when the reserve capacity of the bronchial artery circulation to warm the airways has been overcome, the alveolar gases are probably maintained at core temperature and 100% relative humidity due to the presence of the pulmonary arterial circulation.

### 2.7.1 Changes in the Isothermic Saturation Boundary (ISB) with Inhalation of Cold or Dry Air

During normal resting respiration, the ISB in humans is at the level of the second-generation bronchi (145, 153). The position of the ISB is not static and cycles during
each breath, moving distally on inspiration and proximally on expiration. It also varies with ambient temperature and humidity (145, 153). In a study of 12 patients undergoing anaesthesia for elective surgery, Dery et al (145) demonstrated that the ISB moves distally during ventilation with dry anaesthetic gases. They also found that exhaled gases were less than 37°C. Using the inspiration of air at -17°C in healthy human volunteers, McFadden et al (146, 154) found temperatures as low as 20°C in the trachea and 27°C deep in the right middle lobe. In five healthy human subjects breathing ambient air at -40°C, Cain et al (155) found that exhaled air temperature was 28°C. With increased minute ventilation there is an increase in the volume of air per minute requiring conditioning and the ISB moves distally in the airways (4). Solway et al (156) demonstrated in nine healthy human volunteers, using a single breath temperature washout technique, that airway wall temperatures were cooler when higher volumes and higher airflow rates were inhaled. Therefore, as the demands placed on the airway increase (in terms of volume, temperature, and moisture content of inspired air), then the range and surface area of airway involved in conditioning and recovery of energy and moisture also increase (146).

Disease states have been found to affect the ISB. Caldwell et al demonstrated that patients with chronic obstructive pulmonary disease (COPD) were able to warm and humidify inspired gases as effectively as normal subjects, but that they had an increased total respiratory heat loss due to an increase in the volume of ventilation per unit of oxygen consumption (157). In contrast, Primiano et al (143) showed that CF patients had less efficient and slower water transport than normal individuals.

2.7.2 Effects of Cold or Dry Air on Airway Blood Flow

Many of the physiological studies on vascular blood flow and airway cooling have been conducted in canine models. In contrast to humans, canines have fur covered skin and the lungs are an important means of eliminating excess heat. Changes in
airway blood flow in response to temperature changes are therefore more marked than in humans. However, Cole (142) showed that the same vascular changes associated with total body heat regulation that take place in the lungs in dogs and in the skin in humans were also found in the human nasal respiratory mucosa, thereby supporting the role of the canine airway as a model for the human airway in terms of heat and moisture exchange.

Theoretically, the airway circulation may not increase to re-warm airways which have been cooled as this would decrease the efficiency of the countercurrent mechanism and increase the loss of energy from the airways. However, Baile et al (158) found in a canine model that hyperventilation with cold air caused an increase rather than a decrease in bronchial and tracheal blood flow, although the temperature of the trachea and bronchi still fell below baseline levels. They also demonstrated that warm dry air caused a greater increase in tracheobronchial blood flow than cold air, despite a lesser fall in airway temperature (159). These authors surmised that drying or evaporation was a greater stimulus to vasodilatation than cold alone. Kim et al (160) confirmed in humans that hyperventilating with cold air increased airway blood flow due to the effects of thermal stress on the airway and not due to the hyperventilation itself as hyperventilating warm moist air did not have the same effect.

Solway et al (161) noted in dogs that the bronchial arterial circulation comprised a small percentage of cardiac output and this volume was insufficient to re-warm cooled airway walls. They demonstrated that increased blood flow in the pulmonary circulation, which comprises 100% of cardiac output, rather than the bronchial circulation which comprises around 1% of total circulation in dogs, was responsible for maintaining airway wall temperature during the inspiration of cool gases. Serikov and Fleming (162), using isolated dog lungs and four patients undergoing elective
cardiopulmonary bypass, also compared the effects of pulmonary and bronchial
circulation in heat and moisture exchange in the lung. They found that the bronchial
arterial circulation was inadequate to maintain lung temperature except under
conditions of low thermal stress, whereas the pulmonary circulation was adequate
due to relative blood flows.

Salonen et al (163) isolated the tracheal circulation from 19 dogs and demonstrated a
fall in tracheal vascular resistance when cold dry air inhalation followed warm humid
air inhalation with a 7.8% decrease in tracheal vascular perfusion pressure. They
also demonstrated a decrease in tracheal diameter which would bring a greater
proportion of airflow into contact with the airway wall. In a rat study mimicking
hyperosmolarity of the ASL in response to hyperventilation, tracheal mucosal vessels
were found to dilate in response to the superperfusion of the airway surface of
hyperosmolar fluid (164).

2.7.3 Effects of Cold or Dry Air On Surface Liquid Osmolarity

Conditioning of cold and/or dry inspired gases results in evaporation, thought to
increase the osmolarity of the ASL (165-168). Man et al (165) found an increase in
ASL osmolality in secretions from the trachea during mouth breathing compared to
nose breathing in anaesthetised dogs. Shephard et al (167) exposed isolated guinea
pig trachea to bidirectional flow with dry air, resulting in a decrease in ASL depth and
an increase in ASL sodium ion concentration as measured by microelectrode. In this
technique, ion-sensitive microelectrodes are used to precisely measure the ASL ion
concentration and stimulation of the underlying epithelium is avoided. Freed et al
(168) insufflated dry air via a wedged bronchoscope into a lung segment of dogs and
measured a 40 mmol/L increase in ASL osmolality when samples were collected with
either micropipette or a filter paper pledget. The collected ASL volume increased,
rather than decreased, with exposure to dry air suggesting an increase in ASL flow.
from the peripheral to the central airways in response to the drying stimulus. The sampling method did not affect the sample volume collected. The increase in osmolality was less than expected from evaporative losses measured in humans (169) suggesting significant replacement of the ASL water content from vasculature. In humans, Togias et al (166) demonstrated an increase in the osmolality of nasal ASL in volunteers when inhaling cold dry air. However, the airflow was unidirectional as the volunteers breathed in through the nose and out through the mouth.

The above findings that inhaling dry air, particularly during hyperpnoea, causes an increase in ASL osmolality was challenged by Kotaru et al (170). They studied healthy human volunteers rather than animals, ensured bidirectional flow of air and collected ASL from the upper trachea on filter paper pledgets via bronchoscope. In this study there was no change in ASL volumes or osmolality - indicating rapid replacement of any water lost by evaporation. This was likely to be firstly, through an increase in mucus secretion and secondly, by rapid transport of water from the vasculature.

The degree of airway cooling depends on the temperature and humidity, and also the volume of inspired gas per minute of ventilation. Thus exercising or hyperventilating in cold, and therefore dry, conditions causes the greatest degree of airway cooling. Airway cooling also results in an increase in airway resistance which is more marked in individuals with asthma (151).

Hyperventilation and the inhalation of cold dry air have long been known to cause bronchoconstriction in patients with exercise-induced asthma. As the lower airways of patients with tracheostomies are also exposed to dry gases, findings may be similar (171). With the inhalation of dry gases there is direct injury to the mucosa and this is also found in exercise-induced asthma (172). There is an increase in the
number of epithelial cells shed into the sputum in asthmatics after exercise which is 
associated with the release of histamine and cysteinyl leukotrienes (173). Plasma 
exudation also occurs with epithelial injury and this exudate may contain proteins 
which sensitise the underlying smooth muscle resulting in bronchospasm in 
asthmatics on the next exposure to cold or dry air (174).

Hyperosmolarity of the ASL, which may result from evaporation, causes release of 
inflammatory mediators from mast cells (174). This hyperosmolarity is brief as airway 
epithelial cells are able to rapidly replace ASL volume by shrinking and donating their 
own water. The water of the epithelial cells is then replenished slowly by the mucosal 
vasculature. Epithelial cell shrinkage may also be the stimulus for inflammatory 
mediator release. When the requirement to condition the inspired gases exceeds the 
ability of the epithelium to replace lost ASL water then total airway water losses 
increase and airway secretions become dehydrated (175, 176).

Noguchi et al (177) compared the effects of inspired gases at temperatures from 
15°C to 40°C on pulmonary mechanics and function in tracheostomised dogs. They 
found that gases at 15°C and <40% relative humidity, as well as gases at greater 
than body temperature and at 100% relative humidity, reduced functional residual 
capacity and pulmonary compliance with little difference demonstrated between 20°C 
and 30°C at 100% relative humidity.

Freed et al (178) challenged ventilated dogs with dry or humidified air at 23°C. Dry air 
causd damage to the ciliated epithelium, an increase in peripheral airways 
resistance and an increase in vascular permeability. Freed and Davis (168) subjected 
aanaesthetised dogs to a dry air challenge and a hyperventilation challenge. 
Hyperventilation with dry air caused an increase in ASL osmolarity for a short period 
of time, accompanied by increased airway resistance.
Togias et al (179) found that nasal challenge in dogs with cold dry air resulted in the release of histamine, prostaglandins and kinins and postulated that mast cell degranulation may be one of the mechanisms of bronchoconstriction on exposure to cold. They subsequently found an increase in nasal fluid osmolarity that accompanied the release of inflammatory markers (166) and postulated that evaporation increased the osmolarity of nasal ASL and triggered the release of inflammatory mediators. In a more recent experiment Davis et al (180) demonstrated that inhalation of unconditioned air produce a release of inflammatory mediators, predominantly IL-4, IL-5, and IL-10 with no elevation in levels of IL-1, interferon-gamma (IFN-γ), or tumor necrosis factor-alpha (TNFα). This pattern of inflammation is similar to the pattern that is seen in the majority of adult patients with asthma.

An increase in airway resistance may be found when cold air is inhaled nasally, even though the air is fully conditioned by the time it reaches the pharynx, indicating the presence of cold receptors in the nasal epithelium and the action of neural reflexes (181). Cold receptors have also been found in the larynx (182), although Fonatanari et al (181) did not find the same effects on airway resistance during mouth breathing that they found with nasal breathing.

Increased airway resistance may be observed clinically by the presence of wheeze or an increase in respiratory rate or effort. We, therefore, sought to test the hypothesis that children with tracheostomies will have improved findings on clinical examination when receiving humidification during sleep via a HH compared to via a HME.
2.8 Respiratory Energy Exchange and Total Body Balance

Heat and moisture loss in exhaled gases represents a loss of energy to the body. This loss of energy from the respiratory tract constitutes a significant proportion of body metabolism and varies with ambient conditions. Ryan et al (183) measured the energy workload (humidity and temperature) on the airway with a range of inspired gas conditions and demonstrated that only inspired gas at core body temperature and 100% relative humidity did not impose work on the airway. In infants and young children this work is more likely to have clinical implications due to the relative small body size. In infants up to a third of basal metabolic heat production may be required to condition inspired gases (184, 185) compared to, in adults, 5% at rest and 12% during exertion (157). In this section I will discuss the studies that have measured total body energy loss from the respiratory tract in young children.

In humans, the respiratory system accounts for 21% of total body heat loss and most of this is due to evaporation. Haslam and Nielsen showed in adults that the fall in core body temperature which occurred during anaesthesia, and was greater with higher gas flows, could be reduced with the use of a HME (186). Inhalation of dry gases compared to humidified gases during anaesthesia has been demonstrated to cause a significantly greater fall in body temperature in infants (187-189). The recovery of body temperature post-extubation to baseline levels was also slower, although this was not statistically significant (189). Appropriate conditioning of inspired gases may therefore reduce the thermal burden placed on the infant as a whole.

Infants also have a smaller total body water volume with which to replenish water lost from the airways. In a study of eight newborns requiring ventilation, appropriate humidification of inspired gases reduced insensible water losses by one third (190).
However, there was no difference in the amount of radiant heating required to maintain the infants’ body temperature (190).

A retrospective series of 149 low birth weight infants found less respiratory morbidity and chronic lung disease if the inspired gas temperature was maintained above 36.5°C compared to ≤ 36.5°C during ventilation (191). This effect was not seen in term infants suggesting a possible effect of size, either airway diameter or total body water and energy, although the authors did not discuss lung immaturity as a possible factor. These studies suggest the extra demands of conditioning inspired gases may have clinically significant effects in infants and young children.

2.9 The Effects of Artificial Airways on the Respiratory Mucosa

In this section I will discuss the direct mechanical effects that may result from insertion of a tracheostomy. Some of these effects may also be due to the inhalation of cold or dry gases, the effects of which will be discussed below. The presence of an artificial airway, either a tracheostomy tube or endotracheal tube, affects the tracheal epithelium through direct trauma or rubbing, inadequate humidification, inflammation, or infection, with ongoing injury affecting the repair process resulting in squamous metaplasia of the epithelium (192). The presence of an artificial airway also imposes an increased work of breathing on patients through increased airway resistance due to a narrower airway lumen.

2.9.1 Histopathologic Effects of an Artificial Airway

The effects of an artificial airway have only been studied in animal and adult human subjects. Klainer et al (193) studied the trachea of dogs subjected to two hours of tracheostomy with and without inflating the cuff of the tube. Humidification was maintained throughout the two-hour period with a heated nebuliser. The results were
compared to two post-mortem adult patients who had undergone tracheostomy tube insertion and had the cuffs inflated. Without cuff inflation, the tracheas showed linear areas of loss of cilia, with most cells showing denudation of cilia and the few remaining cells had disoriented and inhomogeneous cilia. With the cuff inflated to a “just seal” point, the trachea showed almost complete denudation of cilia under the tube, particularly under the cuff site. Inflammation and loss of epithelial integrity was seen. A transitional zone was identified with matted cilia and loss of the normal uniform cilia orientation. Dogs allowed to survive for up to seven days following intubation showed gradual regeneration of cilia, although recovery of the epithelium was not complete and the cilia were often matted and disoriented. Intubated human patients showed similar patterns of injury with denudation of cilia and squamous metaplasia. These results suggest that even at a low pressure, inflated tracheostomy tube cuffs cause denudation of cilia and squamous metaplasia independent of any effect of humidification. Loss of cilia was also seen in trachea where the cuff had not been inflated, suggesting that the tube itself was causing injury.

Alexopoulos et al (194) studied surface damage and mucus transport in 26 piglets intubated or both intubated and tracheostomised for two to six hours with cuffed endotracheal tubes. Histological samples were taken from the trachea at the level of the artificial airway tube but above the tube cuff. In the areas without covering mucus, light microscopy and electron microscopy showed epithelial damage with partial to complete loss of cilia and some deep epithelial lesions. In areas covered by mucus where mucus transport was thought to have been arrested, the same injuries were seen but also deeper injuries with loss of the basement membrane and some subepithelial ulcers. These results were correlated with dye studies of mucus transport in the same region and compared to the results for two unintubated control piglets. At or below the level of the cuff there was complete loss of mucus transport with some of the dye running distally toward the carina rather than proximally. In the
areas above the cuff there was irregular or patchy transport of the dye with areas of transport arrest. The stained mucus tended to run in narrow channels. In some piglets there was complete loss of dye transport. Correlating the histological and dye studies, the authors found that in areas with present but impaired transport of mucus, patchy histological changes of injury were present.

Donnelly et al (195) performed autopsies on 99 patients who had undergone orotracheal intubation for periods ranging from 15 minutes to 176 hours in the last 30 days before death. Fifteen patients had undergone tracheostomy. The specific details of the causes of death are not well reported in this study; 40% of patients had been intubated in theatre suggesting a perioperative cause of death with pneumonia and pulmonary embolus mentioned as frequent causes. None of the patients died as a consequence of orotracheal intubation. However, two patients died as a consequence of tracheo-oeophageal fistula secondary to tracheostomy. The findings of the study are primarily related to laryngeal pathology, although patients who had been intubated more than 48 hours showed focal ulceration of tracheal tissues which progressed with time in the same manner. Initially there was loss of laryngeal mucosal epithelium, followed by ischaemic ulceration and necrosis of perichondral tissues. After 72 hours there was prominent connective tissue inflammation above, below and between the levels of these ulcers, proceeding to an inflammatory exudative response with pseudomembrane formation in the ulcers. There was prominent bacterial and fungal colonisation of the ulcers.

Freidberg et al (196) examined the trachea, carina and primary bronchi from 27 deceased patients with tracheostomies and 44 deceased controls. They found a number of patterns of epithelial injury in the tracheostomised patients. Carinal ulceration was found in eight of the tracheostomy patients and was thought to be due to the traumatic effects of suction catheters. Ulceration, denudation of cilia, and
infection with clumps of bacteria or fungi were found in ten patients. A pattern of
denudation, repair and regeneration was found in ten patients and was more likely in
patients with a shorter duration of tracheostomy. Respiratory epithelial metaplasia
was found in almost all patients who had had a tracheostomy for more than five days.
A chronic inflammatory reaction was present in the epithelium of eight
tracheostomised patients, but was found more frequently in the control group which
may have related to the mode of death.

Roessler et al (197) performed bronchial biopsies in ten laryngectomised or
tracheostomised patients and compared them to healthy controls. In the
tracheostomised patients there was decreased ciliation of the trachea with almost
complete absence of cilia at the level of the stoma and at the carina. Squamous
metaplasia of the respiratory epithelium was seen as well as compound cilia and
giant cilia. In the tracheostomised patients there was almost normal ciliation at the
mid-trachea and the origin of the right upper lobe bronchus. The authors were
uncertain as to the cause of decreased ciliation at the carina but postulated that it
may have been due to the increased deposition of inhaled contaminants at that site.
The mechanical impact of repeated suctioning may also have contributed.

Griese et al (198) performed bronchoalveolar lavage on 46 children with chronic
tracheostomies who were currently asymptomatic for infection and 16 control children
undergoing minor elective surgery. The children with tracheostomies had increased
neutrophil counts in the lavage fluid, which was correlated with a decrease in
surfactant protein-D. The other surfactant proteins were not affected. Asada et al
(199) collected lower airway specimens via catheter from 28 tracheostomised
individuals with profound disabilities and found elevated levels of the inflammatory
cytokines interleukin-8 (IL-8), IL-1β, and IL-6 compared to healthy controls. IL-6 and
IL-8 levels in airway secretions also increased during febrile episodes.
In summary, the presence of an artificial airway, whether it is an endotracheal or a tracheostomy tube, is reported to result in pathologic inflammatory changes in the airway mucosa independent of any effects of humidification. Intubation or tracheostomy may cause extensive injury to the cilia and to mucus transport with mucus tending to accumulate at levels of transport arrest. The mucus tends to be transported in narrow channels through areas of patchy injury. However, if the injury creates complete circumferential loss of cilia (“ring barking”) then the mucus stream is blocked, forming a dam. Neutrophilic inflammation has also been found in lavage fluid from children with tracheostomies. These changes will need to be taken into account when considering the effects of adequate or inadequate conditioning of inspired gases.

### 2.9.2 Risk of Infection

In this section I will discuss colonisation of artificial airways and subsequent infections, firstly in patients mechanically ventilated in the intensive care unit (ICU) and secondly in patients with tracheostomies. Patients with an endotracheal tube or tracheostomy are at increased risk of pneumonia due to (200):

- Bypassing of the upper airway filtering and protective mechanisms
- Aspiration of gastric contents around the tube
- Colonisation of the tube lumen with dislodgement of the bacteria by suction or instillation of saline
- Damage to the mucociliary defences
- Aerosols or droplets from nebulisers or condensate from ventilator circuits

Colonisation with an organism may be a risk for subsequent infective illness caused by that organism. Colonisation is the growth of an organism within the body without causing tissue invasion, damage or infection. Infection occurs when the organism
invades tissue and causes damage and/or inflammation. Patterns of microbiological colonisation of the oropharynx, stomach and trachea and associations with infection have been studied in intubated and ventilated patients in the ICU. Neiderman et al took oropharyngeal and tracheal specimens from patients ventilated for at least a week and found colonisation of the lower airways in nine of the fourteen with *Pseudomonas spp* (201). While *Pseudomonas* primarily colonised the lower airways, other gram negative organisms colonised the oropharynx prior to the lower airways. De Latorre et al (202) took gastric and tracheal aspirates from 80 patients in the ICU and found tracheal colonization with bacteria or fungi in 90% of patients. Gram positive organisms were predominant with some *Pseudomonas aeruginosa* and yeast also found. In ten of twelve patients who developed ventilator-associated pneumonia (VAP), an organism previously found on tracheal aspirates was identified as responsible with a weaker relationship for organisms colonising the stomach. Several studies have found that oropharyngeal colonisation was a risk factor for tracheal colonisation, and in turn tracheal colonisation was a risk factor for VAP (203-206). The risk of VAP has been found to be reduced in randomised controlled trials (RCTs) employing suctioning or antibiotics to prevent tracheal colonisation in intubated patients (207-209). However, Ewig et al (204) found that antibiotic prophylaxis reduced the risk of early oropharyngeal colonisation and subsequent VAP with gram positive organisms but that prolonged antibiotics increased the risk of colonisation with gram negative organisms and late onset VAP.

Patients with tracheostomies are also at risk for infection. An early study of 101 surgical ICU patients with recent tracheostomies found 93% of patients were colonised with bacteria on tracheal aspirate (210). A study of 15 adult patients with long-term tracheostomies found gram negative bacteria in 75% of tracheal aspirates (211). *Pseudomonas* species were the most common bacteria identified and patients persistently colonised with *Pseudomonas* were more unwell, required more frequent
antibiotics, were more likely to be mechanically ventilated and developed more lower respiratory tract infections (LRTI). In a study of 135 adult ICU patients undergoing tracheostomy to assist weaning from mechanical ventilation, colonization of the lower airways prior to tracheostomy was a risk factor for both VAP and mortality (212). This was confirmed in a subsequent study of 99 adult ICU patients (213) with *Pseudomonas spp* responsible for most of the episodes of VAP. Organisms present in pre-tracheostomy tracheal aspirates were not the same as those causing VAP, possibly due to the use of prophylactic antibiotics. Bacteria colonising the mouths of ICU patients have also been found on suctioning equipment (214).

The endotracheal tube or tracheostomy itself may act as the source of infection. Inglis et al (215) identified biofilm lining the internal lumen in 30 of 40 endotracheal tubes from patients ventilated in ICU. They postulated this biofilm arose from bacteria colonizing the patients’ stomachs and was a risk factor for VAP. However, in a subsequent study of the ultrastructure of endotracheal tubes, the same authors found that the biofilm was made of layered accumulated respiratory secretions rather than representing a predominantly bacterial biofilm (216). Feldman et al (217) also found biofilms lining the internal lumens of endotracheal tubes from patients in ICU, with gram negative bacteria cultured from most. They also identified a pattern of progression of bacterial colonisation over time from the oropharynx to the stomach to the lower airways. In eight of thirteen cases of VAP the responsible organism had been previously identified colonising the endotracheal tube and lower airways.

Bartlett et al (218) performed serial tracheal aspirates from 16 long-term tracheostomy adult patients and found multiple organisms growing on each tube, with the bacterial species changing over serial cultures. There was a poor relationship between oropharyngeal and tracheal cultures. Harlid et al (219) monitored 39 outpatients with chronic tracheostomies with serial cultures taken from the stoma
site, the trachea and protected bronchial brush specimens over a 12-month period. They found high rates of tracheal colonisation with 83% of tracheal specimens being positive. The main organisms found were *Staphylococcus aureus*, gram negative enteric bacteria, and *Pseudomonas aeruginosa*. However, only 30% of the bronchial specimens were positive. In addition, despite the high rate of tracheal colonisation, there were low rates of infection with 46% of the patients receiving antibiotics for suspected respiratory tract infection and only five cases of pneumonia.

There have been similar findings in children. Cordero et al (220) studied 260 premature infants in a neonatal intensive care unit (NICU) over a five year period. After two weeks of ventilation via endotracheal tube, 80% of infants had lower airway colonisation with gram positive bacteria and 36% with gram negative bacteria. Colonisation with gram negative bacteria was associated with worsened severity of bronchopulmonary dysplasia. Morar et al (221) performed a two and a half year observational study in a paediatric intensive care unit (PICU) and found that 71% of intubated children had bacterial colonisation of the lower airways during intubation. All episodes of infection of the lower respiratory tract were preceded by colonisation. The rate of tracheal colonisation increased to 95% in children who had undergone tracheostomy, although the rate of subsequent infection was lower in these tracheostomised children.

Morar et al (222) conducted a subsequent study of 49 children admitted to PICU who underwent ventilation via endotracheal tube for a median of twelve days followed by long-term ventilation via tracheostomy. Tracheal cultures were taken on admission to the intensive care and then serially thereafter. There was an increased rate of tracheal colonisation during the period of tracheostomy with 87% of the children developing tracheal colonisation. However, there was a trend to a lower rate of infection with tracheostomy placement compared to endotracheal intubation. In
addition, children with tracheostomies were more likely to develop infection with exogenously acquired, rather than endogenous, oropharyngeal bacteria compared to when they had an endotracheal tube. A study of 290 children with burns requiring airway support showed no difference in the rate of LRTI between those requiring ventilation and tracheostomy (223). In contrast, a study of 52 neonates requiring ventilation for tetanus in Africa, found higher rates of pneumonia during a phase of performing tracheostomy as compared to a period of performing prolonged nasotracheal intubation (224).

Brook (225) took serial tracheal cultures from children with long-term tracheostomies and found mixed growth on multiple samples including both aerobic and anaerobic bacteria. Twenty-four of the children developed recurrent chest infections with persistence of the organisms being common despite successful symptomatic treatment with antibiotics. In a study of 22 children with tracheostomies, bacteria were cultured from the subglottic area in 17 children during surveillance laryngoscopy (226). The predominant organisms were group A streptococci and Neisseria species, with 22% being colonised with Pseudomonas. Griese et al (198) performed bronchoalveolar lavage on 46 children with tracheostomies who were asymptomatic for symptoms of respiratory infection and also found high rates of bacterial colonisation with the same organisms: group A streptococci, Neisseria species and Pseudomonas species.

Perkins et al (227) identified bacterial biofilms from ten of eleven tracheostomy tubes removed during routine tube changes from hospitalised children. The extent of biofilm formation did not correlate with the length of time the tracheostomy tube had been in situ. Four of the tracheostomy tubes were cultured for bacteria and multiple bacteria were grown from all four tubes.
In summary, intubated or tracheostomised adult and paediatric patients have high rates of tracheal colonisation with potentially pathogenic bacteria. There is a temporal pattern of colonisation - with oropharyngeal colonisation occurring prior to tracheal colonisation. In intubated patients pneumonia is generally caused by organisms that have colonised the trachea. However tracheostomised patients are more at risk of being infected with exogenous bacteria. In the ICU setting, children with tracheostomies may have a lower rate of LRTI than children who are intubated, however the data is conflicting. In outpatient adults and children with chronic tracheostomies there are relatively low rates of LRTI despite high rates of tracheal colonisation.

2.9.3 Increased Airways Resistance Due to Artificial Airways

Artificial airways also impose an increased work of breathing (228). This is in part due to the resistance of the airway which is determined by the Poiseuille equation with resistance proportional to the length and inversely proportional to the 4\textsuperscript{th} power of the radius during laminar flow, increasing to the 5\textsuperscript{th} power of radius when flow is turbulent. Wright et al (94) demonstrated in ten intubated adult patients and in an \textit{in vitro} artificial lung model that the airflow in an endotracheal tube is turbulent rather than laminar. They also demonstrated that the airway resistance measured \textit{in vivo} was higher than that measured \textit{in vitro}, possibly due to the presence of secretions or to deformation of the endotracheal tube \textit{in vivo} by the anatomy of the upper airway. Chatila et al (96) found a trend toward a reduction in airway resistance following removal of airway secretions by suctioning of the endotracheal tube in 30 intubated and ventilated patients, but this reduction was small and not statistically significant. Davis et al (229) compared the airway resistance of tracheostomy tubes to endotracheal tubes in an \textit{in vitro} lung model. They confirmed that airway resistance was determined by internal diameter and length but also found that for a given internal diameter a tracheostomy tube had a lower resistance than an endotracheal
tube. These findings were replicated in vivo in a study of 20 intubated patients who underwent tracheostomy (230). This may be partly due to the shorter length of the tracheostomy tube and partly due to the soft endotracheal tube being distorted when inserted in the upper airway whereas the more rigid tracheostomy tube maintains its shape. Other authors have shown that the resistance of the tracheostomy tube is higher than the normal upper airway (231, 232). Yung and Snowden (233) measured the in vitro resistance of three commercial tracheostomy tubes manufactured by Jackson, Portex and Shiley and found that the radius of curvature, the roughness of the inner surface, and the length of the tube all contributed to the airway resistance.

In summary, insertion of a tracheostomy tube may increase total airway resistance compared to a normal upper airway. This resistance may be increased by the presence of airway secretions in the tracheostomy lumen. Children have tracheostomy tubes with smaller lumens than those used in adults and the effect of secretions in the lumen may be relatively greater. However, the majority of children undergoing tracheostomy have a structurally abnormal airway and tracheostomy generally decreases the high upper airway resistance in these particular patients.

2.10 The Effects of Inspired Gas with Low Moisture and/or Temperature

As discussed at the beginning of this thesis, insertion of a tracheostomy tube results in inspired gases entering the trachea directly bypassing the normal conditioning that occurs in the upper airways. This results in inadequately warmed and humidified gases entering the trachea and has been found to cause a number of adverse effects including slowing of MCC, atelectasis, inspissation of mucus, acute or chronic infection, obstruction of the airway with mucus, and impaired gas exchange. In this section I will describe studies that assess the effects of inspiring inadequately
conditioned gases. As cold air is also dry and as the process of evaporation to humidify inspired gases causes a fall in airway temperature, it is difficult to separate the effects of cooling and drying on the airways and they will be discussed together. The majority of studies have been conducted in animals or in adults receiving positive pressure ventilation in intensive care so these findings may not be directly translatable to children breathing spontaneously via a tracheostomy tube but reflects the only available literature in this area.

The relative humidity of the inhaled gas seems to be more important than the absolute humidity in terms of causing airway injury. Using a tracheal model, Miyao et al (234) demonstrated that for a given absolute humidity, an inhaled gas with a higher temperature and lower relative humidity deprived the airway of a greater volume of water. Shanks (235) similarly found in intubated patients that the temperature of the inhaled gas was less important than inhaling fully saturated gases. Gases that are already fully saturated are warmed as they travel down the airway and acquire moisture at the same rate as they warm. Cool dry gases warm faster than the rate at which they gain moisture (236) and warm or hot dry gases gain moisture relatively rapidly (234). Airway secretions are therefore at greater risk from dehydration by inhalation of warm dry gases than cooler fully humidified gases. The animal studies described below that used relatively low temperatures such as 22-30°C still found a protective effect from 100% relative humidification (177, 184, 237).

During the polio epidemic in the 1950s the need for humidification in patients receiving long-term positive pressure ventilation via tracheostomy for bulbar palsy was recognised due to patients experiencing difficulties in clearing thick airway secretions (238, 239). Humidification during anaesthesia was also suggested to be useful in the 1960s (240), but it was not until the 1970s that this practice was thoroughly investigated and recommended even for these relatively short periods
(187, 235, 241-244). I will discuss animal studies before describing the findings of clinical studies in humans.

2.10.1 Animal Studies of the Effects of Inhaling Dry and Cold Gases

Studies in animals describing the effects of inhaling dry gases have shown damage and ulceration of the airway, histological inflammation, damage to cilia and slowing of mucus transport and increased airway resistance. Although endotracheal intubation and ventilation cause damage to tracheal mucosa, poorly humidified gases have been shown to cause additional injury (184, 245, 246).

2.10.2 Histologic Injury

Moritz and Weisiger (247) demonstrated that the peripheral airways are protected against cold injury. They exposed dogs to cold inspired gases at -100°C with gases entering the larynx at temperatures as low as -30°C. At the carina the lowest temperature reached was +18°C. The result was an increase in tracheal mucus secretion in all of the dogs and epithelial desquamation and epithelium in the upper trachea of some of the animals. The lower trachea and bronchi epithelium underwent inflammatory change and in only a few animals were there signs of patchy inflammation and atelectasis of the parenchyma, and these lasted less than 24 hours.

Tsuda et al (237) found that inhalation of gases at either < 25 °C or ≥ 35°C by tracheostomised dogs decreased the effects of surfactant and caused damage and matting of cilia. Over-humidification with gases at 40°C was as damaging as under-humidification, although there does seem to have been an effect of anaesthesia itself in affecting the airways of these animals.
Todd et al (245) ventilated newborn lambs with either dry or humidified gases. In both groups mucosal injury was seen but with much more severe injury, including blistering and necrosis, in the dry gas group. The mucosal injury was limited to within 15 cm of the end of the endotracheal tube and did not extend into the main bronchi. However, lambs have relatively long tracheas compared to other experimental animals and humans.

Marfatia et al (184) compared inhaling dry gases to gases conditioned to 22°C and 100% relative humidity during six hours of anaesthesia in twelve-week-old rabbits. Even at this low temperature there was a marked protective effect of humidification. They found that dry gases caused slowing of mucus clearance resulting in plugging of the airways at all levels, and marked histological injury including destruction of cilia and mucus glands, disorganisation of the basement membrane, desquamation of the epithelium, and ulceration. Mucus debris was found in the airways even in the animals sacrificed three weeks after the injury. Hirsch et al (248) exposed intubated dogs to gases at 23°C and <10% relative humidity. They found ulceration, erosion and inflammation in the trachea that was not seen in the dogs exposed to humid gases. Interestingly, tracheal mucus flow was able to be restored with three hours of inhalation of humidified gas despite the histological injury.

This evidence of injury and inflammation led me to test the hypothesis that children with tracheostomies will have less airway inflammation in terms of inflammatory cytokine levels in airway secretions when receiving humidification during sleep via a HH compared to via a HME.

2.10.3 Cilia Activity

Inhalation of dry gases causes matting and breakage of cilia (178, 237, 246, 249) followed by cilia destruction (184) as discussed in the histological section above. This
damage to cilia will affect ciliary function and beat frequency but changes in airway temperature and humidity without histological injury may also affect ciliary function.

Dalham (250) conducted one of the early experiments on the effects of dry gases on cilia beat frequency in excised rat trachea. He found that gases at $\leq 50\%$ relative humidity caused slowing then cessation of cilia beat after 10 minutes exposure. Gases at 75% relative humidity allowed cilia beating to continue for 60 minutes and gases at 100% relative humidity allowed cilia activity to continue for 120 minutes. In an excised rat trachea in vitro model, Horstmann et al (251) showed that inadequate humidification of inspired gases caused damage to cilia and ciliostasis with the effect worsening with longer duration. Mercke and Toremalm (252) used excised rabbit trachea and showed a slowing of mucociliary wave activity (reflected light measurement) with decreasing relative humidity.

2.10.4 Tracheal Mucus Flow

Inhalation of dry and cold air causes an increase in mucus secretion (251) but also a slowing of mucociliary clearance. This may be through effects on ciliary function, on mucus viscoelasticity or through histological injury.

Forbes (253) measured mucus flow rates using a technetium radiotracer technique in the intact trachea of anaesthetised dogs. No difference was found in measured mucus flow rates between measurements taken at 32°C, 37°C and 42°C at 75% relative humidity, or between 75% and 100% relative humidity at 32°C. However, this study was conducted under anaesthesia which may affect cilia activity, and measurements were not performed at 37°C and 100% relative humidity.

Burton (254) studied anaesthetised dogs breathing room temperature air conditioned to 40% relative humidity compared to 37°C and 100% relative humidity using an ink
drop marker method and showed a marked slowing in mucus transport rate with the
drier gases.

King et al (255) exposed ventilated dogs to air at 23°C, 32-34.8°C, and 37°C. In this
study the core body temperature for these dogs under anaesthesia was 32-34 °C.
Inhalation of gases at either 23°C or above core temperature resulted in reduced
tracheal mucus velocity (TMV) and tracheal potential difference compared to gases
at core body temperature. Forbes (256) showed a slowing of TMV in dogs with
ventilation with gases at 37°C and 25-50% relative humidity while gases at 75-100%
relative humidity had no effect on mucus flow. Branson et al (249), in a study of
anaesthetised dogs inhaling dry gases, also showed a slowing in TMV with dry gas
exposure as measured by a Teflon disc cinebroncholofibrescopic method and this
effect worsened with duration of exposure.

Fonkalsrud et al (246) subjected 29 anaesthetised dogs to dry and humid ventilatory
gases and showed that dry gases slowed the clearance of an insufflated tantalum
powder, increased the amount of mucus in the airways, caused matting and fusing of
cilia, but did not affect the results of a nuclear medicine ventilation scan. There were
more marked effects after six hours exposure as compared to two hours of exposure.

Hirsch et al (248) exposed intubated dogs to dry gases at 23°C and less than 10%
relative humidity. They found that this caused marked slowing of TMV after one hour
with complete cessation of mucus flow at three hours. Mucus flow was able to be
restored to baseline values with three hours of inhalation of humid gases despite
histological findings of inflammation and areas of ulceration and erosion. The authors
note that they used an intact trachea model rather than an excised trachea and this
may have had a protective effect on ciliated cells, possibly through the transport of
water via the vasculature. Man et al (165) collected tracheal airway secretions from
anaesthetised dogs and determined that breathing air with lower absolute humidity resulted in a slower rate of secretion collection and increased secretion osmolarity. This study collected upper trachea rather than the lower trachea or bronchial secretions and used a collection technique that may have affected ciliary activity and airway surface liquid secretion.

Hyperventilation of dry gases but not humid gases has been demonstrated to cause a slowing of MCC by nuclear medicine radioaerosol technique in humans (257). There was initial slowing followed by partial recovery in the rate of MCC suggesting rehydration of the ASL. This recovery was able to be slowed by blocking the transport of ions with frusemide suggesting that ion transport is important in the replacement of lost ASL volume (258).

2.10.5 Anaesthetic Studies with Dry Gases in Adults

The studies to be described in this section were conducted in patients undergoing anaesthesia and compared humidified gases to unconditioned gases.

Chalon et al (242) conducted an initial study in 45 adult patients undergoing general anaesthesia showing that patients receiving fully conditioned inspired gases had little or no cytological injury on microscopically examined smears of cells lavaged from the trachea as compared to patients receiving partial or no humidification. In a subsequent larger study of 202 adult patients (187) comparing dry gases to gases at 32°C and 100% relative humidity they replicated these findings and also showed fewer post-operative complications in patients receiving 32°C and 100% relative humidity. Knudsen et al (243) subjected 84 anaesthetic patients to dry or humidified gases in a double-blind controlled study and found no difference in terms of radiological changes on plain chest x-ray (CXR) taken immediately after the operation. However, subsequent authors suggest that CXR is an insensitive measure
of complications from inadequate humidification (242, 244). Gawley et al (244) in a study of 85 patients undergoing abdominal surgery found a reduction in post-operative cough and chest auscultatory changes with humidified gases at 37°C and 100% relative humidity compared to dry gases but again no changes on CXR. They also found an improvement in oxygenation post-operatively.

Lichtiger et al (259) showed a reduction in TMV measured by Teflon disc cinebronchofibrescope in 14 patients receiving anaesthesia with gases at less than 32°C and less than 90% relative humidity after a period of anaesthesia compared to immediately after intubation. They also showed tracheal inflammation in patients receiving inadequate humidification. These effects may be partially due to changes in mucus rheology. Richards and Marriott (260) showed an increase in initial shear stress with exposure to reduced levels of relative humidity as compared to 100% relative humidity in mucus gel samples from patients with bronchitis and asthma.

In summary, studies in anaesthetised adults inhaling dry gases produced similar findings of increased inflammation to animal studies.

### 2.10.6 Anaesthetic Studies with Dry Gases in Infants and Children

There are limited studies of humidification of anaesthetic gases in children. Due to their increased surface area to mass ratio, decreased total warm body mass and decreased total body water volume compared to adults, infants are potentially at greater risk of complications from inadequate warming and humidification of inspired gases.

Sosulski et al (190) measured a 32% reduction in insensible water loss from eight infants when intubated and breathing humidified gases at 31.5°C and 100% relative
humidity compared to when extubated and breathing room air at 27°C and 22% relative humidity. There was no change in heat loss between the two states.

Fonkalsrud et al (188) studied 48 infants undergoing congenital diaphragmatic hernia repair and showed increased atelectasis in infants undergoing surgery who received dry anaesthetic gases compared to those received humidified gases. The latter also had improved temperature control.

Tarnow-Mordi et al (191) found a reduction in respiratory morbidity in those infants receiving higher gas temperatures in the first 96 hours of life. This study took place when many commercially available humidifiers did not deliver adequately warmed and humidified gases to ventilated neonates (261). The authors felt that the study should be replicated prospectively with properly controlled gas conditions (191).

In an early observational study of 26 neonates during introduction of a humidifier to a NICU, infants ventilated with gases at 60-70% relative humidity had a ten times greater risk of endotracheal tube occlusion compared to those ventilated with gases at 70-80% relative humidity (262).

Following these studies it has become accepted that inhaling dry gases is inappropriate even for short duration anaesthesia and some form of humidification has now become standard practice. The few paediatric studies comparing inhalation of dry gases to humidified gases during anaesthesia show increased water loss, endotracheal occlusion and respiratory complications such as atelectasis.

2.11 The Effects of Excess Moisture (aerosols)

Humidification therapy may cause adverse effects through the delivery of excess water to the airway and lungs, through the delivery of water in mass form as droplets
or through the loss of the normal temperature and humidification gradient that exists in the trachea of the normal individual.

Excess humidity can only be delivered with gases that are at higher than core body temperature because the maximum amount of humidity that gases can carry is 100% relative humidity. Normally, inspired gases are cooler and drier than 37°C and 100% relative humidity and the airways donate energy and moisture to the gases. Once inspired gases reach airways that are at core body temperature and 100% relative humidity, no further exchange of water takes place. Gases that are at higher than airway temperature will cool till they reach the same temperature as the airway, resulting in condensation. Once steady state is achieved no further condensation can occur.

A pathology study in dogs by Modell et al (263) showed that the inhalation of an aerosol from an ultrasonic nebuliser resulted in atelectasis and consolidation, neutrophilic inflammation and haemorrhage. These changes were exaggerated when normal saline rather than distilled water was nebulised. Stehlin and Schare (264) showed focal microabscess formation, pulmonary oedema, haemorrhage and atelectasis in the lungs of rabbits exposed to a nebulised aerosol. Although, they found more severe problems in those exposed to water rather than normal saline. John et al (265) found in rabbits that inhaling air with nebulised moisture during ventilation for six hours caused interstitial and intra-alveolar oedema in rabbits as well as an increase in pulmonary artery thickness, systemic hypotension and mortality.

Melville et al (266) subjected healthy, spontaneously breathing individuals to an atmosphere containing nebulised moisture and showed an increase in specific airway resistance with increasing humidity when breathing gases conditioned with nebulised
tap water. The authors postulated that this was due to excess moisture causing mucosal swelling and thought that the situation was worsened by contaminates in the tap water.

Several studies have demonstrated a fall in arterial oxygen levels in ventilated patients exposed to nebulised aerosols for humidity (267, 268) and a controlled study in spontaneously breathing intubated patients showed that aerosol therapy reduced arterial oxygen compared to using a HH (269). Delivery of excess moisture in aerosol form may also result in hyponatraemia (270).

Some authors have expressed concern that delivery of inspired gases at 37°C and 100% relative humidity abolishes the normal physiological temperature and moisture gradient that exists in the trachea of the normal individual breathing spontaneously through the upper airway (185, 271). Inspiring air at 37°C and 100% relative humidity prevents the trachea acting as a source of heat and water loss in order to maintain homeostasis. The loss of water may have an important role in regulating the volume of ASL that is cleared from the lungs. Dery (271) notes that delivering gases at full humidification does not increase moisture delivery to the airway but prevents the loss of warmth and moisture from the airway by shifting the ISB proximally to the airway entrance (the mouth). Dery also demonstrated adverse events in the nasal tract from breathing gases at this condition and emphasised the risk of burn injury.

Other commentators suggest that the delivery of gases at any condition other than 37°C and 100% relative humidity imposes a burden in terms of water and energy on the airway (183, 272). This is an acceptable burden in the normal airway, but in the intubated patient the airway may not cope. It should be noted that these publications were supported financially by Fisher and Paykel Healthcare who manufacture the HHs used both in those studies and the studies we undertook for this thesis.
2.12 The Effects of Hot Air

During oral inspiration, temperatures up to 47°C at 100% relative humidity can be tolerated without any adverse events (273). Higher temperatures cause a burning sensation at the lips with temperatures greater than 55°C resulting in lip or laryngeal burns. Inhalation of hot gases via an artificial airway would bypass the conditioning system of the mouth and has been shown to cause extensive tracheal damage at 60-70°C (274). Klein et al (275) reported a case study of a patient who received humidified gases at an excess temperature of 43°C due to a faulty thermometer and suffered a severe tracheobronchial burn injury.

Hortsmann et al (251) showed that hot dry air caused cilia and cytoplasmic disarray and destruction in the airways of rats. Mecklenburg et al (276) demonstrated that hot moist air at 42°C delivered to in vitro segments of rabbit trachea caused fusing of cilia, with the formation of submembranous vesicles that formed club-like projections at the tips of the cilia. With periods of longer than 165 minutes the vesicles disappeared, the cilia were completely fused ("coagulated" in the words of the authors) with total loss of cilia activity.

2.13 Humidification Devices

There are a variety of methods of delivering humidified gases for patients; Heated Humidifiers (HHs), cold humidifiers, Heat and Moisture Exchangers (HMEs), and nebulisers. I will describe each in turn.

2.13.1 Heated Humidifiers

HHs function by passing inspired gases over, or bubbling the gases through, a heated water bath. The conditioned gases are then transported via hosing to the patient. The water bath can be set to any desired temperature and will generate gases conditioned to that temperature and 100% relative humidity. However, the
gases will cool as they travel along the hosing resulting in condensation or “rain out”. Therefore the hosing itself requires heating to maintain the temperature of the gases and reduce condensation. A sensor is placed to measure the temperature of gases at the patient end of the hosing and servo-controlled heated wiring within the hosing maintains the temperature of the gases along the length of the hose. Heated humidifiers may deliver 100% relative humidity in the presence of high air flows (277). Cold humidifiers utilise a similar water bath to HHs but the water and the hosing is not heated. The water bath is initially at room temperature, but cools with evaporation, and the inspired gases are, therefore, not well conditioned.

In the past there have been concerns that the use of HHs would result in bacteria breeding in the water chamber and being delivered to the patient’s airway. Theoretically, this could not occur because HHs generate humidified gas rather than creating aerosols. The water in humidified gas is in molecular rather than droplet form and these particles are too small to transport bacteria. However, some humidifiers condition gases by bubbling them through the water bath which may create droplets of water which could then deliver bacteria to the patient (278). There is the possibility that condensate may form within the hosing of the humidification circuit and that this could then pour into the patient’s lungs, carrying bacteria with it. This can be avoided by appropriate positioning and checking of the hosing so that any condensate drains back into the humidification chamber.

Initial studies using HHs aimed to deliver gases at 32-34°C to replicate the normal conditions of inspired gases in the trachea. However, the work of Williams et al (183, 272) suggests that inspired gases conditioned to any state other than core body temperature and 100% relative humidity impose a burden on the patient’s airways. Conditioning of inspired gases to core body temperature and 100% relative humidity will be referred to as “full humidification”.

71
There have been concerns expressed that this strategy removes the normal temperature gradient in the airway thereby abolishing a normal physiological counter-current mechanism and eliminating the loss of heat and evaporated water from the airways (185). As mentioned previously, supporters of full humidification respond that the intubated airway is not normal and that it is important to remove any burden imposed on the airway by inspired gases (183, 272). There is also the possibility that humidifiers could deliver excess water to the airway. However, as HHs can only generate a maximum of 100% relative humidity, this would occur only through the delivery of gases at excess temperatures and full saturation. Nevertheless, airway injury may result if the temperature of the HH is not controlled and extreme temperatures result (275).

The first humidification circuits resulted in cooling of the gases in the hosing so that the gases delivered to the patient were not at the target conditions. This was a particular concern in ventilated infants where the hosing travelled within the infant's crib and the gases were initially cooled resulting in condensation, then warmed in the crib resulting in the delivery of warm dry gases (279, 280). Positioning the temperature probe as close as possible to the patient was found to be vital (281, 282). This reduced the length of hosing that was exposed to ambient temperatures beyond the sensor without heated wiring. Insulating the hosing also improved humidification of the delivered gases (281).

The humidification circuits that we elected to use in the current study are insulated, employ advanced temperature servo-control, and have the temperature sensor as close as possible to the patient. The humidifier is set so that the temperature of the gases is 38°C at the end of the hosing, in anticipation that there will be a slight fall in
gas temperature between the hosing and the patient’s trachea and thus the gas temperature at the point of inhalation will be 37°C.

### 2.13.2 Heat And Moisture Exchangers

HMEs consist of a core of hydrophobic material and a plastic housing. The hydrophobic material may be a simple piece of filter paper. The housing connects on to the tracheostomy and inspired and expired gases pass through the housing and core material. A proportion of warmth and moisture in expired air condenses on the core material and is then available to warm and humidify the next inspired breath.

The first HME, manufactured from aluminium foil, was designed in Sweden by Toremalm (283) and hence HMEs are commonly referred to as Swedish noses.

HMEs can be made more efficient by impregnating the core material with a hygroscopic salt, such as lithium or calcium, or by using hygroscopic foam which results in increased water content of the inspired gases. These HMEs are commonly known as Hygroscopic Condenser Humidifiers (HCHs) but will be referred to as “HCH-HMEs” in this thesis. If the hygroscopic salt used is lithium, the lithium may be systemically absorbed and reach potentially toxic levels, so HCH-HMEs containing lithium are best avoided for long-term use, especially in small infants (284, 285).

Currently available commercial HMEs generally use a calcium salt. At Starship Children’s Hospital (Auckland, New Zealand), non-hygroscopic HMEs are usually prescribed although HCH-HMEs are available. HMEs can be further modified to function as an effective bacterial filter. This only applies to HMEs used in ventilator circuits and not to those used for spontaneously breathing tracheostomised patients.

HMEs vary in the amount of warmth and moisture they deliver (286) and the efficiency of HMEs varies with the ambient conditions – improving as room temperature rises (287). Using a model of a mechanically ventilated adult lung with
inspired gases at 21°C and expired gases at 34°C, Branson and Davis (286) showed that the moisture output of 21 different HMEs varied from 19.6 to 33.2 mg H₂O/L. The non-hygroscopic HMEs all delivered less than 30 mg H₂O/L. Using a model of a spontaneously breathing laryngectomised adult, Grolman et al (288) found that the moisture output of four HMEs was below 25 mg H₂O/L.

In vivo studies have been limited technically by difficulties developing temperature probes with the rapid response times required to measure the cycle of changing temperatures with inspiration and expiration. Hygrometers also become inaccurate when condensate forms on their surfaces which is common in in vivo models. Thomachot et al (138) compared a HH, a HME and a cold humidifier and assessed the temperature and humidity of the inspired gases using a rapidly responsive temperature probe with ten patients receiving each of the treatments in a random order. After 24 hours, the HME (Trach-Vent® filter, Gibeck Respiration AB, Sweden) delivered gases at a mean of 29.6°C and 98.2% relative humidity. This was similar to the HH which had been set to deliver gases at between 30°C and 32°C. No clinical outcomes were measured. McRae et al (289) measured inspired gas temperature and humidity in 25 laryngectomised adult patients and found that inspired gases were delivered at 29°C and 19 mg/L absolute humidity using a HME selected on the basis of its airway resistance properties. However, the aim of this study was to look at airway resistance not humidification and the probe used had a long response time. Keck et al (290) measured tracheal temperature and humidity in 20 laryngectomised adult patients using a thermocouple device. The use of a HME (Prim-Air System, Heimomed, Kerpen, Germany) compared to breathing room air raised intra-tracheal end-inspiratory temperature from 28°C to 29.5°C and absolute humidity from 13 mg/L to 20 mg/L (all results approximate as read from figure in publication). There was a rapid return to near baseline on removal of the HME. These authors also found that the use of a HME reduced evaporative and total respiratory energy losses from the
patients but not convective heat losses (291). Conversely, Zuur et al (292) developed a novel rapidly responsive device to measure \textit{in vivo} intra-tracheal temperature and humidity which was resistant to the confounding effects of condensation. A HME (Provox HME, type “Regular”, Atos Medical, Hörby, Sweden) in ten adult laryngectomised patients delivered temperature on inspiration of 26.9°C and absolute humidity of 26.6 mg/L compared to 21.4°C and 23.3 mg/L without the HME. The authors argued that the observed decrease in temperature of inspired gases with the HME was due to evaporative energy losses and proposed increasing the thermal capacity of HME materials.

A more recent advance is to add a heating plate or heated circuit to the HME to increase its efficiency (293, 294). However, these devices are not yet widely available and even these deliver inspired gases below 32°C at a mean of 31.9°C and 34.3 mg/L absolute humidity \textit{in vitro}, with similar performance \textit{in vivo} in adult patients being mechanically ventilated for acute respiratory failure. These authors also assessed the performance of two standard HMEs \textit{in vitro} and found they delivered inspired gases at a mean below 30°C and 30 mg/L absolute humidity.

There are few studies assessing the effectiveness of HMEs in children. Schiffman et al (295) found that in infants, during six hours of anaesthesia, a HCH-HME delivered inspired gases at 32-34 mg H₂O/L. Fassassi et al (296) compared a Humidvent® mini HME (Gibeck, Upplands Vasby, Sweden) to a HH (MR 730® AGM, Fisher & Paykel, New Zealand) set to deliver inspired gases at 37°C and 40 mg/L absolute humidity in fourteen ventilated premature and term neonates. Gases delivered via the HME ranged in temperature from 29.8°C to 38°C after 15 minutes of ventilation depending on the temperature of the incubator in which the baby was placed. Delivered humidification also varied from 27.8 mg/L to 37.7 mg/L. Gases delivered via the HH also varied in temperature with the incubator temperature but were higher than with
HME and no patient received gases less than 32°C. There was no difference in work of breathing as measured by transpulmonary pressure between the two devices.

Extrapolating from these studies, a non-hygroscopic HME may deliver less than 32 mg H₂O/L of moisture in infants, which is below the current American Thoracic Society guidelines (3). The HME used as standard practice at Starship Children's Hospital and planned to be used in our study is the Sims/Portex Thermovent T Heat and Moisture Exchanger which delivers 25 mg/L H₂O at International Organization for Standardization (ISO) testing conditions which is a tidal volume of 1000 mL and ten breaths per minute (product information sheet). However, the efficiency of HMEs falls as expiratory flow increases (297). We would therefore expect the performance of HMEs in children to be better than stated by the manufacturer as children have lower flow rates than those used in ISO testing. The efficiency of HMEs also falls in the presence of an airway leak such as a loose connection or leak around the vocal cords (298).

HMEs add an additional dead space and resistance to the ventilation circuit or airway which increase the work of breathing (299-302). Secretions, blood, moisture, or pulmonary oedema adherent to the filter also further increase the resistance of the HME (303, 304). This may result in complete occlusion of the filter and difficulty ventilating the patient (305-308). HMEs should not be used in the same circuit as a HH because of this risk (305). The additional resistance of a HME is generally not significant (309, 310) but may become important in patients with acute respiratory failure resulting in a rise in the partial pressure of carbon dioxide in arterial blood (PaCO₂) or a compensatory rise in minute ventilation and difficulty weaning from invasive ventilation (311-316). In spontaneously breathing tracheostomised patients a HME was found to impose a resistance that was significant at high ventilation volumes but not significant during quiet breathing (317, 318). The measured
resistance of HMEs used for tracheostomised adults is slightly lower than that of the normal intact upper airway, but the resistance of the tracheostomy tube itself was not included in this comparison (288, 318).

Any increased dead space or resistance imposed by a HME is more significant in infants and may cause problems even before the accumulation of moisture on the HME (319). Chau et al (320) measured the effect of adding a bacterial filter HME (Brathwaites Oliver Medical Aquesure Anesthesia Bacterial/Viral Filter with Gas Sampling Port) to the anaesthetic circuit in 20 children under the age of two years undergoing anaesthesia. They found a mean increase in minute ventilation of 112.6 ± 60% was required to maintain end-tidal carbon dioxide at 4.6 kPa due to the increase in dead-space. There was a strong inverse relationship between required increased minute ventilation and patient weight. In the same journal issue, Bell et al (321) assessed the effect of adding a HME (Clear-Therm® micro-HMEF, Intersurgical Ltd, Wokingham, UK) to the anaesthetic circuit on work of breathing in ten infants. Measurements were taken toward the end of anaesthesia and after reversal of any paralysing agents. These authors found a 43% (95% CI, 25–138%) increase in work of breathing with the addition of the HME to the circuit as compared with a HH (Fisher and Paykel, Auckland, New Zealand). Unlike the previous study, there was no relationship with patient weight.

2.13.3 Nebulisers

Nebulisers are a further option for the humidification of inspired gases. Nebulisers generate an aerosol of droplets, usually of normal saline, which is then inspired by the patient. The aerosol delivers the water droplets to the respiratory mucosa but also generates some humidity through evaporation of water from the droplets.
Nebulisers have a number of disadvantages: the delivery of bacteria in the droplets (322), atelectasis caused by the droplets, and the potential to deliver excess water to the airways. These issues are discussed above in section 2.11 Effects of Excess Moisture. Because of these adverse effects nebulisers were not considered for this study and will not be discussed further.

2.14 Clinical Studies Comparing Humidification Techniques

In this section I will describe clinical trials that have directly compared HMEs to HHs. These studies have compared the effects on the work of breathing, on airway suctioning and the need for suctioning, as well as more significant clinical outcomes such as endotracheal blockages and episodes of pneumonia. It should be noted that many of these studies excluded patients with thick secretions and these excluded patients were treated with heated humidification.

Williams et al (323) reviewed the literature on humidification of inspired gases and pooled the data from the then available experimental studies in 1996. Their interpretation was that inspiring inadequately conditioned gases causes a burden in terms of moisture and energy on the airways and this burden results in a range of effects that are dependent on the degree of burden and the duration of exposure. Initially mucus becomes thick, then tracheal mucus flow ceases, then cilia cease beating and, lastly, there is cell death. Excess humidification causes the same effects. Given that the effects of inadequate humidification worsen with duration of exposure and that the intubated airway is abnormal due to the intubation itself and the underlying state of the patient, they felt that the ideal inspired gases would be that which placed no burden on the airway, i.e. 37°C and 100% relative humidity. In a subsequent experiment this group demonstrated that only inspired gases at 37°C and 100% relative humidity did not impose energy work on the airway to condition the gases (183).
The studies comparing HMEs to HHs suffer from a number of controversies that evolved with improving knowledge. Initial studies in vivo in ventilated ICU patients used non-hygroscopic HMEs which were found to be ineffective. The later studies using effective HCH-HMEs have been conflicting as to whether HHs or HMEs had better outcomes. Most studies have used a HH set to deliver gases at 30-34°C as this has been the standard of care until the late 1990s, with few studies using 37°C.

There has also been controversy around the use of saline instillation as a source of additional moisture. Some studies used instillation on a regular schedule whereas others used instillation on an as needed basis. The use of saline instillation may bias results by eliminating the difference between heated humidification and the HME. In later studies regular saline instillation has not been used as it is not a recommended clinical practice (324-327).

Lastly, there is controversy over the ideal level of conditioning at which inspired gases should be delivered with some authors recommending that inspired gases should be delivered at the same conditions as exist in the normal intact trachea, 32-34°C and 90-100% relative humidity, while other authors recommend delivering inspired gases at core body temperature and 100% relative humidity.

### 2.14.1 Work Of Breathing

The addition of a HME increases the dead space in the ventilation circuit or on the end of the tracheostomy tube. This does not occur with the use of a HH. In addition, the additional resistance of the filter may be significant with the use of a HME.

Johnson et al (300) measured the resistance in eleven commercially available HMEs after 24 hours of use by a group of 50 adult patients. This resistance was then added
via a resistor to the circuit of 40 patients who were ventilated or on continuous positive airway pressure (CPAP), resulting in a small but significant decrease in peak flow and minute volume.

Romano et al (310) found a small, clinically unimportant but statistically significant increase in PaCO2 (33.9 mmHg vs. 32.6 mmHg, P < 0.05) in 81 adult patients with the use of a HME added to a ventilatory circuit. A HH was not used in that study. Iotti et al (301) and Pelosi et al (311) compared the ventilatory effects of HMEs versus a HH in ten and fourteen adult patients respectively ventilated in ICU. Using a HME increased dead space and inspiratory resistance and hence ventilatory requirements, although almost all the increase in inspiratory work was imposed on the ventilator rather than the patient. The increased resistance was higher in vivo than expected from preparatory in vitro measurements. There was also an increase in dynamic positive end-expiratory pressure (PEEP) with the HME which resulted in pulmonary hyperinflation. Neither study showed a change in arterial blood gases, probably due to the compensatory increase in ventilation (311).

Le Bourdelles et al (328) studied 15 adult patients being weaned from mechanical ventilation in a randomised cross-over study and found an increase in minute ventilation, respiratory rate and PaCO2 (44 vs. 42 mmHg, p< 0.005) but not tidal volume with a HME compared to a HH. Jaber et al (312) found an increase in minute ventilation and a small but statistically significant increase in PaCO2 (43.4 vs. 40.8 mmHg, p < 0.005) with the HME in 24 adult patients on NIV in a cross-over study comparing a HME to a HH.

In a non-randomised study, Prin et al (315) studied eleven patients with Acute Respiratory Distress Syndrome (ARDS) with patients developing hypercapnoea on HME being changed to HH. This resulted in an improvement in pH and PaCO2 (67
vs. 56 mmHg, p = 0.003) but, unlike the previous studies, no change in respiratory rate, minute ventilation, or intrinsic PEEP was observed. Prat et al (314) studied ten patients with ARDS and found that replacing the HME with a HH resulted in a significant improvement in pH and PaCO$_2$ (80.3 vs. 63.6 mmHg, p < 0.05) with the same ventilatory findings as Prin et al. Indalecio et al (329) also found a reduction in PaCO$_2$ (46 vs. 40 mmHg, P < 0.001) and an improvement in respiratory compliance with the substitution of a HH for a HME in 17 patients with ARDS.

These studies show that the use of a HME as compared to HH adds airway resistance and dead-space to the respiratory system sufficient to cause an increase in work of breathing and a rise in PaCO$_2$. This rise in PaCO$_2$ is usually not clinically significant but in severely unwell patients clinically significant rises are seen.

### 2.14.2 Effects On Mucus And Requirement For Suctioning

Nakagawa et al (330) showed no difference in mucus rheologic properties in 21 ICU patients randomly assigned to treatment with a HCH-HME or a HH set to deliver gases at 32°C. Boots et al (331) performed a large RCT in 116 patients ventilated in ICU with patients assigned to a HCH-HME or a HH set to deliver gases at 35°C. In contrast to other studies, they found that the HH patients had slightly thicker secretions and required more suctioning than the HME patients. Although the HH circuits were more readily colonised with bacteria, there was no difference in rates of VAP.

Alagar et al (332) presented a poster of a randomised trial comparing a Pall HME to a HH set to deliver 37°C. The HME group required more saline instillations and nebulisers to maintain thin secretions. Following these studies, I sought to test the hypothesis that children with tracheostomies will have improved airway secretion
characteristics (volume, colour and thickness) when receiving humidification during sleep via a HH compared to via a HME.

2.14.3 Endotracheal Tube Blockages

Cohen et al reported experience with ETT occlusions during a period of HME use compared to a subsequent period of HH use (333). During the 8-month HME period there were 15 episodes of ETT occlusion compared to one ETT occlusion in the 4-month HH period with a total of 170 patients treated. Most of the occlusions occurred in patients with minute volumes greater than 10 L/min. There was also a statistically significant increase in the incidence of pneumonia and atelectasis during the HME period.

Martin et al (334) conducted a study in 42 patients ventilated in ICU comparing a Pall filter HME to a HH set to deliver 30-32°C. The HME group had thicker airway secretions and six of the HME patients experienced tracheostomy tube blockages, one of whom died. No patients in the HH group experienced ETT or tracheostomy tube blockages. The authors noted that all the patients with tube blockages were being ventilated at minute volumes greater than 10 L/min and felt that the HME in this study did not perform adequately at these high volumes. They performed two follow-up studies at minute volumes greater than 10 L/min (335, 336) and demonstrated that the Pall filter BB50 (a passive HME) did not perform as well at these volumes as a HH set to deliver 32-34°C. Two HCH-HMEs (Pall Ultipor HME and Hygrobac filter HME) performed close to the HH systems but performance declined over 24 hours in one HCH-HME. Sottiaux et al (337) independently confirmed the poor performance of the Pall BB50 HME compared to the two HCH-HMEs used in these studies. Subsequent studies have not used the Pall BB50.
Misset et al (338) also compared a HME to an HH in 56 patients ventilated long term and noted that secretions became thicker and more saline instillations were required by day five. However, the use of HH resulted in a greater nursing workload due to dealing with condensation and more frequent circuit changes so the authors recommended that HMEs were a viable option for up to five days if used cautiously.

Branson et al prospectively used a similar protocol and compared up to five days of HME to HH in an ICU (339). Patients were allocated to start on HCH-HME (88 patients) unless they had thick secretions (32 patients). Subsequently ten patients were switched to HH due to thick secretions. Patients treated with HCH-HME had thicker secretions but by monitoring secretions and limiting HCH-HME use to five days they were able to prevent ETT occlusions and reduce costs. In a randomised study of 300 patients in an ICU, Kollef et al (340) were able to use a HCH-HME for seven days without any tube occlusions with close patient monitoring.

Roustan et al (341) also compared a HH set to deliver 31-32°C to a HCH-HME. They studied 116 patients undergoing prolonged ventilation in ICU and found a decreased rate of ETT occlusion in the HH group (0 vs. 9, p<0.001).

Villafane et al (342) demonstrated a reduction in the internal diameter of ETT by the accretion of secretions in 23 ventilated patients in ICU using HME versus HH. There were 3 ETT occlusions in the HME group and 1 in the HH group but this difference was not significant. The authors noted that occluded ETTs had dried secretions relatively homogenously adherent to the inside of the ETT. In a further study (343), the same group compared HH to HME in 24 patients ventilated long term and noted a greater increase in reduced ETT internal volume and increased resistance in the HME treated versus the HH treated patients which started at about five days and was definite by ten days of treatment. There was no difference in occlusions in this study.
Hurni et al (344) compared a HCH-HME to a HH delivering 32°C in 115 patients receiving ventilation for at least 48 hours. Over five to seven days ventilation there was no difference in episodes of endotracheal occlusion or in cytology of the ciliated epithelium.

Luchetti et al (345) randomised patients to one of two HHs or HME (the Hygrobac HCH-HME). Patients in the HME group had a lower tracheal temperature and lower inspired absolute humidity and also an increased requirement for saline instillations (p<0.05) and increased ETT occlusions (3 vs. 0, p<0.05).

The recommended duration of use of a single HME without replacement has increased from 48 hours to seven days, based on evidence from RCTs. During this time period, Kapadia et al (346) noted a trend toward increased incidence of ETT occlusions in their database of 5046 patients ventilated in ICU in a retrospective review of all airway accidents. Interestingly, and in contrast to a previous retrospective study by the same authors (347), there was no difference in the rate of occlusions between tracheostomies and ETTs.

2.14.4 Pneumonia

The intensive care literature suggests that HHs may result in an increase in pneumonia in long-term ventilated patients. Some authors have suggested that HMEs are preferable to HHs as they act as a filter and reduce bacterial colonisation of the ventilator circuit. However, Dreyfuss et al (348) performed a careful quantitative bacterial study and showed that keeping the ventilator circuit clean of bacteria did not affect the rate of pneumonia and that the circuits are therefore not the source of infection.
Blin et al (349) presented a retrospective review comparing the rates of nosocomial pneumonias in different ICUs in different hospitals. Those patients ventilated in hospitals using HHs had a higher rate of nosocomial pneumonias than patients ventilated in hospitals using HMEs, with more gram negative infections. A further retrospective review comparing two treatment periods in an ICU involving 3585 patients showed no overall difference in VAP between a HME and a HH but a significant difference in patients ventilated greater than 48 hours (350). In contrast, Piedalue, in a review of change in practice over four years, reported a decrease in VAP with the use of a HH delivering gases at 37°C compared to 30-32°C (351).

In a RCT comparing a HME to a HH (334), those in the HH group had a higher rate of colonisation of their circuits and their airways. There was an increased incidence of nosocomial bronchopneumonia in the HH group (19% vs. 7%) although this did not reach statistical significance.

In contrast, Kollef et al (340) randomised patients to HCH-HME for up to seven days or HH (delivering 35-36°C) and showed no difference in the risk of VAP (9.2% vs. 10.2%, p 0.766). Dreyfuss et al (348) and Memish et al (352) also demonstrated no difference in the rates of VAP between a HCH-HME and HH (temperature not stated but assumed to be delivering 32-34°C).

Kirton et al randomised ICU trauma patients to HCH-HME or HH utilising a water bath at 37°C (353) and showed a significant increase in the rates of nosocomial pneumonia in the HH group (15.7% vs. 6.4%, p < 0.05). There was no difference in the incidence of partial or complete ETT occlusions. The authors also found no difference to the work of breathing.
Kola et al (354) performed a meta-analysis of eight RCTs involving 1368 patients comparing HME to HH regarding the rate of VAP and found a reduced relative risk of 0.69 (95% CI 0.51-0.94) with the use of HME or 0.57 (95% CI 0.38-0.83) in patients ventilated greater than seven days. Only four studies used a microbiologically confirmed diagnosis of VAP and the pooled relative risk from those papers was 0.83 (95% CI 0.49–1.42). The results were dominated by the numbers from one study (353). The authors noted that generalisation of the results is limited as many of the studies excluded patients with thick secretions or other potential contra-indications to HME use prior to enrolment.

In the short-term clinical trials described, all the studies found an increase in the thickness of airway secretions with the use of a HME versus HH. However, this resulted in an increase in the more clinically significant outcome of ETT blockages in only some trials. This should be interpreted cautiously as HME technology has significantly improved making these devices more effective. HH technology has also improved and the trend in the later studies appears to be that HHs are still more effective in reducing the risk of ETT blockage. The meta-analysis by Kola et al (354) found that there is an increase in VAP with HH compared to HME. However, the authors noted that patients with thick secretions have been excluded from trials and should be treated with HH. In addition, they recommended that after five to seven days all patients should be switched to HH as secretions become thick after this period of time.

The use of HMEs should continue to be avoided in patients with thick airway secretions. Although the use of HME has been shown to be adequate for short-term use it also appears to be a lower standard of care as all patients who remain intubated for more than a week need to be transferred to humidification via HH.
Therefore, HME use in this population should be reserved only for those patients who are anticipated to require a short-term period of intubation.

The conflicting data on the effects of HH on the incidence of pneumonia led me to test the hypothesis that children with tracheostomies will have fewer clinical events (chest infections, admissions to hospital, courses of antibiotics, and episodes of tracheostomy tube obstruction) when receiving humidification during sleep via a heated humidifier (HH) compared to via a heat and moisture exchanger (HME).

2.14.5 Comparative Studies in Infants and Children

There have been very few studies comparing HHs to HMEs in infants and children. The available studies are short-term during anaesthesia and are not of sufficient duration to generalise the findings to long-term spontaneously breathing patients. Bissonnette et al (173) randomly assigned 30 infants undergoing surgery to ventilation with gases humidified with a HH to 37°C and 100% relative humidity, gases conditioned with an HME or unconditioned gases. Core body hypothermia was best maintained with the HH. The HME delivered significantly less well humidified gases than the HH and took 60 minutes to reach a level of 80% relative humidity. However, the authors judged the performance of the HME to be clinically acceptable for short term anaesthesia. Schiffman et al (287) randomised 40 infants and neonates requiring mechanical ventilation to a HH delivering gases at 32°C and 34 mg/L absolute humidity or HME for a 6-hour period. They found no difference in delivery of absolute humidity between the two devices and no difference in clinical outcomes over a 6-hour period. They estimated significant potential financial savings with the HME due to a decreased frequency of ventilatory circuit changes.
2.15 Clinical Studies In Spontaneously Breathing Tracheostomised Patients

Although HMEs were utilised early in the 1970s and 1980s for ventilated patients, the use of humidification techniques for spontaneously breathing tracheostomy patients occurred much later, and in many countries is still not routine for adult patients. The studies below compare the use of a HME to no humidification in laryngectomised adults. There are no published long-term studies in children.

Myer et al (355) showed that the use of a HME in 18 tracheostomised dogs reversed the tracheal inflammatory changes that were seen with the inhalation of dry gases. In humans, Hilgers et al (356) showed that the use of HME compared to no humidification reduced the respiratory symptoms in 42 adult patients after total laryngectomy with a significant reduction found in the volume of airway secretions and the need for airway clearance as well as symptoms of fatigue and malaise. Vittaca et al (357) showed in a RCT of 40 patients that the addition of a HCH-HME compared to no humidification for a ten-day period improved the colour and viscosity of airway secretions. In addition, the patients treated with the HCH-HME acquired fewer new organisms in the airways during the study period.

Vitacca et al (317) assessed the respiratory mechanics in 21 adult patients breathing spontaneously through tracheostomies. The addition of a HME did not change breathing mechanics during quiet breathing or maximum voluntary ventilation compared to no humidification. Laryngectomy causes loss of the normal upper airway resistance and a subsequent deterioration in oxygenation (289, 358) which is thought to be due to decreased lung volumes (359). This is distinct to the situation in a child with a tracheostomy where the tracheostomy tube itself has some resistance.

Jones et al (358) designed a HME device to replace the normal filtering,
humidification and resistive function of the upper airway. In a RCT of 50 patients they reported decreased cough, mucus production and episodes of pneumonia with an improvement in oxygenation on arterial blood gas. However, there was also a high patient drop-out rate in subsequent clinical use. In contrast, Zuur et al (360) found no benefit on transcutaneous oxygen levels over a two-hour period from a resistive HME compared to no HME in a cross-over study of 20 laryngectomised adults.

Ackerstaff et al (361) conducted a multi-centre trial involving 81 adult laryngectomised patients. Participants were asked to compare symptoms before and after three months of HME use. Results from 59 regular users were presented showing 68% had decreased cough, 73% had decreased mucus production and 60% required less forceful clearing of secretions. However, this was not a randomised study and only subjective outcomes from a selected sub-group of the study population were presented.

In a small study, Keck et al (362) randomised ten adult tracheostomised patients to either intermittent HH use four times daily for 20 minutes or four times daily administration of an aerosol water spray. After one week of treatment there was no difference in symptom scores or in temperature or humidification measurements between the two treatments. Participants preferred the spray to the HH due to convenience.

2.17 Conclusion

The airway plays an important role as a heat and moisture exchanger, taking in gases that are relatively cool and dry and conditioning them to core body temperature and 100% relative humidity. This conditioning process occurs over a length of the airway, so that gases inspired at room temperature and humidity are generally at 32-34°C at the carina with further conditioning occurring in smaller
airways. The structure of the airway mucosa includes a layer that is predominantly water and acts as a store of large amounts of energy and moisture in the form of water. This store can be replenished from the mucosal cells and from the vascular supply to meet the demands of changes and extremes of inspired gases so that the intact airway is resistant to both frigid and hot gases.

Insertion of an artificial airway bypasses the upper airway which under normal conditions has the chief role in this heat and moisture exchange. Artificial airways also disrupt the function of the mucosa by obstructing mucus flow and by causing trauma to the mucosa through rubbing. The combination of an artificial airway and the inhalation of inadequately conditioned gases therefore results in inflammation, atelectasis, thick mucus, inspissation of secretions, and ETT or tracheostomy tube obstruction.

The current recommendations are for inspired gases to be delivered at conditions that match the natural conditions at the level of the carina, i.e. 32-34°C and 100% relative humidity (3). In the ICU or anaesthetic setting, HMEs are cheaper and require less nursing time to manage than HHs. However, they may not be as effective as HHs at delivering the required conditions and the in vitro performance data of commercially available HMEs for tracheostomy patients show that they deliver temperatures to the upper airway lower than those recommended. In addition, the effects of inadequate humidification become more marked with time and clinical trials show that in ventilated patients HMEs are only suitable for periods of up to seven days. In addition, patients with thick or blood-stained secretions have been excluded from studies comparing HMEs to HHs as these patients are felt to require the full benefits of heated humidification. However, there is a risk of increased infection with HH in patients ventilated in ICU which may due to bacterial colonization.
of condensate on hosing and equipment. It is uncertain how this translates to spontaneously breathing tracheostomised patients.

Some authors suggest that the intubated airway is abnormal and is unable to perform its heat and moisture exchange function efficiently (272). Full humidification, delivering inspired gases at 37°C and 100% relative humidity, is therefore recommended. This can only be achieved with the use of heated humidification and with the use of novel circuit hosing and advanced temperature servo-control. As this technology is only relatively recently available, this strategy has not yet been adequately tested in clinical trials. Furthermore, the spontaneously breathing tracheostomised patient is subject to different conditions than the intubated ventilated patient. Although chronic inflammation is present, the spontaneously breathing patient takes in gases at ambient room conditions rather than cold dry anaesthetic gases. This would suggest that less humidification therapy is required and current practice is that most adult patients do not receive any humidification treatment at all, although the clinical trials discussed in this chapter suggest that an HME improves clinical status as compared to no humidification therapy.

Children may be less able to cope with unconditioned inspired gases than adults due to:

- Their relative smaller size
- Their reduced ability to replace lost warmth from total body energy
- Their reduced ability to replace lost moisture from total body water
- An increased risk of occlusion due to smaller tracheostomy tubes

Current recommendations for spontaneously breathing tracheostomised children are the same as those for intubated ventilated adults; that they receive inspired gases
conditioned to the same conditions as are found at the carina in the normal airway, i.e. 32-34°C and 100% relative humidity (3). The HMEs available for children may not be adequately efficient to perform this level of conditioning and based on the literature on ventilated ICU patients, this strategy may be inadequate for long-term periods.

This literature review has found no clinical trials in children with tracheostomies comparing humidification devices or strategies for either short- or long-term periods. Based on anecdotal experience and one case series of two patients described in Chapter 1 (5) we postulated that spontaneously breathing tracheostomised children would have better outcomes when receiving inspired gases via a HH compared to a HME.
Chapter 3 Study Design and Statistical Methods

In this chapter I will describe the overall study design and statistical methods employed for conducting the studies that form this thesis. The specific methodologies for the technical measurement of clinical outcomes, mucociliary clearance and airway inflammation will be described together with the results in dedicated chapters. I performed two separate quantitative clinical studies and one qualitative study for this thesis, both being randomised partially observer-blinded two treatment cross-over studies. I will differentiate these studies as “the short-term study” and “the long-term study” respectively. I also performed, as an addendum to the long-term study, a qualitative study which I will discuss in Chapter 9.

3.1 The cross-over study design

The two studies for this thesis were both cross-over studies. A cross-over study is one in which each participant receives multiple treatments or interventions in separate treatment periods. When there are two treatments, there are two treatment periods and all participants receive both treatments, as in the studies for this thesis, the study is referred to as an “AB/BA” design. A cross-over design was selected for both the short-term and long-term studies due to the small numbers of available potential participants and because of the heterogeneity of the study population. This study design increases the power of a study compared to a parallel study design due to the use of paired statistical methods, elimination of baseline variability and the use of within-subject comparisons (363). This was important in the current study as children with tracheostomies form a highly heterogeneous group at variable ages, with a variety of diagnoses and co-morbidities.
The disadvantage of cross-over studies is an increase in burden to participants: each participant is in the study for a longer time, undergoes the risk of multiple treatments and multiple investigations and endures the inconvenience of more assessment visits than in a parallel-design study. This increases the risk of participants dropping out partway through the study and of having incomplete data collection (363).

Although cross-over design has statistical advantages in terms of statistical power and fewer subjects, there are problems with “carry-over effect” during analysis and controversies over how this problem should be handled. Carry-over is “the persistence (whether physically or in terms of effect) of a treatment applied in one period in a subsequent period of treatment” (363). This results in a form of bias where the effects of one treatment are contaminated by a previous treatment. There are two approaches to this problem which have been heavily debated in the literature. The first is to perform a two-stage statistical analysis to detect the presence of any significant carry-over and then to adjust the analysis accordingly (364, 365). However, this approach inflates the risk of a Type I error (363, 366).

The alternate approach, which does not inflate the risk of Type I error, is to design the study so that there is no carry-over effect by ensuring adequate time between assessments (363). This was the approach I employed for our study. This may be performed by using a washout period of no treatment between each period of sufficient duration that the effect of the first treatment has completely worn off. This method was used in the short-term study conducted for this thesis, where each child underwent a four-hour washout period with no treatment prior to each active treatment. For the long-term study I was concerned that a longer washout period would be necessary to affect clinical as opposed to physiological
outcomes. I also believed that participants required treatment with one of the two proposed treatments at all times (3). I, therefore, incorporated a two week “wash-in” period of active treatment to eliminate the effect of the previous treatment rather than a “washout” period of no treatment. During this wash-in period clinical outcomes were excluded from subsequent analysis, except for the outcome of “withdrawal from the study”.

In addition to the problem of carry-over effect, the conduct of a cross-over study assumes that participants are in a steady state and will not vary over time. For the short-term study this assumption can be held to be true. For the long-term study, I made this assumption on the basis that all the children were chronically tracheostomised and unlikely to vary in their clinical state until decannulation or removal of the tracheostomy occurred, followed by establishment of a normal airway. All analyses were adjusted for period-effect in case this assumption did not prove to be correct.

The data were analysed using the linear effects model commonly employed for cross-over studies (363, 364). In describing this model I have avoided the Greek symbols commonly used in statistical texts for easier understanding. In this model, the results (expected values) for an outcome at the end of a treatment period for subjects within each group can be predicted from a formula which contains effects for the treatment (A or B), the period (1 or 2), a subject effect and a carry-over effect. This study was designed so that carry-over effects would be negligible and the carry-over effect will be dropped from the equations presented for this discussion. So, for instance, for Subject X in Group One undergoing Treatment A in Period One, the Expected result would be expressed as follows:

\[ \text{Expected}(T\alpha P\beta S\gamma) = \text{Treat}(A) + \text{Period}(1) + \text{Subject}(X) \]
Subject Y in Group 2 would undergo Treatment B in Period One and would have the following Expected result expressed as follows:

\[ \text{Expected}(T_{B}P_{1}S_{y}) = \text{Treat}(B) + \text{Period}(1) + \text{Subject}(Y) \]

General or generalised linear models utilising the above model were used for this study and were able to be programmed directly using the SAS statistical software. An alternative analysis would be to compare the mean period differences between the two groups, utilising paired statistics (363). For normally distributed data this can be estimated using a paired Student t-test. Non-parametric rank tests, such as the Wilcoxon-matched pairs test for continuous data and the McNemar test (363, 364) for binary outcomes may also be utilised with this approach.

### 3.2 Treatment concealment

The two studies were both partially observer-blinded studies. As the two treatments in this study involved the use of pieces of equipment by the parents of participants, it was, therefore, not possible to conceal treatment allocation from the parents, medical staff, nursing staff or me. It is contra-indicated to use a HME in conjunction with a HH, due to increased airway resistance in the filter, so it was not possible to modify the equipment to attempt treatment concealment. In order that I personally managed treatment and the conduct of the studies it was also not desirable for me to be blinded to treatment allocation.

However, treatment allocation was able to be concealed from individuals performing certain of the measurements in this study. Specifically, this included measurements of mucociliary clearance, cilia beat frequency, airway biopsy
inflammation, airway secretion cytokine levels, airway secretion cell counts and microbiological culture. Individuals conducting these measurements did not have direct contact with the participants and were unaware of treatment allocation. Clinical assessment and examination were not blinded. Clinical outcomes such as tracheostomy tube occlusions, emergency changes and withdrawal from the study were reported by parents and not controlled by study investigators. Admissions were determined by the attending physician and were not influenced by participants being involved in the research study.

3.3 Description of the Short-term study

Treatment for the short-term study was preceded by a night of treatment with a HH followed by a four hour “washout period” with no humidification treatment (Figure 3.1). Participants (children with tracheostomies) were randomised to receive 20 hours of humidification treatment with either a HME or HH. Assessments were performed at baseline (following the washout period), after two hours of treatment and after a further 18 hours of treatment (20 hours total). Participants then received a period of treatment overnight with HH. Prior to the second period of treatment participants underwent a repeat four-hour washout period with no humidification treatment from either device. Participants then received 20 hours of treatment with the alternate treatment, either HH or HME. Assessments took place at the same time points as the first treatment period (Table 3.1). Each participant received both treatments for 20 hours. Treatment allocation was performed according to computer generated random number tables.
HH = heated humidifier, HME = heat and moisture exchanger. Humid = humidification treatment (either HH or HME).

Figure 3.1: Study design for short-term study.
### Table 3.1: Timing of assessments for short-term study.

<table>
<thead>
<tr>
<th></th>
<th>Enrolment</th>
<th>Baseline Each Period (1200h)</th>
<th>After 2 Hours Treatment Each Period (1400h)</th>
<th>Overnight During Treatment Each Period</th>
<th>End Each Treatment Period (0800h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture and gram stain</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Clinical Examination</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Overnight oxygenation</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suction frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

### 3.3.1 Inclusion and Exclusion Criteria Short-term Study

The aim was to study infants and children with tracheostomies during a relatively stable period. In order to maximise recruitment I approached families soon after insertion of the tracheostomy but prior to discharge from hospital. Some children with a longer prior duration of cannulation were also included. The inclusion criteria for the short-term study were:

- A tracheostomy tube change had been performed safely
- Child is a hospital inpatient while parents receive education or is a resident at a rehabilitation facility
- Parents gave written informed consent

The exclusion criteria for the short-term study were:

- Thick airway secretions or other contraindication to stopping heated humidification
- Known Cystic Fibrosis (CF)
- Known Primary Ciliary Dyskinesia (PCD)
- Known Primary Immune Deficiency (PID)

Recruitment for the short-term study was conducted from November 2005 to August 2007.

3.3.2 Statistical Methods Short-term Study

Data was entered onto a Microsoft Access © 2003 database (Microsoft, Seattle, USA) and analysed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). Microsoft Excel © 2003 (Microsoft, Seattle, USA) was used to produce some figures. The analysis plan was conducted following the recommendations of a textbook on the analysis of cross-over studies (363) with additional advice from a professional biostatistician (Mr Alistair Stewart, School of Population Health, The University of Auckland). Paired comparisons allowing for period effects and fixed subject effects were employed through general and generalised linear models and within-subject contrasts. For non-normally distributed data diagnostic plots of the residual distributions were performed and log or square root transformations performed if the residual plots did not show an appropriate distribution.

3.3.3 Sample Size Calculation for Short-term Study

For the short-term study a power calculation was performed for the primary outcome of mucus viscoelasticity impedance. The sample size calculation assumed a difference between the means of 0.3 and a standard deviation of the difference of 0.5 showed that a sample size of 15 gave a power of 80% and significance of 5%. Regrettably, this outcome subsequently was unable to be assessed due to late difficulties in communicating with and transporting samples to co-investigators in Canada. Therefore, other outcomes are reported for this study.
3.4 Description of Long-Term Study

In the long-term study participants were randomised to an initial ten weeks of humidification treatment at night with either the HH or the HME (Figure 3.2). All participants used the HME during the day to enable mobility and normal development. There was no washout period for prior treatment, instead the first two weeks of treatment were considered a “wash-in” period with active treatment followed by eight weeks of full active treatment. This was because it was considered unethical not to provide an active treatment based on current treatment guidelines (3). Participants underwent assessment at baseline prior to the wash-in period and at the end of the 10-week treatment period (Table 3.2). They then received treatment with the alternate treatment regimen of either the HME or HH at night, undergoing assessment at the same time points as in the first treatment period.

Randomisation was according to a computer-generated random number table. In order to maintain concealment of treatment allocation until enrolment was complete, a computer-generated table was created by an independent individual. Treatment allocations were double-sealed inside envelopes which were opened in recruitment order.
Fig. 3.2: Study design for long-term study.

HH = heated humidifier, HME = heat and moisture exchanger, HRQOL = health-related quality of life, MCC scan = mucociliary clearance scan.
Table 3.2: Timing of assessments for long-term study.

3.4.1 Inclusion and Exclusion Criteria for Long-term Study

For the long-term study the inclusion criteria were designed to enrol chronically tracheostomised children during a clinically stable period and were:

- Children under the care of the Starship Ear Nose and Throat (ENT) or Respiratory service who have a tracheostomy tube in place
- Tracheostomy in situ for at least three months
- Age greater than six months
- Tracheostomy scheduled to be in situ for the study duration (>20 weeks)
- Parents gave written informed consent

The exclusion criteria for the long-term study were designed to avoid selecting children with an underlying disorder which might result in thick mucus and/or affect the results of the study and were:
- Tracheostomy likely to be removed before the end of the study
- HH or HME not tolerated in the past
- Not tolerating heated humidification at least five nights per week for most of their sleep
- Not adherent to heated humidification three or more nights per week
- Thick airway secretions or other contraindication to stopping heated humidification
- Known CF, PCD or PID
- Palliative care (expected or likely death during study period)

Recruitment for the long-term study ran from November 2004 to August 2006.

### 3.4.2 Statistical Analysis for Long-term Study

Data was entered onto a Microsoft Access © 2003 database (Microsoft, Seattle, USA) and analysed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). Microsoft Excel © 2003 (Microsoft, Seattle, USA) was used to produce some figures. Analysis was conducted following the recommendations of a textbook on the analysis of cross-over studies (363) with additional advice from a professional statistician (Mr Alistair Stewart, School of Population Health, The University of Auckland). Paired comparisons allowing for period effects and fixed subject effects were employed through general and generalised linear models and within-subject contrasts. Diagnostic plots were performed to ensure normal distribution of the residuals and data square root or log-transformed if the residuals were not normally distributed.

Time-to-event comparisons were performed for this study using survival analysis statistical techniques described by Feingold and Gillespie (367). These authors proposed a modification of a permutation test initially proposed by Wilcoxon. This test is also recommended in the statistical text followed for this research (363).
3.4.3 Sample Size Calculation for Long-term Study

For the long-term study a sample size analysis was conducted for the primary outcomes of the occurrence of a clinical event and for the outcome of the mucociliary clearance (MCC) scan. The sample size calculation was based on the MCC scan and assumed a difference between the means of 10% and a standard deviation of 15% and showed a sample size of 24 would give a power of 90% and significance of 5%. To allow for drop-outs and missing data, a sample size of 30 was chosen for the study.

3.5 Devices Used in the Study

As described in the literature review (Chapter One), HMEs capture exhaled warmth and moisture on filter paper or on hygroscopic material. This energy and moisture is then available to warm and humidify the next inspired breath. The HME used in this study was the Sims/Portex Thermovent-T Heat and Moisture Exchanger (Sims Portex, Myers, Florida, USA). This device weighs 5 grams, has a filter resistance of 2 mm H₂O, dead space of 7 mL and delivers humidification of 25 mg H₂O/L and 34°C at a tidal volume of 500mL according to the manufacturer’s specifications. The HME is a small barrel-like object constructed of plastic housing which fits onto the end of the child’s tracheostomy (Figures 1.4 – 1.6). At each end of the barrel is a length of corrugated filter paper which acts as the heat and moisture exchanger.

The HH used in this study (Figures 1.2 and 1.3) was a Fisher & Paykel Healthcare MR850 humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) set to deliver air conditioned to 37°C and 100% relative humidity. The heated humidification circuit comprised a HC211 CPAP unit, to generate air flow and the MR850 HH with the HC300 or MR290 humidifier chamber (Fisher & Paykel Healthcare) (Figure 1.2). A resistor and blow-off piece were incorporated
into the circuit which enabled a pre-determined flow based on the child’s weight to be delivered in order to prevent accumulation of carbon dioxide in the circuit dead-space. The humidified air was delivered via heated hosing (HC505 Fisher & Paykel) and a paediatric tracheostomy mask (Hudson RCI, Arligton Heights, Illinois, USA) to the patient’s tracheostomy (Figure 1.3). The heated hosing incorporated temperature sensors so that servo-control within the MR850 enabled the humidified air to be delivered to the child at the correct temperature. The HC211 CPAP unit, which blows the air to be humidified, was fitted with software that enabled the number of hours of use to be measured. This was used to assess compliance.
Chapter 4 Clinical Outcomes Short-term Study

In this chapter I will describe the clinical outcomes for the short-term study. These outcomes include demographic details from enrolment, responses to questionnaires, findings on clinical examination, physiological recordings and clinical events. The chapter is divided into a Methods and a Results section.

As described in Chapter Three this was a cross-over study with two treatment periods. Each treatment period was preceded by four hours of a wash-out period with no treatment. The treatment period was for 18 hours with either the HME or the HH. The treatment order was randomised although allocation and treatment were not concealed for clinical outcomes.

4.1 Methods

4.1.1 Clinical Examination

Clinical examination was performed at each assessment time point (midday, 1400h and 0800h) while the child was awake. Examination was performed five minutes after suctioning to allow any tachypnoea or respiratory distress caused by excess mucus in the airway or by suctioning to resolve. Clinical examination was performed by the principal investigator (either Dr Jaksic or myself) according to a written schedule and standardised criteria (Table 4.1) derived from a previous study in children with asthma and bronchiolitis (368). This scoring system was selected from other scoring systems as it had been validated between both medical and nursing staff demonstrating good inter-observer agreement. The score incorporates a four-point (0-3) scoring system for severity for the following four items:

- Respiratory rate measured over one minute compared to normal for age
- Retractions
- Wheeze
- Dyspnoea judged according to feeding, activity and level of consciousness
- Crepitations or crackles on auscultation of the chest

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Dyspnoea</strong></td>
<td>None: Normal feeding, vocalisation and activity</td>
</tr>
<tr>
<td><strong>Retractions</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Wheeze</strong></td>
<td>No wheeze</td>
</tr>
<tr>
<td><strong>Crackles</strong></td>
<td>Normal breathing, no crackles present</td>
</tr>
</tbody>
</table>

Table 4.1 Scoring criteria for clinical examination findings (368).

Five minutes after suctioning, oxygen saturation was measured by a pulse oximeter (Masimo Radical Oximeter, Masimo, Irvine, California) during a period of quiet breathing. A representative measurement was taken from observing for one minute's duration.
4.1.2 Suctioning of Tracheostomy

In addition to clinical examination, a score was also applied to the appearance of the mucus which was suctioned from the tracheostomy (Table 4.2). Suctioning of the tracheostomy and assessment of secretions was performed by the principal investigator according to a standardised technique. The HME was removed and the external lumen of the tracheostomy tube wiped clean with sterile gauze. A size 8g French suction catheter with thumb trap (Triflo suction catheter with control port, Allegiance Healthcare Corporation) was inserted down the tracheostomy tube lumen to a predetermined depth of one centimetre beyond the terminal end of the tube. Suction was applied at 100 mmHg and the suction catheter slowly withdrawn until it was at the tracheostomy stoma opening. Gentle swirling of the catheter occurred during withdrawal. The catheter was then reinserted, rotated 90 degrees with suction continuing to be applied. The catheter was then completely withdrawn and the HME replaced. In cases for which no aspirate was obtained in the suction catheter on the first attempt, 0.1 mL of normal saline was gently introduced into the tracheostomy. After a 30-second pause suctioning was repeated. The sample of airway secretions was retained in the thumb trap and transferred to a 0.5 mL nunc tube with o-ring for subsequent analysis (Chapter 7).

The secretions aspirated from the tracheostomy were then inspected visually and a score on a three-point scale applied to the thickness of the secretions after one mL of normal saline had been aspirated through the catheter (339, 369). Scores were also applied to the difficulty of catheter insertion, the colour of the secretions and the volume of the secretions.
Table 4.2 Scoring criteria for assessing airway secretions following suctioning of the tracheostomy (339).

4.1.3 Overnight Oxygenation

Overnight oxygenation was assessed by continuous recordings downloaded from a Masimo Radical Oximeter (Masimo, Irvine, California) with the averaging time set to eight seconds. The data held on the oximeter was cleared prior to recording. The oximeter was attached to a finger or toe as per standard hospital protocol. Preferentially this was a toe and a sock worn over the probe to prevent interference by ambient light. For children on oxygen staff were asked to keep oxygen flow constant if possible and to record any changes in delivered oxygen levels. Children on oxygen were excluded from statistical analysis as fractional inspired oxygen concentration could not be replicated between the HH and the HME. In the morning the data was downloaded from the oximeter onto Profox software (Profox Escondido, California). For analysis, periods of artefact or poor signal quality were excluded and the average baseline saturation through the night recorded.
4.1.4 Overnight Cares

Ward staff and parents were asked to record overnight suctioning and any changes in oxygen delivery on a prepared form. The frequency of suctioning required was compared between treatments. Tracheostomy tube blockage was defined as obstruction of the tracheostomy tube with secretions which did not clear with suctioning, and required an emergency tracheostomy tube change.

4.2 Results

Fifteen children were enrolled in the study, eight male and seven female (Table 4.3 and 4.4). The mean age at enrolment was 4.34 years (range 0.08 – 17.08) and mean duration of tracheostomy 1.41 years (range 0.02 – 16.75). Craniofacial abnormalities, including Pierre Robin sequence, were the most common indication for tracheostomy, followed by neurological causes and subglottic stenosis. Ten of the children had other co-morbidities, as listed in table 4.3, with neurological problems being the most common. The majority of children were identified as New Zealand European or Pakeha with significant proportions of Maori and Pacific Island. All children completed the study with no protocol violations.
<table>
<thead>
<tr>
<th>Participant</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Age at enrolment (years)</th>
<th>Age at tracheostomy (years)</th>
<th>Duration of tracheostomy (months)</th>
<th>Indication for tracheostomy</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Maori</td>
<td>1.08</td>
<td>0.92</td>
<td>30.00</td>
<td>Failed extubation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>NZE</td>
<td>2.08</td>
<td>2.00</td>
<td>1.00</td>
<td>Crouzon's syndrome</td>
<td>Chiari malformation</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Pacific Island</td>
<td>0.67</td>
<td>0.58</td>
<td>2.00</td>
<td>Cystic hygroma</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Pacific Island</td>
<td>0.17</td>
<td>0.08</td>
<td>0.50</td>
<td>Tracheomalacia</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>Brazilian</td>
<td>0.17</td>
<td>0.21</td>
<td>0.25</td>
<td>Subglottic stenosis</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>Maori</td>
<td>15.75</td>
<td>15.67</td>
<td>1.00</td>
<td>Trauma</td>
<td>Brain injury</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>NZE</td>
<td>0.17</td>
<td>0.17</td>
<td>0.25</td>
<td>Haemangioma</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>NZE</td>
<td>17.08</td>
<td>0.33</td>
<td>201.00</td>
<td>Neurologic laryngomalacia</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>NZE</td>
<td>16.08</td>
<td>15.17</td>
<td>12.00</td>
<td>Bulbar palsy</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>NZE</td>
<td>10.50</td>
<td>10.50</td>
<td>0.75</td>
<td>Hunter's syndrome</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>Chinese</td>
<td>0.08</td>
<td>0.02</td>
<td>0.50</td>
<td>Pierre Robin sequence</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>Pacific Island</td>
<td>0.25</td>
<td>0.17</td>
<td>1.00</td>
<td>Treacher Collins</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>Maori</td>
<td>0.33</td>
<td>0.29</td>
<td>0.75</td>
<td>Subglottic stenosis</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>NZE</td>
<td>0.33</td>
<td>0.25</td>
<td>0.50</td>
<td>Pierre Robin sequence</td>
<td>Pierre Robin sequence</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>Pacific Island</td>
<td>0.33</td>
<td>0.17</td>
<td>2.00</td>
<td>Tracheomalacia</td>
<td>Pierre Robin sequence</td>
</tr>
</tbody>
</table>

NZE = New Zealand European

Table 4.3: Individual participant demographic details at enrolment for short-term study.
Table 4.4: Summary table showing participant’s demographic details at enrolment for short-term study.

<table>
<thead>
<tr>
<th></th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female</td>
<td>8 : 7</td>
</tr>
<tr>
<td>Mean child’s age at enrolment</td>
<td>4.34 years (range 0.08 – 17.08)</td>
</tr>
<tr>
<td>Mean child’s age at tracheostomy</td>
<td>3.10 years (range 0.02 – 15.70)</td>
</tr>
<tr>
<td>Mean duration of tracheostomy at enrolment</td>
<td>1.41 years (range 0.02 – 16.75)</td>
</tr>
<tr>
<td>Indication for tracheostomy</td>
<td>Subglottic stenosis 2</td>
</tr>
<tr>
<td></td>
<td>Vocal cord paralysis 1</td>
</tr>
<tr>
<td></td>
<td>Tracheomalacia 1</td>
</tr>
<tr>
<td></td>
<td>Pierre Robin sequence 3</td>
</tr>
<tr>
<td></td>
<td>Other craniofacial syndrome 3</td>
</tr>
<tr>
<td></td>
<td>Central neurological cause 3</td>
</tr>
<tr>
<td></td>
<td>Haemangioma 1</td>
</tr>
<tr>
<td></td>
<td>Trauma 1</td>
</tr>
<tr>
<td>Children with co-morbidities</td>
<td>Total 10</td>
</tr>
<tr>
<td></td>
<td>Cardiac 2</td>
</tr>
<tr>
<td></td>
<td>Neurological 6</td>
</tr>
<tr>
<td></td>
<td>Other 2</td>
</tr>
<tr>
<td>Child’s ethnicity</td>
<td>NZ European 6</td>
</tr>
<tr>
<td></td>
<td>Maori 3</td>
</tr>
<tr>
<td></td>
<td>Pacific Island 4</td>
</tr>
<tr>
<td></td>
<td>Indian 1</td>
</tr>
<tr>
<td></td>
<td>Latin American 1</td>
</tr>
</tbody>
</table>

Examination findings are shown in Table 4.5 and 4.6 and in Figures 4.1 and 4.2.

Respiratory rate was significantly lower on HH compared to HME (at 2 hours 38.5 ± 18.8/min vs. 44.1 ± 17.4/min and at 20 hours 40.5 ± 16.7/min vs. 42.5 ± 18.6/min, p = 0.038). Oxygen saturation in children breathing room air was significantly higher on HH compared to HME (at 2 hours 97.8% ± 1.7 vs 97.5% ± 1.6 and at 20 hours 97.9% ± 1.7 vs. 96.7% ± 2.4, p=0.012). The summary respiratory examination score was significantly lower during treatment with HH compared to HME (at 2 hours 2.4 ± 2.2 vs. 3.6 ± 2.4 and at 20 hours 2.5 ± 2.0 vs 3.7 ± 2.6, p < 0.001). There were also significant differences in the components of the summary score severity of retractions (p = 0.011) and severity of wheeze (p = 0.20).
There was no difference between treatments in terms of secretion assessment findings with limited variability in findings between treatments and across time assessments within treatments (Table 4.7).
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Two hours</th>
<th>Twenty hours</th>
<th>Overall study period effect p value</th>
<th>Overall study treatment effect p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HH (± standard deviation)</td>
<td>HME (± standard deviation)</td>
<td>HH (± standard deviation)</td>
<td>HME (± standard deviation)</td>
<td>HH (± standard deviation)</td>
</tr>
<tr>
<td>Mean pulse rate (beats per minute)</td>
<td>134.1 ± 28.1</td>
<td>125.7 ± 28.1</td>
<td>128.2 ± 24.7</td>
<td>125.3 ± 26.8</td>
<td>125.5 ± 25.3</td>
</tr>
<tr>
<td>Mean respiratory rate (breaths per minute)</td>
<td>39.3 ± 20.9</td>
<td>38.1 ± 20.8</td>
<td>38.5 ± 18.8</td>
<td>44.1 ± 17.4</td>
<td>40.5 ± 16.7</td>
</tr>
<tr>
<td>Mean oxygen saturation (percent)</td>
<td>97.0% ± 2.1</td>
<td>96.6% ± 2.8</td>
<td>97.8% ± 1.7</td>
<td>97.5% ± 1.6</td>
<td>97.9% ± 1.7</td>
</tr>
</tbody>
</table>

*p value < 0.05

HH = heated humidifier, HME = heat and moisture exchanger.

Table 4.5: Significance tests for continuous variable examination findings for short-term study. Data analyses using general linear model repeated measures analysis allowing for treatment, period, time of measurement, and subject effects with subject treated as a fixed.
<table>
<thead>
<tr>
<th></th>
<th>HH</th>
<th>HME</th>
<th>HH</th>
<th>HME</th>
<th>HH</th>
<th>HME</th>
<th>Overall study period effect p value</th>
<th>Overall study treatment effect p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median respiratory rate score (10^{th} – 90^{th} centile)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.953</td>
<td>0.084</td>
</tr>
<tr>
<td>Median dyspnoea score (10^{th} – 90^{th} centile)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.988</td>
<td>0.083</td>
</tr>
<tr>
<td>Median retractions score (10^{th} – 90^{th} centile)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.191</td>
<td>0.011*</td>
</tr>
<tr>
<td>Median wheeze score (10^{th} – 90^{th} centile)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.079</td>
<td>0.020*</td>
</tr>
<tr>
<td>Median crackles score (10^{th} – 90^{th} centile)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.658</td>
<td>0.658</td>
</tr>
<tr>
<td>Mean summary respiratory examination score (± standard deviation)</td>
<td>2.9 ± 2.1</td>
<td>3.4 ± 2.2</td>
<td>2.4 ± 2.2</td>
<td>3.6 ± 2.4</td>
<td>2.5 ± 2.0</td>
<td>3.7 ± 2.6</td>
<td>0.380</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

p value < 0.05.

*Summary score from categorical variable examination findings treated as a continuous variable.

HH = heated humidifier, HME = heat and moisture exchanger.

Table 4.6: Significance tests for categorical clinical examination findings for short-term study. Data analyses for categorical analysis performed using marginal effects model generalized linear model repeated measures analysis for ordinal categorical data allowing for treatment, period, time of measurement and fixed subject effects.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Overall study period effect p value</th>
<th>Overall study treatment effect p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HH</td>
<td>HME</td>
<td>HH</td>
<td>HME</td>
<td>HH</td>
<td>HME</td>
<td></td>
</tr>
<tr>
<td>Median difficulty of inserting suction catheter (10th – 90th centile)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>0.943</td>
</tr>
<tr>
<td>Median colour of secretions score (10th – 90th centile)</td>
<td>2 (2 – 2)</td>
<td>2 (2 – 2)</td>
<td>2 (1 – 2)</td>
<td>2 (1 – 2)</td>
<td>2 (1 – 2)</td>
<td>2 (2 – 3)</td>
<td>0.482</td>
</tr>
<tr>
<td>Median volume of secretions score (10th – 90th centile)</td>
<td>2 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 3)</td>
<td>1 (1 – 2)</td>
<td>2 (1 – 2)</td>
<td>0.511</td>
</tr>
<tr>
<td>Median thickness of secretions score (10th – 90th centile)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (2 – 3)</td>
<td>0.075</td>
</tr>
<tr>
<td>Mean summary secretion score† (± standard deviation)</td>
<td>6.9 ± 1.5</td>
<td>6.5 ± 1.0</td>
<td>6.5 ± 1.2</td>
<td>6.5 ± 1.1</td>
<td>6.5 ± 1.4</td>
<td>7.4 ± 1.3</td>
<td>0.310</td>
</tr>
</tbody>
</table>

†Summary score from categorical variable examination findings treated as a continuous variable. HH = heated humidifier, HME = heat and moisture exchanger.

Table 4.7: Significance tests for categorical airway secretion assessment findings for short-term study. Data analyses using marginal effects model generalised linear model repeated measures analysis for ordinal categorical data allowing for treatment, period, time of measurement and fixed subject effects.
Figure 4.1: Mean treatment differences for summary respiratory examination score. Increased abnormalities result in a higher score and therefore negative values favour HH. Error bars indicate 95% confidence limits of the mean.
Figure 4.2: Mean treatment differences for summary secretion score. Error bars indicate 95% confidence limits of the mean. Increased abnormalities result in a higher score and therefore negative values favour HH.

HH = heated humidifier, HME = heat-and-moisture exchanger.
For overnight events there were no significant differences between HH compared to HME for the outcomes of mean overnight oxygen saturations (97.4% ± 1.3 vs. 97.7% ± 1.3, p= 0.456), mean pulse rate (115.7 ± 26.9/min vs. 112.3 ± 31.8/min, p = 0.536), number of overnight suctioning (6.8 ± 5.0 vs. 7.7 ± 5.0, p = 0.326), or number of suctioning requiring normal saline instillation (1.40 ± 2.16 vs. 1.07 ± 1.39, p = 0.420) (Table 4.8). No episodes of tracheostomy occlusion occurred during either treatment period. There was one unscheduled tracheostomy tube change which was performed for oxygen desaturation events persisting despite suctioning and took place during treatment with HH.
<table>
<thead>
<tr>
<th>Record</th>
<th>HH (± standard deviation)</th>
<th>HME (± standard deviation)</th>
<th>Mean treatment differences HH – HME (95% confidence interval)</th>
<th>Period Effect p value</th>
<th>Treatment Effect p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overnight oxygen saturation†</td>
<td>97.4 ± 1.3</td>
<td>97.7 ± 1.4</td>
<td>-0.4 ( -1.3 to 0.6)</td>
<td>0.435</td>
<td>0.456</td>
</tr>
<tr>
<td>Mean overnight pulse rate</td>
<td>115.7 ± 26.9</td>
<td>112.3 ± 31.8</td>
<td>3.2 ( -7.2 to 13.6)</td>
<td>0.950</td>
<td>0.538</td>
</tr>
<tr>
<td>Mean number of suctions performed overnight†</td>
<td>6.8 ± 5.0</td>
<td>7.7 ± 5.0</td>
<td>-0.9 ( -2.9 to 1.0)</td>
<td>0.189</td>
<td>0.326</td>
</tr>
<tr>
<td>Mean number of suction events with saline</td>
<td>1.40 ± 2.16</td>
<td>1.07 ± 1.39</td>
<td>0.3 ( -0.6 to 1.3)</td>
<td>0.921</td>
<td>0.420</td>
</tr>
</tbody>
</table>

†Five patients on oxygen excluded
†Variable square root transformed for analysis.
HH = heated humidifier, HME = heat and moisture exchanger.

Table 4.8: Comparison of overnight events. Significance tests for overnight oxygen saturation and pulse rate calculated by marginal effects model generalised linear model analysis and for numbers of suctions calculated by poisson regression.
Chapter 5 Clinical Outcomes Long-term Study

In this chapter I will describe the clinical outcomes for the long-term study. These outcomes include demographic details from enrolment, responses to questionnaires, findings on clinical examination, physiological recordings and clinical events. The chapter is divided into a Methods and a Results section.

As described in Chapter 3, this was a cross-over study with two treatment periods. The treatment period was for ten weeks with either HH or HME. The treatment order was randomised although allocation and treatment were not able to be concealed to myself as I recorded the clinical outcomes. Each treatment period commenced with a two-week wash-in period of active treatment on the assigned treatment. Baseline measurements took place prior to the first wash-in period and were utilised to describe the baseline characteristics of the participants.

5.1 Methods

5.1.1 Clinical Events

For the long-term study the primary outcome for the study was the occurrence of any of the following major events:

- Episodes of acute lower respiratory tract infection (LRTI)
- Acute admission to hospital for any cause
- Acute admission to hospital for a respiratory cause
- Episodes of tracheostomy tube occlusion
- Episodes of emergency tracheostomy tube changes
- Withdrawal from the study
- Treatment failure
Parents of participants were asked to contact the primary investigator if any of these events occurred and were also contacted by phone on a fortnightly basis during the study to collect data on any clinical events. Following completion of the study, the medical notes of participants were reviewed to ensure completeness of data.

“Treatment failure”, or failure to tolerate one of the treatments, was deemed to have taken place when any of the following occurred:

- Airway secretions that were persistently thick, requiring hourly suction for a period of 3 or more days
- The parent/caregiver believed it was unsafe to continue
- The primary medical team or the investigator believed it was unsafe to continue

If treatment failure occurred during overnight treatment with the HME, parents were asked to restart their child on HH overnight for 3 nights and then restart overnight treatment with HME. If treatment failure recurred then overnight HME treatment was terminated. Participants were given two opportunities to fail HME treatment to ensure that the treatment failure was not due to an intercurrent illness. We then arranged early assessment for which parents were asked to apply two nights of overnight treatment with the HME so that this early assessment would be on the assigned treatment. Following this assessment those children who failed to tolerate HME treatment crossed to the next treatment or ended the study if they had already received the ten weeks of overnight treatment with HH. Treatment with the HH was judged to be the standard of care for this study and therefore treatment failure was not able to occur on HH.
Acute LRTI was defined as an increase in respiratory effort and airway secretions associated with new changes on chest xray or on auscultation and where a medical practitioner prescribed a course of either oral or intravenous antibiotics. Where there were thick airway secretions during an acute LRTI and the child was on overnight HME treatment, parents were asked to commence overnight HH treatment for three nights. This was to ensure maximum safety of the participants during intercurrent illnesses.

Tracheostomy tube occlusion was defined as all of the following: obstruction of the tracheostomy tube with secretions, not clearing with suction, and requiring an emergency tracheostomy tube change.

Emergency tracheostomy tube changes were defined as any non-scheduled tracheostomy change performed for airway occlusion, tracheostomy tube displacement, or acute respiratory distress.

5.1.2 Clinical Examination

Clinical examination was performed and recorded as described in Section 4.1.1. Clinical examination was performed by an experienced research nurse under supervision of the principal investigator (either myself or Dr Jaksic) and while all children were wearing the HME for purposes of partial treatment concealment.

5.1.3 Suctioning of Tracheostomy

Suctioning of the tracheostomy and inspection of the airway secretions were performed as described in Section 4.1.2. Suctioning of the tracheostomy and assessment of secretions was performed by the principal investigator (either myself or Dr Jaksic).
5.1.4 Questionnaires and Health-Related Quality of Life

Questionnaires were administered to parents at baseline and at the end of each treatment period. These questionnaires included assessment of the child and parents’ health-related quality of life (HRQOL) as well as specific questions related to symptoms of inadequate humidification and satisfaction with humidification. The HRQOL questionnaires administered were the Pediatric Tracheostomy Health Survey Index (PTHSI) (32, 370) and the SF36v2. The PTHSI was selected as a previously validated disease-specific measure of HRQOL which would be sensitive to change while the SF36v2 was used as a generic measure of HRQOL to validate the PTHSI.

The PTHSI is based on the Child Health Questionnaire (CHQ), a widely used and well validated generic measure of paediatric HRQOL. The PTHSI was developed by Hartnick et al (370) using the internet and a sample of 130 parents of children with tracheostomies and validated in a subsequent study of 154 families assessing the impact of tracheostomy on HRQOL (32). The PTHSI comprises 34 items making up four domains:

- Child physical health
- Health visits
- Child stress
- Parent stress

The individual items are scored on a 5-point Likert scale from “excellent” to “poor”. The initial validation population of 154 families for the PTHSI was in the United States and included 70% with major co-morbidities, 15% with neoplasms and may have included a proportion dependent on home ventilation (32). During planning for the current study, five parents of children with tracheostomies were asked to comment on the questionnaires. For the domain health visits, all five
parents indicated they would select “not applicable” or “none” for all of the items in that domain. This domain was therefore re-written to more closely reflect the New Zealand health system and then re-tested on the parents (Table 5.1). The five parents indicated that they would provide a range of responses in other domains and these were left unaltered from the original PTHSI for the current study. Permission was obtained from the author of the PTHSI to use this survey for the current study.

<table>
<thead>
<tr>
<th>Original questions for health visits domain</th>
<th>Revised questions for health visits domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately how many doctor visits (Pulmonary or ENT Doctor) did your child have for tracheostomy related problems during the last three months?</td>
<td>Approximately how many visits to see a doctor did your child have for breathing or tracheostomy related problems during the last 2 months?</td>
</tr>
<tr>
<td>Approximately how many emergency room visits did your child have for tracheostomy related problems during the last three months?</td>
<td>Approximately how many chest infections did your child have during the last 2 months?</td>
</tr>
<tr>
<td>Approximately how many hospitalizations did your child have for tracheostomy related problems during the last three months?</td>
<td>Approximately how many hospitalizations did your child hospitalizations for breathing or tracheostomy related problems during the last 2 months?</td>
</tr>
<tr>
<td>How many hours per day do you feel you need home nursing?</td>
<td>How often do you feel you need a nurse to visit you at home?</td>
</tr>
<tr>
<td>How many hours per day do you receive home care nursing?</td>
<td>How often do you receive a nurse to visit you at home?</td>
</tr>
<tr>
<td>How many days per week do you feel you need home nursing?</td>
<td>How often do you feel you need respite care for your child (for example Carer Support, Family Options, or other family members looking after your child)?</td>
</tr>
<tr>
<td>How many days per week do you receive home nursing?</td>
<td>How often do you receive respite care for your child (for example Carer Support, Family Options, or other family members looking after your child)?</td>
</tr>
</tbody>
</table>

Table 5.1: Original and revised questions for health visits domain for the Pediatric Tracheostomy Health Survey Index (PTHSI).

The SF-36v2 is the second version of the SF-36 survey, a widely used and validated generic measure of HRQOL. The questionnaire consists of 36 items
scored on either a five-point or a three-point Likert-like scale contributing to two major summary scales – a physical component subscale and a mental component subscale – and eight domains:

- Physical functioning
- Social functioning
- Role limitation due to physical problems
- Role limitation due to emotional problems
- Mental health
- Energy and vitality
- Bodily pain
- General perception of health

Appropriate permissions were obtained and licensing fees were paid for the use of this survey in the current study (US$238.50 for a two year licence).

Parent satisfaction with treatment was measured by three items on effectiveness, convenience and overall satisfaction with an additional item on overall preference. The original five-point scale was reduced to a three-point scale (positive, neutral, negative) for analysis.

Parents were also asked to describe the quality of their child’s secretions on the morning of assessment and asked how often they had performed suction in the past week. They were also asked to retrospectively recall the following clinical events from the preceding 2 months:

- Antibiotic use
- Chest infections
- HME blockages
- Tracheostomy tube occlusions
• Emergency tracheostomy tube changes

5.1.5 Compliance with heated humidifier

Compliance with the HH was measured using Compliance Maximizer Software (Fisher & Paykel Healthcare) which counts the hours the HH is switched on but of course that does not determine whether the machine was applied to the patient when running.

5.1.6 Compliance with heat and moisture exchanger

Parents were asked to collect all used HMEs in a plastic container. These were then counted and the number of HMEs used averaged over the number of days that parents had collected the devices. Days in hospital were excluded unless the HMEs were also all collected in that time.

5.2 Results

A total of thirty-six children with long-term tracheostomies were identified during the period of the study (Figure 5.1). Four were considered ineligible due to dependence on home ventilation and four were deemed ineligible for consent reasons – they were under state care or their parents were considered unable to give appropriately informed consent. Of the 26 approached families, 12 declined consent. The reasons for declining consent were given by parents as:

• 5 parents did not want to stop using HH for any part of study
• 2 parents did not wish to use HH (preferred HME alone)
• 2 parents found travel to research centre too difficult (one with twins and one lived in a remote area only accessible by aircraft)
• 2 parents were too busy to be involved in a research study
• 1 parent did not want their child to be involved in any research
Fourteen children were enrolled in the study, eight male and six female. Children enrolled in the study had a mean age of 2.94 years (range 0.42 – 15.25) with a mean duration of tracheostomy of 2.29 years (range 0.17 – 15.59) (Table 5.2 and 5.3). Tracheomalacia was the most common indication for tracheostomy, occurring in seven children, and subglottic stenosis and Pierre Robin sequence were each indications in three children. In the children with tracheomalacia four had laryngomalacia or another additional cause of upper airway obstruction. Nine of the children had co-morbidities, the most common being cardiac abnormalities in four children, congenital syndromes resulting in developmental delay in four children and other neurologic problems in three children. Two of the children had chronic lung disease of prematurity. None of the children were exposed to environmental tobacco smoke according to their parents although no specific measures of cotinine were performed. Seven of the children were identified as New Zealand European or Pakeha, three as Maori and four as Pacific Island. Parents had a mean age of 37.3 years (range 28-45) with a range of education from no secondary school qualifications to completion of a university degree.

Two children withdrew during the first period due to the parents not wishing to remain in a research study. Both these children were on treatment with HME at the time of withdrawal. Due to parental concerns about using the HME alone one family declined the randomisation order and had treatment order reassigned to HH then HME following randomisation and one child underwent the two treatment periods separated by 12 months.
HH = heated humidifier, HME = heat and moisture exchanger.

Figure 5.1: Diagram showing numbers of children eligible, enrolled and withdrawn and final treatment preference as stated by parents.
<table>
<thead>
<tr>
<th>Participant</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Age at enrolment (years)</th>
<th>Age at tracheostomy (years)</th>
<th>Duration of tracheostomy (months)</th>
<th>Indication for tracheostomy</th>
<th>Co-morbidities</th>
<th>Parent Age</th>
<th>Parent ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Pacific Island</td>
<td>0.67</td>
<td>0.25</td>
<td>5</td>
<td>Pierre Robin sequence</td>
<td>Prader Willi syndrome</td>
<td>44</td>
<td>Pacific Island</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Pacific Island</td>
<td>0.67</td>
<td>0.08</td>
<td>7</td>
<td>Pierre Robin sequence</td>
<td>Patent ductus arteriosus</td>
<td>44</td>
<td>Pacific Island</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>NZE</td>
<td>2.25</td>
<td>0.33</td>
<td>23</td>
<td>Subglottic stenosis</td>
<td></td>
<td>34</td>
<td>New Zealand european</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Maori</td>
<td>3.08</td>
<td>0.08</td>
<td>36</td>
<td>Tracheomalacia</td>
<td>Goldenhar syndrome</td>
<td>28</td>
<td>Maori</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>NZE</td>
<td>15.25</td>
<td>0.33</td>
<td>180</td>
<td>Tracheomalacia</td>
<td>Laryngomalacia Degenerative neurologic syndrome</td>
<td>45</td>
<td>New Zealand european</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>Maori</td>
<td>1.42</td>
<td>1.17</td>
<td>3</td>
<td>Caustic ingestion</td>
<td></td>
<td>39</td>
<td>New Zealand european</td>
</tr>
</tbody>
</table>

(Table 5.2 continued over page)
<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Diagnosis</th>
<th>Associated Conditions</th>
<th>No. Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Female</td>
<td>NZE</td>
<td>1.42</td>
<td>0.00</td>
<td>5</td>
<td>Tracheomalacia</td>
<td>CHARGE association</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>NZE</td>
<td>4.50</td>
<td>0.67</td>
<td>48</td>
<td>Tracheomalacia</td>
<td>Laryngomalacia Pulmonary stenosis</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>NZE</td>
<td>2.50</td>
<td>2.25</td>
<td>3</td>
<td>Tracheomalacia</td>
<td>Laryngomalacia</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>NZE</td>
<td>2.08</td>
<td>2.08</td>
<td>2</td>
<td>Crouzon's syndrome</td>
<td>Chronic lung disease of prematurity, Gastric reflux with aspiration</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>NZE</td>
<td>1.42</td>
<td>0.33</td>
<td>14</td>
<td>Subglottic stenosis</td>
<td>Chronic lung disease of prematurity</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>Pacific Island</td>
<td>1.00</td>
<td>0.50</td>
<td>6</td>
<td>Subglottic stenosis</td>
<td>Developmental delay</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>Pacific Island</td>
<td>0.42</td>
<td>0.08</td>
<td>4</td>
<td>Tracheomalacia</td>
<td>Chronic lung disease of prematurity</td>
<td>32</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>Maori</td>
<td>4.50</td>
<td>0.00</td>
<td>48</td>
<td>Pierre Robin sequence</td>
<td>Treacher Collins syndrome</td>
<td>38</td>
</tr>
</tbody>
</table>

NZE = New Zealand European.

**Table 5.2: Individual participant demographics at enrolment to long-term study.**
Table 5.3: Summary table showing participant’s demographic details at enrolment to long-term study.

For the primary outcome of a major clinical event (Table 5.4 and Figure 5.2) there was a significant reduction in the number of participants experiencing a major clinical event during HH compared to HME treatment during sleep (5 vs. 12, p = 0.005). Due to missing data for the second period for two participants who withdrew in the first period, we also performed a sensitivity analysis substituting absence (p = 0.0032) or presence of an event (p = 0.009).
In terms of individual outcomes there was a trend toward fewer participants experiencing acute respiratory admissions (2 vs. 5, $p = 0.069$) and a trend toward reduced numbers of participants experiencing chest infections (4 vs. 9, $p = 0.061$) and the combined outcome of tracheostomy tube occlusions and emergency changes (2 vs. 5, $p = 0.179$). There was also a difference in the numbers of participants experiencing the combined outcome of treatment failures or study withdrawal (0 vs. 5, $p = 0.076$) but this was not statistically significant due to the small sample size.

The data for major clinical events was also secondarily analysed for time-to-event (Table 5.5) which showed significant differences between HH compared to HME treatment during sleep for time to a major event (median 43 vs. 26 days, $p = 0.004$), and a trend toward an increase in time to acute admission (median 56 vs. 42 days $p = 0.171$) and time to chest infection (median 56 vs. 26 days, $p = 0.123$). Due to the small sample size this data is best displayed graphically as at the end of the chapter. Figure 5.7 shows a Kaplan-Meier plot of time-to-event data for the pooled outcome of any major clinical event, while Figures 5.8 to 5.13 show individual participant results for the time-to-event data.
<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events with HH</th>
<th>Number of events with HME</th>
<th>Median treatment difference events per child: HH – HME (10th – 90th centile)</th>
<th>Number of participants experiencing event on HH</th>
<th>Number of participants experiencing event on HME</th>
<th>Period effect p value for experiencing event</th>
<th>Treatment effect odds ratio for experiencing event (95% confidence limits)</th>
<th>Treatment effect p value for experiencing event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Admissions</td>
<td>4</td>
<td>7</td>
<td>0 (-1 to 1)</td>
<td>2</td>
<td>6</td>
<td>0.289</td>
<td>0.197 (0.034 – 1.134)</td>
<td>0.069</td>
</tr>
<tr>
<td>Acute respiratory admissions</td>
<td>4</td>
<td>6</td>
<td>0 (-1 to 2)</td>
<td>2</td>
<td>5</td>
<td>0.211</td>
<td>0.30 (0.032 – 1.660)</td>
<td>0.145</td>
</tr>
<tr>
<td>Chest infections</td>
<td>5</td>
<td>15</td>
<td>-1 (-2 to -1)</td>
<td>4</td>
<td>9</td>
<td>0.338</td>
<td>0.138 (0.017 – 1.095)</td>
<td>0.061</td>
</tr>
<tr>
<td>Tracheostomy tube occlusion and Emergency</td>
<td>3</td>
<td>7</td>
<td>0 (-2 to 0)</td>
<td>2</td>
<td>5</td>
<td>0.598</td>
<td>0.300 (0.052 – 1.737)</td>
<td>0.179</td>
</tr>
<tr>
<td>Treatment Failure and Withdrawal from</td>
<td>0</td>
<td>5</td>
<td>0 (-1 to 0)</td>
<td>0</td>
<td>5</td>
<td>0.149</td>
<td>0.377 (0.128 – 1.109)</td>
<td>0.076</td>
</tr>
<tr>
<td>study†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All main clinical events</td>
<td>9</td>
<td>24</td>
<td>-1 (-3 to 1)</td>
<td>5</td>
<td>12</td>
<td>0.096</td>
<td>0.377 (0.003 – 0.343)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

*p < 0.05. All significance calculations performed allowing for missing values except † which is calculated substituting event occurrence for missing data. †Outcomes combined due to low number of participants affected. HH = heated humidifier, HME = heat and moisture exchanger.

Table 5.4: Participants experiencing major clinical events during overnight treatment with HH or HME. Calculations performed utilising a generalised linear marginal effects model and generalised estimating equations.
Acute admissions
Acute respiratory admissions
Chest infections
Tracheostomy tube occlusions & emergency changes
Treatment failure and Withdrawal from Study
All major clinical events

*p < 0.05
HH = heated humidifier, HME = heat and moisture exchanger.

Figure 5.2: Numbers of participants experiencing major clinical events during overnight treatment with HH or HME.
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Median Time To Event With HH (Days)</th>
<th>Median Time To Event With HME (Days)</th>
<th>Period Effect p value for Time-to-event</th>
<th>Treatment Effect p value for Time-to-event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Admissions</td>
<td>56</td>
<td>42</td>
<td>0.543</td>
<td>0.171</td>
</tr>
<tr>
<td>Acute respiratory admissions</td>
<td>56</td>
<td>51</td>
<td>0.457</td>
<td>0.429</td>
</tr>
<tr>
<td>Chest infections</td>
<td>56</td>
<td>26</td>
<td>0.104</td>
<td>0.123</td>
</tr>
<tr>
<td>Tracheostomy tube occlusion and emergency tracheostomy tube changes†</td>
<td>56</td>
<td>56</td>
<td>0.267</td>
<td>0.400</td>
</tr>
<tr>
<td>Treatment failure and withdrawal from study†</td>
<td>56</td>
<td>56</td>
<td>1.0</td>
<td>0.300</td>
</tr>
<tr>
<td>All major clinical events</td>
<td>43</td>
<td>26</td>
<td>0.128</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

*< 0.05  
†Outcomes pooled due to small event numbers  
HH = heated humidifier, HME = heat and moisture exchanger.  

Table 5.5: Time-to-event data for major clinical events during treatment with HH or HME.
There was a trend which did not reach statistical significance toward more parents reporting the HH to be effective as compared to the HME (11 vs. 7 effective, 0 vs. 2 not effective, \( p = 0.636 \)) but also a trend towards more parents reporting inconvenience with the HH (5 vs. 1 not convenient, 6 vs. 10 convenient, \( p = 0.186 \)) (Figure 5.3). There was a significantly higher number of parents reporting overall satisfaction with the HH as compared to the HME (11 vs. 9 satisfied, 0 vs. 2 not satisfied, \( p = 0.018 \)) and a strong trend to a final preference for the HH (8 vs. 2, \( p = 0.070 \)).

![Graphs showing perceived effectiveness, convenience, overall satisfaction, and final preference.](image)

HH = heated humidifier, HME = heat and moisture exchanger.

**Figure 5.3:** End of study parental perceived effectiveness, convenience, overall satisfaction and treatment preference. Significance values calculated with exact version of chi square test.

On clinical physical examination and on inspection of airway secretions there was no difference between treatments for any of the clinical findings (Tables 5.6 – 5.8).
<table>
<thead>
<tr>
<th></th>
<th>Baseline (± standard deviation)</th>
<th>HH (± standard deviation)</th>
<th>HME (± standard deviation)</th>
<th>Mean treatment difference: HH – HME (95% confidence interval)</th>
<th>Period Effect p Value</th>
<th>Treatment Effect p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean respiratory rate</td>
<td>39.2 ± 14.0</td>
<td>32.4 ± 9.1</td>
<td>36.5 ± 14.0</td>
<td>-3.6 (-10.6 – 3.5)</td>
<td>0.118</td>
<td>0.200</td>
</tr>
<tr>
<td>(breaths per minute)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulse rate</td>
<td>130.6 ± 25.0</td>
<td>121.8 ± 14.8</td>
<td>122.8 ± 18.3</td>
<td>-1.1 (-11.8 – 9.6)</td>
<td>0.070</td>
<td>0.570</td>
</tr>
<tr>
<td>(beats per minute)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean oxygen saturation</td>
<td>97.4% ± 1.9</td>
<td>97.5% ± 2.8</td>
<td>97.4% ± 2.3</td>
<td>0.1 (-1.8 – 1.9)</td>
<td>0.522</td>
<td>0.987</td>
</tr>
<tr>
<td>(percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P values < 0.05
HH = heated humidifier, HME = heat and moisture exchanger.

**Table 5.6: Clinical examination findings for continuous variables for long-term study. Significance tests performed using general linear model.**
<table>
<thead>
<tr>
<th></th>
<th>Baseline (10th – 90th centiles)</th>
<th>HH (10th – 90th centiles)</th>
<th>HME (10th – 90th centiles)</th>
<th>Treatment difference: HH – HME (10th – 90th centiles)</th>
<th>p value for period effect</th>
<th>p value for treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median respiratory rate score</td>
<td>1 (1 – 3)</td>
<td>1 (1 – 3)</td>
<td>1 (1 – 2)</td>
<td>0 (-1 to 1)</td>
<td>0.613</td>
<td>0.613</td>
</tr>
<tr>
<td>Median dyspnoea score</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
<td>0 (-1 to 1)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Median retractions score</td>
<td>1.5 (0 – 3)</td>
<td>0.5 (0 – 2)</td>
<td>0.5 (0 – 3)</td>
<td>0 (-2 to 1)</td>
<td>0.515</td>
<td>0.515</td>
</tr>
<tr>
<td>Median wheeze score</td>
<td>0 (0 – 2)</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 1)</td>
<td>0 (-1 to 0)</td>
<td>0.996</td>
<td>0.413</td>
</tr>
<tr>
<td>Median crackles score</td>
<td>0 (0 – 2)</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
<td>0 (-1 to 1)</td>
<td>0.287</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean summary respiratory examination score† (± standard deviation)</td>
<td>4.0 ± 2.6</td>
<td>2.6 ± 1.7</td>
<td>3.5 ± 2.4</td>
<td>-0.6 (-2.1 – 0.9)</td>
<td>0.835</td>
<td>0.465</td>
</tr>
</tbody>
</table>

†Summary scores from summed categorical findings treated as continuous variables.
HH = heated humidifier, HME = heat and moisture exchanger.

Table 5.7: Significance tests for clinical examination ordinal categorical for long-term study. Significance tests calculated with multinomial regression.
<table>
<thead>
<tr>
<th></th>
<th>Baseline (10&lt;sup&gt;th&lt;/sup&gt; – 90&lt;sup&gt;th&lt;/sup&gt; centiles)</th>
<th>HH (10&lt;sup&gt;th&lt;/sup&gt; – 90&lt;sup&gt;th&lt;/sup&gt; centiles)</th>
<th>HME (10&lt;sup&gt;th&lt;/sup&gt; – 90&lt;sup&gt;th&lt;/sup&gt; centiles)</th>
<th>Median treatment difference: HH – HME (10&lt;sup&gt;th&lt;/sup&gt; – 90&lt;sup&gt;th&lt;/sup&gt; centiles)</th>
<th>p value for period effect</th>
<th>p value for treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median ease of catheter insertion</td>
<td>1 (1 – 2)</td>
<td>1 (1 – 1)</td>
<td>1 (1 – 2)</td>
<td>0 (-1 to 0)</td>
<td>0.987</td>
<td>0.773</td>
</tr>
<tr>
<td>Median colour of secretions</td>
<td>2 (1 – 3)</td>
<td>1 (1 – 2)</td>
<td>2 (1 – 3)</td>
<td>0 (-1 to 1)</td>
<td>0.160</td>
<td>0.213</td>
</tr>
<tr>
<td>Median volume of secretions</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 2)</td>
<td>2 (1 – 3)</td>
<td>0.5 (-2 to 1)</td>
<td>0.056</td>
<td>0.887</td>
</tr>
<tr>
<td>Median thickness of secretions</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>0 (-1 to 1)</td>
<td>0.119</td>
<td>0.684</td>
</tr>
<tr>
<td>Mean summary secretion score† (± standard deviation)</td>
<td>7.2 ± 1.4</td>
<td>6.2 ± 1.0</td>
<td>6.7 ± 2.7</td>
<td>-0.5 (-2.4 – 1.4)</td>
<td>0.462</td>
<td>0.948</td>
</tr>
<tr>
<td>Numbers of neutrophils seen on gram stain from swab of canula</td>
<td>0 (0 – 3)</td>
<td>0 (0 – 2)</td>
<td>1 (0 – 2)</td>
<td>-1 (-2 to 1)</td>
<td>0.457</td>
<td>0.374</td>
</tr>
<tr>
<td>Bacterial growth from canula (none to heavy)</td>
<td>2 (0 – 3)</td>
<td>2 (0 – 3)</td>
<td>1 (0 – 3)</td>
<td>0.5 (-1 to 2)</td>
<td>0.727</td>
<td>0.338</td>
</tr>
</tbody>
</table>

†Summary scores from summed categorical findings treated as continuous variables. HH = heated humidifier, HME = heat and moisture exchanger.

Table 5.8: Significance tests for airway secretion ordinal categorical findings for long-term study. Significance tests calculated with multinomial regression.
Parents had significantly lower HRQOL as measured by the SF36v2 at baseline compared to New Zealand national norms (Table 5.9 and Figure 5.4) in the domains of general health (44.1 ± 13.0 vs. 50 ± 10, p = 0.034), energy and vitality (42.1 ± 12.6 vs. 50 ± 10, p = 0.005), social functioning (43.3 ± 12.8 vs. 50 ± 10, p = 0.017), emotional health (43.7 ± 11.7 vs. 50 ± 10, p = 0.024), and the summary mental component score (42.6 ± 13.2 vs. 50 ± 10, p = 0.008). Comparing the period of treatment with HH to HME there was a trend across all the domains towards improved parental QOL as measured by the SF36v2 (Figure 5.5) but this was not statistically significant (Table 5.9) and for most of the domains was below the minimally clinically significant difference of five points. There was no difference between treatments in terms of impact on the child’s or parent’s HRQOL as measured by the PTHSI (Table 5.10 and Figure 5.6). At baseline only three parents (25%) rated their child's overall health and HRQOL as "fair" and none rated their child's health or HRQOL as "poor". Six parents (50%) described their own HRQOL as "fair" or "poor". Seven parents (58%) reported their sleep was disturbed "often" or "all the time". There appeared to be a good match between parents perceived need for frequency of homecare nursing visits and actual frequency of visits. However, parents reported a greater perceived need for respite care in the home than they received. Three parents (25%) reported receiving respite care in the home less than once per week whereas all parents reported a need for respite at least one day per week and no parents received respite for six or seven days per week while two parents (16%) reported a need for this level of support.

As the PTHSI is a relatively new instrument and one domain was changed for this study, data are presented assessing the reliability of the PTHSI from baseline measurements at enrolment. Internal consistency (Cronbach's alpha) of all the
domains was strong except for the child physical health domain (Table 5.11). There were moderate to strong correlations between the domains child physical health, health visits and parental stress (0.514 – 0.658). Comparison between the child stress domain and the other domains was poor. Correlation between the domains of the PTHSI and the SF36v2 (Table 5.12) showed strong negative correlations between the PTHSI domain of parental stress and SF36v2 domains measuring parent vitality (-0.730, p=0.007) and parent mental health (-0.737, p=0.006). There were also strong negative correlations between the SF36v2 domain of parent general health and PTHSI domains of child physical health (-0.610, p=0.035) and health visits (-0.653, p=0.021). Child physical health was also negatively correlated with SF36v2 parent bodily pain (-0.594, p=0.042).
<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline (mean ± standard deviation)</th>
<th>p value for difference between baseline and national norms</th>
<th>HH (mean ± standard deviation)</th>
<th>HME (mean ± standard deviation)</th>
<th>Mean treatment difference: HH – HME (95% confidence interval)</th>
<th>p value for period effect</th>
<th>p value for treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of responses</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>47.4 ± 12.0</td>
<td>0.340</td>
<td>47.5 ± 10.9</td>
<td>47.8 ± 8.9</td>
<td>-0.2 (-3.9 to 3.4)</td>
<td>0.510</td>
<td>0.765</td>
</tr>
<tr>
<td>Role limitation physical</td>
<td>46.0 ± 7.9</td>
<td>0.148</td>
<td>48.2 ± 7.5</td>
<td>44.8 ± 7.8</td>
<td>3.4 (-1.7 to 8.5)</td>
<td>0.135</td>
<td>0.078</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>47.7 ± 11.5</td>
<td>0.416</td>
<td>44.4 ± 11.5</td>
<td>42.0 ± 12.0</td>
<td>2.4 (-3.7 to 8.5)</td>
<td>0.008</td>
<td>0.064</td>
</tr>
<tr>
<td>General health</td>
<td>44.1 ± 13.0</td>
<td>0.034*</td>
<td>39.8 ± 13.3</td>
<td>38.3 ± 14.0</td>
<td>1.5 (-2.6 to 5.6)</td>
<td>0.045</td>
<td>0.152</td>
</tr>
<tr>
<td>Energy and vitality</td>
<td>42.1 ± 12.6</td>
<td>0.005*</td>
<td>40.8 ± 13.1</td>
<td>38.7 ± 12.3</td>
<td>2.1 (-4.2 to 8.4)</td>
<td>0.164</td>
<td>0.270</td>
</tr>
<tr>
<td>Social functioning</td>
<td>43.3 ± 12.8</td>
<td>0.017*</td>
<td>44.7 ± 9.2</td>
<td>38.4 ± 12.2</td>
<td>6.4 (-2.1 to 14.9)</td>
<td>0.317</td>
<td>0.089</td>
</tr>
<tr>
<td>Role limitation emotional</td>
<td>45.1 ± 8.9</td>
<td>0.076</td>
<td>48.3 ± 6.6</td>
<td>45.5 ± 8.1</td>
<td>2.8 (-3.0 to 8.6)</td>
<td>0.322</td>
<td>0.220</td>
</tr>
<tr>
<td>Emotional health</td>
<td>43.7 ± 11.7</td>
<td>0.024*</td>
<td>46.4 ± 12.6</td>
<td>43.5 ± 12.8</td>
<td>2.9 (-5.3 to 11.0)</td>
<td>0.251</td>
<td>0.298</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>47.4 ± 10.5</td>
<td>0.355</td>
<td>44.9 ± 11.0</td>
<td>43.8 ± 95</td>
<td>1.1 (-1.8 to 3.9)</td>
<td>0.074</td>
<td>0.177</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>42.6 ± 13.2</td>
<td>0.008*</td>
<td>45.4 ± 10.9</td>
<td>41.3 ± 13.6</td>
<td>4.2 (-4.2 to 12.6)</td>
<td>0.254</td>
<td>0.188</td>
</tr>
</tbody>
</table>

* P < 0.05
HH = heated humidifier HME = heat and moisture exchange.

Table 5.9: Parents' Quality of Life SF36v2 data. A higher score indicates a better health-related quality of life. Data are normalised to the 1996 New Zealand Health Survey data for females so that a score of 50 equals the national average.
Figure 5.4: Difference between parents’ health-related quality of life (HRQOL) SF36v2 data standardised t-scores and national New Zealand norms (if the scores were the same the difference would be plotted at 0). Error bars indicate standard error of mean. Dashed line indicates minimal clinically significant difference of five points.
Figure 5.5: Mean treatment differences for parents’ health-related quality of life (HRQOL) SF36v2 data t-scores. Positive values favour HH (improved quality of life). Error bars indicate 95% confidence limits of the mean.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline (mean ± standard deviation)</th>
<th>HH (mean ± standard deviation)</th>
<th>HME (mean ± standard deviation)</th>
<th>Mean treatment difference: HH – HME (95% confidence limits)</th>
<th>p value for period effect</th>
<th>p value for treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of responses</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child physical health</td>
<td>53.0 ± 19.3</td>
<td>49.7 ± 17.1</td>
<td>54.4 ± 19.7</td>
<td>-4.7 (-10.2 – 0.8)</td>
<td>0.747</td>
<td>0.130</td>
</tr>
<tr>
<td>Health visits</td>
<td>40.0 ± 19.2</td>
<td>35.1 ± 17.6</td>
<td>32.5 ± 17.6</td>
<td>2.6 (-5.9 – 11.1)</td>
<td>0.318</td>
<td>0.717</td>
</tr>
<tr>
<td>Child's stress</td>
<td>45.4 ± 25.0</td>
<td>37.7 ± 13.1</td>
<td>45.5 ± 25.2</td>
<td>-7.7 (-21.9 – 6.5)</td>
<td>0.980</td>
<td>0.300</td>
</tr>
<tr>
<td>Parental stress</td>
<td>47.2 ± 16.7</td>
<td>45.9 ± 16.8</td>
<td>48.8 ± 16.2</td>
<td>-2.9 (-12.1 – 6.2)</td>
<td>0.124</td>
<td>0.255</td>
</tr>
</tbody>
</table>

HH = heated humidifier, HME = heat and moisture exchanger.

**Table 5.10: Child’s and parents’ health-related quality of life (HRQOL) data from Pediatric Tracheostomy Health Survey Index (PTHSI). A higher score indicates a higher impact or lower HRQOL.**
Figure 5.6: Mean treatment differences for children’s and parents’ health-related quality of life (HRQOL) data from Paediatric Tracheostomy Health Survey Index (PTHSI). Negative values favour HH (reduced impact). Error bars indicate 95% confidence limits of the mean.

HH = heated humidifier, HME = heat and moisture exchanger.
Table 5.11: Reliability statistics for Paediatric Tracheostomy Health Survey Index (PTHSI) measured from baseline results.

<table>
<thead>
<tr>
<th></th>
<th>Standardised Cronbach's alpha within domain</th>
<th>Child physical health</th>
<th>Health visits</th>
<th>Child stress</th>
<th>Parental stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child physical health</td>
<td>0.569</td>
<td>1.000</td>
<td>0.658</td>
<td>-0.104</td>
<td>0.514</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.020*</td>
<td>0.749</td>
<td>0.088</td>
</tr>
<tr>
<td>Health visits</td>
<td>0.815</td>
<td>0.658</td>
<td>1.000</td>
<td>0.030</td>
<td>0.536</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.020*</td>
<td>0.927</td>
<td>0.072</td>
</tr>
<tr>
<td>Child's stress</td>
<td>0.839</td>
<td>-0.104</td>
<td>0.030</td>
<td>1.000</td>
<td>-0.116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.749</td>
<td>0.927</td>
<td></td>
<td>0.721</td>
</tr>
<tr>
<td>Parental stress</td>
<td>0.883</td>
<td>0.514</td>
<td>0.536</td>
<td>-0.116</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.088</td>
<td>0.072</td>
<td></td>
<td>0.721</td>
</tr>
</tbody>
</table>

* P < 0.05
## Pearson Correlation Coefficients, N = 12

**Prob > |r| under H0: Rho=0**

<table>
<thead>
<tr>
<th>PTHSI Domain</th>
<th>Physical functioning (t)</th>
<th>Role-physical (t)</th>
<th>Bodily pain (t)</th>
<th>General health (t)</th>
<th>Vitality (t)</th>
<th>Social functioning (t)</th>
<th>Role-emotional (t)</th>
<th>Mental health (t)</th>
<th>Physical component summary score (t)</th>
<th>Mental component summary score (t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child physical health</td>
<td>0.084</td>
<td>-0.184</td>
<td>-0.594</td>
<td>-0.610</td>
<td>-0.473</td>
<td>-0.082</td>
<td>-0.286</td>
<td>-0.545</td>
<td>-0.238</td>
<td>-0.390</td>
</tr>
<tr>
<td></td>
<td>0.796</td>
<td>0.568</td>
<td>0.042*</td>
<td>0.035*</td>
<td>0.120</td>
<td>0.800</td>
<td>0.367</td>
<td>0.067</td>
<td>0.457</td>
<td>0.210</td>
</tr>
<tr>
<td>Hospital/health visits</td>
<td>0.046</td>
<td>-0.399</td>
<td>-0.564</td>
<td>-0.653</td>
<td>-0.454</td>
<td>-0.183</td>
<td>-0.364</td>
<td>-0.451</td>
<td>-0.325</td>
<td>-0.372</td>
</tr>
<tr>
<td></td>
<td>0.887</td>
<td>0.199</td>
<td>0.056</td>
<td>0.021*</td>
<td>0.139</td>
<td>0.569</td>
<td>0.245</td>
<td>0.142</td>
<td>0.303</td>
<td>0.233</td>
</tr>
<tr>
<td>Child’s stress</td>
<td>0.235</td>
<td>0.120</td>
<td>-0.173</td>
<td>0.119</td>
<td>0.501</td>
<td>0.452</td>
<td>0.457</td>
<td>0.551</td>
<td>-0.074</td>
<td>0.556</td>
</tr>
<tr>
<td></td>
<td>0.463</td>
<td>0.711</td>
<td>0.591</td>
<td>0.712</td>
<td>0.097</td>
<td>0.141</td>
<td>0.136</td>
<td>0.063</td>
<td>0.819</td>
<td>0.061</td>
</tr>
<tr>
<td>Parental stress</td>
<td>-0.026</td>
<td>-0.299</td>
<td>-0.450</td>
<td>-0.530</td>
<td>-0.730</td>
<td>-0.331</td>
<td>-0.309</td>
<td>-0.737</td>
<td>-0.202</td>
<td>-0.584</td>
</tr>
<tr>
<td></td>
<td>0.937</td>
<td>0.345</td>
<td>0.142</td>
<td>0.076</td>
<td>0.007*</td>
<td>0.293</td>
<td>0.328</td>
<td>0.006*</td>
<td>0.528</td>
<td>0.046*</td>
</tr>
</tbody>
</table>

* p < 0.05. Bold indicates correlation co-efficient > 0.5.

HRQOL = health-related quality of life.

(t) = t-score

**Table 5.12: Correlation between domains of Pediatric Tracheostomy Health Survey Index (PTHSI) and SF-36v2 t-scores measured from baseline results.**
Retrospective recall of events indicated a significantly higher number of participants experiencing chest infections during overnight treatment with HME compared to HH (5 vs. 7, p=0.045) but no difference for tracheostomy tube occlusions, or emergency changes (Table 5.13). The number of parents reporting tracheostomy tube occlusions was higher for the retrospective than the prospective data.

Children receiving HH during sleep used a significantly fewer mean number of HMEs per day (3.3 ± 1.9 vs 4.0 ± 1.7, p = 0.02). Compliance data for the period during treatment with HH during sleep was able to be downloaded for nine participants and showed the HH was switched on for 94.8% of days (standard deviation 9.2%) and was switched on for a mean of 11.8 hours per day on days used (standard deviation 2.8 hours).
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Number of events HH (median)</th>
<th>Number of events HME (median)</th>
<th>Participants experiencing event HH</th>
<th>Participants experiencing event HME</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Period effect p Value</th>
<th>Treatment effect p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Infections</td>
<td>0</td>
<td>1.5</td>
<td>5</td>
<td>7</td>
<td>0.16 (0.03 – 0.96)</td>
<td>0.400</td>
<td>0.045*</td>
</tr>
<tr>
<td>Courses of antibiotics</td>
<td>0.5</td>
<td>1.5</td>
<td>6</td>
<td>7</td>
<td>0.20 (0.03 – 1.43)</td>
<td>0.237</td>
<td>0.107</td>
</tr>
<tr>
<td>Tracheostomy blockages</td>
<td>0</td>
<td>0.5</td>
<td>5</td>
<td>4</td>
<td>0.94 (0.21 – 4.20)</td>
<td>0.784</td>
<td>0.936</td>
</tr>
<tr>
<td>Emergency tracheostomy changes</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0.63 (0.22 – 1.77)</td>
<td>0.633</td>
<td>0.377</td>
</tr>
</tbody>
</table>

*P value < 0.05
HH = heated humidifier, HME = heat and moisture exchanger.

Table 5.13: Parents’ retrospective recall of clinical events for treatment period or past eight weeks. Significance tests calculated using binomial regression calculated using generalized linear model and generalised estimating equations with fixed subject effects. Two children excluded from analysis due to treatment failure early in HME period.
HH = Heated humidifier, HME = Heat and moisture exchanger. Cross = censored event.

Figure 5.7: Kaplan-Meier plot for outcome of all main clinical events.
Figure 5.8: Time-to-event plot all major clinical events. Lines are presented by participant and in treatment order from top to bottom.

HH = Heated humidifier, HME = Heat and moisture exchanger.
Figure 5.9: Time-to-event plot for outcome of acute admission. Lines are presented by participant and in treatment order from top to bottom.
Figure 5.10: Time-to-event plot for outcome of acute respiratory admissions. Lines are presented by participant and in treatment order from top to bottom.

HH = Heated humidifier, HME = Heat and moisture exchanger.
HH = Heated humidifier, HME = Heat and moisture exchanger.

Figure 5.11: Time-to-event plot for outcome of chest infections. Lines are presented by participant and in treatment order from top to bottom.
Figure 5.12: Time-to-event plot for combined outcome of tracheostomy tube occlusions or emergency tracheostomy change. Lines are presented by participant and in treatment order from top to bottom.
HH = Heated humidifier, HME = Heat and moisture exchanger.

Figure 5.13: Time-to-event plot for combined outcome of treatment failure or study withdrawal. Lines are presented by participant and in treatment order from top to bottom.
Chapter 6 Measures of Mucociliary Clearance

Mucociliary clearance (MCC) is the process by which mucus and debris are removed from the airway by the beating of cilia. Total mucus clearance is a combination of MCC and cough clearance. Ciliary activity may be measured by observing the effectiveness of the ciliary wave form and by measuring the ciliary beat frequency (CBF) (371-374). Mucociliary transport may be measured in vivo in three ways; firstly by the clearance over time of an inhaled radioaerosol; secondly by the measurement of the transport of an inhaled bolus or bronchoscopically placed sample of radioisotope; and thirdly by video or x-ray monitoring of the transport of a bronchoscopically placed particle (375, 376). In children bronchoscopy requires general anaesthetic which could not be justified for this research study. Thus, the clearance of an inhaled radioaerosol was the method of choice. As a primary outcome of the long-term study we measured the clearance of mucus from the airways by measuring the clearance of a nebulised aerosol of technetium-99 (Tc-99) tin colloid deposited on the airways over a period of two hours with the main outcome being clearance from the central region of the right lung at 60 minutes. Although the term MCC scan is used for this study, the results may represent total mucus clearance as it was not possible to control coughing in the participants and some participants required suctioning of excess airway secretions during the two hour scan period. As a secondary outcome CBF was also measured from tracheal samples obtained during routine surveillance bronchoscopy under general anaesthetic.
6.1 Measurement of ciliary beat frequency

6.1.1 Pilot study of CBF measurement in adults with tracheostomies

A group of adults with tracheostomies were recruited for a pilot study to assess whether CBF could be measured from participants with tracheostomies without the need for anaesthetic. The primary outcome was specimen adequacy with the secondary outcome being tolerability of the technique. We aimed to recruit ten participants but the study was terminated early due to the poor quality of samples obtained after six subjects.

6.1.2 CBF measurement in children with tracheostomies

According to local clinical guidelines all children with tracheostomies are recommended to undergo surveillance laryngoscopy and bronchoscopy under general anaesthetic each six months. We therefore planned to obtain samples for CBF measurement for the children in our study under the assumption that they would each undergo laryngoscopy and bronchoscopy once during the study time frame of five months.

6.1.3 Methodology for CBF measurement

CBF was measured according to an established technique (371-374). A 2.4 mm nylon cytology brush (Olympus, New Zealand) was moistened in cell culture medium (Medium 199 with Earle Salts, GIBCO). For the pilot study in adults with tracheostomies the cytology brush was inserted by the participant via the tracheostomy and a sample taken by rotating the brush firmly against the tracheal wall just distal to the end of the tracheostomy tube. For children, who were participants in the clinical study, samples were taken by inserting the cytology brush via a rigid bronchoscope and rubbing the brush firmly against the posterior tracheal wall in the distal third of the trachea. Following withdrawal of the brush
from the airway the brush was agitated vigorously in a tapered plastic tube containing the medium in order to transfer the sample to the medium. The specimen was then stored at 37°C in an incubator (Thermolyne) until functional analysis was performed within 1-2 hours after sampling. Fifty microlitres of medium, containing fragments of epithelium, were then pipetted onto a standard microscope slide. The preparation was sealed by applying silicone gel around the edges of the cover-slip preventing the specimen from drying out during analysis. The preparation was placed on the heated (37°C) stage (Murray Design) mounted on the Zeiss Axioplan 2 microscope. The cilia were then visualised using a 40 x phase objective lens. The CBF was measured in Hertz (Hz) using a photometer mounted on the microscope aligned with a circular 1.5 micron aperture. Ten measurements of CBF at ten different points on the epithelium were made. The ciliated strip used was required to be greater than 50 μm long. The coefficient of variation of the CBF was calculated. The normal range for CBF from nasal and upper airway samples is 11-18Hz (373, 377-379).

In addition to measurement of the CBF, the samples were assessed on three-point Likert-scales for:

- Overall adequacy of sample (poor or unacceptable, adequate, excellent)
- Amount of mucus (none or slight, moderate, copious)
- Numbers of squamous epithelial cells (none or slight, moderate, copious)
- Numbers of ciliated epithelial cells (none or few, adequate, excellent)

For the pilot in adult participants the researchers also rated on three-point Likert-like scales:

- Ease of obtaining a sample (easy, moderate, difficult)
- Observed discomfort (none or slight, moderate, very uncomfortable)
• Observed cough (none or slight, moderate, severe)

The adult participants were asked to rate the discomfort of the procedure on a 0 – 10 overall pain rating and via the McGill Pain Questionnaire (380) which is a 15 question assessment of discomfort quality and severity. Participants were also asked to compare the discomfort to the discomfort of normal tracheostomy suctioning and were contacted 24 hours after the procedure and asked about residual discomfort or any post-procedure haemoptysis or bleeding.

6.1.4 Results of pilot study of CBF measurement in adults with tracheostomies

Six adult patients with tracheostomies took part (three male, age range 22-79 years). The indications for tracheostomy were bilateral vocal cord paralysis in three participants and laryngeal cancer, relapsing polychondritis, and gunshot wound each in one participant. Two were past smokers and four were never smokers.

Five strips of ciliated epithelial cells with CBF were able to be measured from only two of the participants, as samples with fewer than five cilia strips from three participants and there were no suitable strips obtained from one participant. The median mean CBF in the samples from five participants where strips of ciliated epithelium were visualised was 12.6 Hz (median standard deviation 1.7, median co-efficient of variation 14.4%) and was generally higher in participants with better quality samples (Figure 6.1).

Five of the six participants had “moderate” or “copious” numbers of squamous cells and three of the six had moderate or copious amounts of mucus. Overall
sample quality was described as poor for four participants, acceptable for one participant and excellent for one participant.

The procedure was well tolerated with all the participants stating they would be willing to undergo the procedure again if needed. The median discomfort score following the procedure for overall discomfort was mild at two (range 0 - 4 out of a possible total of 10) and two on the McGill Pain Scale (range 0 - 4 out of a possible total of 45). The researchers assessed the observed discomfort as moderate in three participants and assessed the observed cough as moderate in all participants. None had severe cough or discomfort. At 24 hour follow up by phone one participant reported flecks of blood in the airway secretions overnight after the procedure and one participant reported a small amount of pain (2/10). There was no correlation between discomfort, ease of obtaining the sample and quality of the sample or of number visible strips of ciliated epithelium (Fisher’s Exact test, p > 0.05).

At the conclusion of this pilot study it was decided that specimens for the measurement of CBF could not be obtained reliably in children without general anaesthesia.
6.1.5 Results of CBF measurement in children with tracheostomies

Despite the local clinical protocol recommending six monthly bronchoscopy for children with tracheostomies, only five of the fourteen participants underwent bronchoscopy during the study period with one participant having samples obtained under both treatment conditions. Therefore only descriptive results are provided with no statistical tests of significance performed.

All samples provided four or five strips for analysis. Three samples were judged to be of poor quality and three samples of adequate or excellent quality. The amount of mucus was none or slight for all the four samples taken after overnight treatment with HH and moderate for both samples taken after overnight treatment with HME. The number of squamous cells was variable across the HH samples and moderate in both HME samples. For observed numbers of ciliated epithelial cells after treatment with HH the numbers were low for two samples and
moderate for two samples. The numbers of ciliated cells were low in both samples after treatment with HME.

For participants on HH treatment overnight the mean CBF was 9.9 Hz (median 10.3 Hz) and for children on HME the mean CBF was 10.3 Hz (median 10.3 Hz) (Figure 6.2). The mean co-efficient of variation was 26.8% for HH and 18.0% for HME.

![Figure 6.2: Cilia beat frequency measurements in samples from the mid to lower tracheas of children with tracheostomies participating in long-term study.](attachment:image.png)

Open triangles indicate adequate quality specimens; closed circles indicate poor quality specimens.

HH = heated humidifier, HME = heat and moisture exchanger.
6.2 Mucociliary clearance scans

MCC scans have not previously been described in children or in participants with tracheostomy tubes in situ. We developed this technique for this study following descriptions of studies in adults (257, 381-390). The development of the technique required selection of a colloid, selection of a nebuliser, selection of an appropriate driving pressure, and an appropriate means and timing of image acquisition for children.

Initial determinations of radiation exposure for the planned MCC scans were made in adult volunteers who were researchers involved in the study. As shown in the results section this was approximately 0.05 millisieverts (mSv) which is similar to the effective radiation dose of a chest xray for an adult: 0.02 to 0.05 mSv for a posterior-anterior (PA) chest xray and 0.1 mSv for both a PA and lateral chest xray (391). In children, the effective radiation dose for a chest xray is lowered to 0.01 to 0.02 mSv for an antero-posterior film and we estimated that the effective radiation dose from the planned MCC scans was equivalent to two chest xrays, including lateral films, for a child. Following the scans in the adult volunteers, permission for performing MCC scans for a pilot study in three children with tracheostomies and for the long-term study was obtained from the National Radiation Laboratory (NRL) and the Auckland Regional Ethics Committee with permission granted for effective radiation doses of up to 0.8 mSv per child. Considerably lower doses than 0.8 mSv were used.

Clearance of an inhaled radioaerosol from the lungs is a two-stage process with an initial rapid stage of approximately 24 hours representing mucociliary and cough clearance from the tracheobronchial airways followed by a very slow stage thought to be related to macrophage ingestion (392, 393). The mechanisms of
retention and clearance of particles from the bronchi, bronchioles and alveoli during the slow phase is unclear. The initial rapid stage may be prolonged beyond 24 hours in patients with defects in bronchial mucociliary clearance. The rapid phase demonstrates curvilinear clearance over time with a very rapid clearance seen in the first 45 minutes followed by a relatively slower and linear clearance phase over the remainder of the scan time period. In addition, mucociliary clearance is more rapid from central rather than peripheral airways (382) and techniques of measuring MCC usually attempt to maintain a constant pattern of deposition with some authors correcting for the deposition pattern during data analysis (393). For our study we planned to develop a technique that would produce a consistent and centrally dominated pattern of deposition. Statistical analysis of the data also incorporated a measure of the deposition pattern into the analysis.

6.2.1 Selection of Colloid

A range of particles have been employed in previous studies for the performance of MCC scans. These include Teflon particles produced at a uniform size by rotating disk, human serum albumin microparticles and sulfur colloid. Tin colloid has not been previously used but is commonly used in lung ventilation-perfusion studies at the Department of Nuclear Medicine, Auckland City Hospital. Given the extensive local clinical experience with this material, tin colloid was selected for this study. Tin colloid could be expected to have the same performance as sulfur colloid with a reduced risk of allergic reaction due to the absence of the sulphur component.

6.2.2 Nebuliser device

The Pari LC Plus nebuliser (Part #22F81 with inspiratory valve cap and filter, PARI Respiratory Equipment, Inc.) was selected for this study on the basis of its
documented performance when being selected for studies of high dose
tobramycin in patients with CF (394, 395). The Pari LC Plus nebuliser is a
reusable and sterilisable nebuliser with breath-activated valves to entrain air and
increase nebuliser output. For our study the valves were closed to maintain a
constant flow and consistent particle size output. The nebuliser is generally used
with flow rates of 4-6 L/min and generates nebulised particles with a mass
median diameter (MMD) of three to five μm (manufacturer’s specifications).

The nebuliser was connected to the tracheostomy via a plastic t-piece connector
and Omniflex connector (Allegiance Healthcare Corporation, Jackson, MI, USA)
(Figure 6.3). All exhaled and non-inspired gas was filtered through a Gibeck
Humid-Vent Compact Filter (HudsonRCI, Illinois, USA) to prevent exposure of
staff and parents to nebulised material. In addition, the nebuliser was contained
in a lead canister during nebulisation to reduce radiation exposure to participants,
caregivers and staff.
6.2.3 Flow Rate

The driving gas for nebulisation for this study was medical compressed air from a size A cylinder (0.443 m³ volume). Oxygen was not used to avoid any effects of 100% oxygen on cilia or MCC. Nebulisation with dry gases has been shown to result in particle size changes post-nebulisation due to evaporation (396) and therefore, the gas from the cylinder was warmed and humidified by passing it through a Hudson Aquapak humidification chamber (HudsonRCI, Illinois, USA) placed in a passive water-bath warmed to between 38 and 42°C.

In order to determine an appropriate driving gas flow rate measurements of nebuliser aerosol droplet size were conducted with a Malvern Mastersizer S Longbench set-up laser diffraction device (Malvern Instruments Ltd,
Worcestershire, UK) with 300mm F lens at the Department of Earth Sciences, Waikato University. Mastersizer2000 version 2.14 software was used for analysing the data. Measurements were conducted in a darkened room and while nebulising normal saline. A suction source was placed opposite the nebuliser in order to direct the nebuliser flow across the lens. Starting at a distance of 5 cm, the nebuliser was advanced toward the lens until an appropriate normal distribution of measured particle size was observed. This was to place the nebuliser spray far enough away from the lens so as not to allow droplets to land on the lens resulting in measurement artefact and possible lens damage but also close enough for accurate measurement. A final optimal distance of 1 cm was selected. The nebuliser was held in position in front of the Mastersizer lens using retort stands and clamps. The temperature of the water bath was checked prior to each measurement. Serial measurements of particle size were conducted at gradually increasing flow rates with five measurements conducted at each flow rate. Each measurement involved sampling the aerosol output for 45 seconds. The nebuliser was recharged with normal saline after every seven minutes of nebulisation to prevent "sputtering".

Results from the laser diffraction were used to calculate droplet size using Mie theory, which is one of several mathematical models used for particle size assessment (397). These models convert the measurements of light diffraction patterns into particle size measurement. Mie theory requires the operator to know the refractive index of the particles measured and provides the exact mathematical solution and the most accurate results, whereas the other available models, Fraunhoffer and anomalous theory, use assumptions about the optical properties of particles and are less mathematically intensive. Anomalous theory is only appropriate in specific circumstances where light absorption is weak. Fraunhoffer theory has been used commonly in the past, but is not accurate in
measuring small droplets (397). Mie theory is the default method used by the Mastersizer2000 analysis software.

As seen from Figure 6.4, decreasing flow rates resulted in increasing particle size. However, there was also a decrease in obscuration (the proportion of light from the laser absorbed by the aerosol sample) with decreasing flow rates, indicating decreased droplet output from the nebuliser.

A flow rate of 5 L/min was selected for this study as this generated particles measured at mass median diameter MMD 5.8 micrometres (Figure 6.4). Flow rates below this resulted in obscuration of less than 10% which is below the recommended ideal range (10-30%) for accurate measurement (Mastersizer2000 software instruction manual). Previous studies of mucociliary clearance have generated particles with MMD in the range of 3-5 μm. A larger MMD was selected for this study as the breathing pattern could not be controlled and we wished to increased particle deposition in the central airways near the carina.
Figure 6.4: Plot of measured aerosol mass median diameter (MMD) with dotted lines indicating 10th and 90th centiles of droplet size. Obscuration is also plotted demonstrating a significant fall below 10% at flow rates of less than 5 L/min.

6.2.4 Definition of Lung Regions and Calculation of Penetration Index

The rate of clearance of inhaled particles from the lung is dependent on the location of deposition with peripherally deposited particles being cleared more slowly than centrally deposited particles (382). It is therefore necessary to correct clearance for the penetration index (PI) which is equal to the ratio of the peripheral to central activity per pixel per second in the initial scan (383). The central, intermediate and peripheral regions have previously been defined for the right lung (398). The left lung is excluded due to interference from swallowed material in the stomach. The central region is defined as the part of the lung closest to the hilum and within 50% of the height and width of the lung (Figure 6.5). The intermediate region is then drawn so that 75% of the height and width of the lung is enclosed, excluding the central region. The peripheral zone is the region between the intermediate region and the lung contour.
Figure 6.5: Division of right lung into central, intermediate and peripheral regions for calculation of "penetration index" and clearance from central region.

6.3 Description of mucociliary clearance scan technique

The preparation of the nebuliser solution and labelling of colloid (Amerscan™ Hepatate II™ agent, Nycomed Amersham Health Inc., London, U.K.) with Tc-99 was performed by a registered medical radiation technologist as per standard technique using commercial tin colloid and manufacturer’s instructions. Aseptic technique was used throughout. A vial was placed in a suitable shielding container and the rubber closure swabbed with the sanitised swab provided. Using a 10 mL syringe between 3 and 9 mL of the eluate from a Tc-99m sterile generator was injected into the shielded vial. This volume depended on the activity of the Tc-99. An equal volume of gas was withdrawn from the space above the solution to normalise the pressure in the vial. The vial was inverted several times to ensure complete dissolution of the powder. The total activity was assayed and the vial labelled. The vial was incubated for 20 minutes at room
Following preparation the vial was administered within six hours of reconstitution.

Between 3-6 mL of saline, depending on the volume of eluate used, were added to the vial of tin colloid. I placed 1 mL liquid containing 200 megaBecquerel (MBq) of radioactivity in the bowl of the Pari LC Plus Nebuliser. In order to make a total nebuliser charge volume of 4 mL, 3 mL of normal saline was added to the nebuliser bowl. The nebuliser was then placed in a lead canister. The patient-side outlet of the nebuliser was attached to the tracheostomy via a Fisher and Paykel Healthcare tracheostomy t-piece and Omni-flex connector. In order to create a closed circuit, a Gibeck Humid-Vent Compact Filter was placed on the end of the t-piece. The participant was seated upright during nebulisation with the child sitting on the caregiver’s lap (Figure 6.3). The nebuliser was run for 6 minutes with a driving gas flow rate of 5 L/min using medical air from a size A compressed gas cylinder. Prior to reaching the nebuliser bowl the medical air was passed through a HudsonRCI Aquapak which was warmed by placing it in a passive water-bath at between 38 and 40°C measured by digital thermometer prior to commencement of nebulisation.

For children in the clinical studies, but not those in the pilot study, the tracheostomy was suctioned five minutes after nebulisation to remove excess signal from the upper airway.

For lung image acquisition, children were placed supine in a restraining cradle used routinely for clinical imaging in the nuclear medicine department (Figure 6.6). Children were entertained by their parents and staff using toys and books. Children were allowed to get out of the cradle between images and families were encouraged to have a protracted rest between the last two images. Images were
acquired using a gamma scintigraphic camera (GE Starcam 4000 series, General Electric, Milwaukee, Wisconsin) with a 300 second image acquisition time. The camera was placed below the supine participant as close as possible with a consistent participant-camera distance between images.

![Image of child in restraining cradle during image acquisition. The gamma scintigraphic camera is placed as close as possible underneath the child. The caregiver is shown using toys to distract the child during image acquisition.](image)

**Figure 6.6:** Child in restraining cradle during image acquisition. The gamma scintigraphic camera is placed as close as possible underneath the child. The caregiver is shown using toys to distract the child during image acquisition.

Baseline images were taken at ten minutes following completion of nebulisation with further images taken at 30, 45, 60 and 120 minutes following the baseline image. The primary outcome was mucociliary clearance from the central region at 60 minutes expressed as a proportion or percentage of initial deposition and corrected for radioactive decay and background activity. Regions of interest (ROIs) were drawn using commercial software supplied with the camera and lung
images were divided into total lung, central, intermediate, and peripheral regions. The ROIs were determined from the baseline image and realigned for subsequent images to compensate for any movement of the participant relative to the camera between images. Measurements of counts per pixel per second were taken from each ROI. Clearance was corrected for the background activity and for decay of the Tc-99. As participants were allowed to mobilise between scans to improve the tolerability of the procedure for young children, we were unable to monitor the frequency of coughing or if suctioning of the tracheostomy was performed between the 60 and 120 minutes scans.

6.4 Trials in Adult Volunteers

Measurements of MCC using this technique were initially piloted in three adult non-smoking volunteers who were researchers involved in the study (Table 6.1 and Figure 6.7). The mean effective radiation dose exposure was 0.052 ± 0.023 mSv for these scans. The first two volunteers underwent three scans with the first scan being performed with slow deep breaths. As seen in Figure 6.7 this resulted in low rates of mucociliary clearance. The last two scans for all the volunteers (labelled as scans two and three for all subjects) were performed with rapid breaths with a 1:2 inspiratory to expiratory ratio to increase central deposition. Volunteers one and two showed improved consistency and clearance with this breathing pattern although there was not a measured decrease in the penetration index. Volunteer three had persistently poor clearance in both scans.
<table>
<thead>
<tr>
<th>ID</th>
<th>Scan</th>
<th>Effective Dose of Radiation (mSv)</th>
<th>Penetration Index</th>
<th>Right central lung region retention at 60 mins</th>
<th>Right whole lung retention at 60 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.021</td>
<td>0.629</td>
<td>0.992</td>
<td>0.949</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.066</td>
<td>0.502</td>
<td>0.842</td>
<td>0.845</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.062</td>
<td>0.754</td>
<td>0.677</td>
<td>0.860</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.027</td>
<td>0.510</td>
<td>0.967</td>
<td>0.915</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.055</td>
<td>0.699</td>
<td>0.906</td>
<td>0.847</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.079</td>
<td>0.663</td>
<td>0.866</td>
<td>0.873</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.032</td>
<td>0.760</td>
<td>0.939</td>
<td>0.902</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.076</td>
<td>1.025</td>
<td>0.969</td>
<td>0.951</td>
</tr>
</tbody>
</table>

Table 6.1: Results from mucociliary clearance scans in three adult volunteers. Results expressed as a proportion of initial deposition.
Figure 6.7: Results from mucociliary clearance scans for three adult volunteers.
6.5 Trials in Three Children

We next performed MCC scans in a pilot study of three children with tracheostomies (Figure 6.8 and 6.9). The mean effective radiation dose was 0.065 ± 0.026 mSv for these scans. Good quality images were obtained with two of the children demonstrating MCC. One child had an increase in signal between 0 and 60 minutes. This was thought to represent movement between images rendering the measurements inaccurate but may also have been due to retrograde flow of signal from the trachea or tracheostomy into the central lung region as high deposition was seen on the tracheostomy tube itself (an example of this from the long-term study is shown in Figure 6.11). Following this pilot we instituted suctioning of the tracheostomy tube after nebulisation but before the baseline image in order to reduce artefact from deposited signal on the tracheostomy tube.

6.6 Repeatability Measurements

During the long-term study we were able to perform repeat scans on four children while on HH to assess repeatability of the measurements (Table 6.2). This included one scan from the pilot study so repeated scans were taken up to 12 months apart and the results may reflect some long-term variance.
Table 6.2: Results of mucociliary clearance scans in participants with repeated scans to assess repeatability performed during treatment with heated humidifier

<table>
<thead>
<tr>
<th>Participant</th>
<th>Initial scan on heated humidifier</th>
<th>Additional scan to assess repeatability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual elapsed time (minutes)</td>
<td>Penetration index</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>0.181</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>0.599</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>0.158</td>
</tr>
<tr>
<td>13</td>
<td>60</td>
<td>0.147</td>
</tr>
</tbody>
</table>
Figure 6.8: Mucociliary clearance scan imaged from one of the children in the pilot study. The baseline image shows some increased signal in the heat and moisture exchanger thought to be due to coughing after nebulisation. Regions of interest have been drawn on the 30 minute image.
**Figure 6.9:** Results from mucociliary clearance scans from three children in pilot study.
6.7 Results from long-term study

For the long-term study comparing overnight treatment with either HH or HME, the MCC scans were performed at the end of the ten-week treatment period on eleven children - with valid data available on nine children. One child did not undergo scanning due to a past history of anaphylaxis. One child refused nebulisation. Individual scans from two children were excluded due to apparent measurement errors showing increasing rather than decreasing retention.

The results of the MCC scans did not show a significant treatment effect for the primary outcome of right central region clearance over the first 60 minutes \( (p = 0.194) \) or clearance from the right whole lung over the first 60 minutes \( (p = 0.092) \) (Table 6.3 and 6.4). Clearance at the 60-minute assessment point was \( 0.508 \pm 0.271 \) during HH treatment compared to \( 0.607 \pm 0.217 \) with HME (mean treatment difference: \(-0.090, 95\% CI -0.496 – 0.315, p = 0.24\) in the right central lung region and \( 0.479 \pm 0.271 \) compared to \( 0.607 \pm 0.217 \) (mean treatment difference: \(-0.070, 95\% CI -0.322 – 0.181, p = 0.157\)). There was a significant treatment effect for the secondary outcome of clearance from the whole right lung over 120 minutes \( (p = 0.027) \).

There was a significant period effect for right central region clearance over the first 60 minutes \( (p < 0.001) \). This was not explained by a difference in the penetration index by treatment or period \( (p= 0.762 \text{ and } 0.142 \text{ respectively}) \).

The penetration index had a highly significant effect on clearance for all the measured outcomes and was retained in the linear model for analysis (Figure 6.12). Figure 6.13 shows scan results from two different participants and the within-subject effects of penetration index on retention.
Figure 6.10: Mucociliary clearance scans from one of the children in the long-term study demonstrating clearance over two hours, particularly from central region. Increased signal is seen on the tracheostomy tube at baseline image.

Figure 6.11: Mucociliary clearance scan images from one of the participants in the long-term study showing probable retrograde flow of signal from the trachea into the central lung regions between the baseline and 30 minute scan images.
<table>
<thead>
<tr>
<th>Participant</th>
<th>Assessment elapsed time (minutes)</th>
<th>Actual elapsed time (minutes)</th>
<th>HH Right whole lung</th>
<th>HH Right central region</th>
<th>HH Right peripheral region</th>
<th>HME Right whole lung</th>
<th>HME Right central region</th>
<th>HME Right peripheral region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>35</td>
<td>0.442</td>
<td>0.344</td>
<td>0.689</td>
<td>1.805</td>
<td>2.317</td>
<td>0.925</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>48</td>
<td>0.437</td>
<td>0.338</td>
<td>0.683</td>
<td>45.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>0.428</td>
<td>0.321</td>
<td>0.705</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>125</td>
<td>0.409</td>
<td>0.319</td>
<td>0.656</td>
<td>143.000</td>
<td>0.364</td>
<td>0.259</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>0.478</td>
<td>0.285</td>
<td>0.978</td>
<td>30.710</td>
<td>0.575</td>
<td>0.856</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>45</td>
<td>0.466</td>
<td>0.247</td>
<td>0.946</td>
<td>45.070</td>
<td>0.571</td>
<td>0.907</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>0.467</td>
<td>0.249</td>
<td>0.911</td>
<td>60.723</td>
<td>0.579</td>
<td>0.890</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>120</td>
<td>0.425</td>
<td>0.214</td>
<td>0.879</td>
<td>120.753</td>
<td>0.426</td>
<td>1.145</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>0.674</td>
<td>0.513</td>
<td>0.842</td>
<td>30.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>45</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>45.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>0.658</td>
<td>0.462</td>
<td>0.885</td>
<td>61.085</td>
<td>0.729</td>
<td>0.915</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>113</td>
<td>0.634</td>
<td>0.462</td>
<td>0.839</td>
<td>120.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>20</td>
<td>0.820</td>
<td>0.744</td>
<td>0.831</td>
<td>30.0956</td>
<td>0.942</td>
<td>0.921</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>45</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>46.0976</td>
<td>0.846</td>
<td>1.265</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>74</td>
<td>0.523</td>
<td>0.353</td>
<td>0.893</td>
<td>74.931</td>
<td>0.811</td>
<td>1.109</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>142</td>
<td>0.432</td>
<td>0.286</td>
<td>0.734</td>
<td>120.907</td>
<td>0.732</td>
<td>1.332</td>
</tr>
</tbody>
</table>

(Table 6.3 continues over page)
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0</th>
<th>1.000</th>
<th>1.000</th>
<th>1.000</th>
<th>0</th>
<th>1.000</th>
<th>1.000</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>0.948</td>
<td>0.990</td>
<td>0.814</td>
<td>31</td>
<td>0.419</td>
<td>0.331</td>
<td>0.553</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>0.926</td>
<td>1.017</td>
<td>0.730</td>
<td>46</td>
<td>0.373</td>
<td>0.329</td>
<td>0.440</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>45</td>
<td>0.879</td>
<td>0.981</td>
<td>0.725</td>
<td>61</td>
<td>0.388</td>
<td>0.331</td>
<td>0.486</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>0.739</td>
<td>0.679</td>
<td>0.755</td>
<td>121</td>
<td>0.398</td>
<td>0.241</td>
<td>0.886</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>0.901</td>
<td>0.830</td>
<td>0.964</td>
<td>31</td>
<td>0.633</td>
<td>0.415</td>
<td>0.994</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>45</td>
<td>0.859</td>
<td>0.785</td>
<td>0.950</td>
<td>45</td>
<td>0.599</td>
<td>0.401</td>
<td>0.904</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>0.894</td>
<td>0.824</td>
<td>1.007</td>
<td>61</td>
<td>0.657</td>
<td>0.371</td>
<td>1.050</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>120</td>
<td>0.882</td>
<td>0.794</td>
<td>1.030</td>
<td>125</td>
<td>0.449</td>
<td>0.301</td>
<td>0.734</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>31</td>
<td>0.785</td>
<td>0.706</td>
<td>0.887</td>
<td>30</td>
<td>0.933</td>
<td>0.901</td>
<td>1.014</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>46</td>
<td>0.843</td>
<td>0.782</td>
<td>0.888</td>
<td>45</td>
<td>0.893</td>
<td>0.798</td>
<td>1.039</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>59</td>
<td>0.925</td>
<td>0.771</td>
<td>1.086</td>
<td>60</td>
<td>0.809</td>
<td>0.747</td>
<td>0.946</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>119</td>
<td>0.838</td>
<td>0.733</td>
<td>0.953</td>
<td>120</td>
<td>0.713</td>
<td>0.537</td>
<td>0.991</td>
</tr>
</tbody>
</table>

(Table 6.3 continues over page)
HH = heated humidifier, HME = heat and moisture exchanger.

**Table 6.3: Individual participant results for mucociliary clearance scans expressed as retention (proportion remaining of originally deposited activity).**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0</th>
<th>0.000</th>
<th>0.000</th>
<th>0.000</th>
<th>0</th>
<th>0.000</th>
<th>0.000</th>
<th>0.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td>0.450</td>
<td>0.305</td>
<td>0.879</td>
<td>30</td>
<td>0.910</td>
<td>0.971</td>
<td>0.910</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>46</td>
<td>0.329</td>
<td>0.152</td>
<td>0.857</td>
<td>45</td>
<td>0.869</td>
<td>0.959</td>
<td>0.813</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>61</td>
<td>0.361</td>
<td>0.166</td>
<td>0.851</td>
<td>60</td>
<td>0.863</td>
<td>0.910</td>
<td>0.873</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>121</td>
<td>0.311</td>
<td>0.154</td>
<td>0.740</td>
<td>120</td>
<td>0.825</td>
<td>0.832</td>
<td>0.839</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td>0.513</td>
<td>0.379</td>
<td>0.992</td>
<td>31</td>
<td>0.738</td>
<td>0.722</td>
<td>0.707</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>45</td>
<td>0.477</td>
<td>0.364</td>
<td>0.947</td>
<td>45</td>
<td>0.740</td>
<td>0.753</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>0.473</td>
<td>0.370</td>
<td>0.890</td>
<td>61</td>
<td>0.709</td>
<td>0.653</td>
<td>0.753</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>120</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>120</td>
<td>0.553</td>
<td>0.401</td>
<td>0.768</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td>1.016</td>
<td>0.969</td>
<td>1.133</td>
<td>30</td>
<td>0.628</td>
<td>0.448</td>
<td>0.884</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>48</td>
<td>0.817</td>
<td>0.750</td>
<td>0.848</td>
<td>45</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>74</td>
<td>0.686</td>
<td>0.588</td>
<td>0.795</td>
<td>60</td>
<td>0.566</td>
<td>0.333</td>
<td>0.912</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>136</td>
<td>0.567</td>
<td>0.389</td>
<td>0.926</td>
<td>120</td>
<td>0.534</td>
<td>0.319</td>
<td>0.868</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HH (mean ± standard deviation)</td>
<td>HME (mean ± standard deviation)</td>
<td>Mean treatment difference: HH – HME (95% confidence limits)</td>
<td>p value for penetration index</td>
<td>p value for period effect</td>
<td>p value for treatment effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of scans with valid data</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetration Index (central/peripheral activity)</td>
<td>0.348 ± 0.311</td>
<td>0.426 ± 0.258</td>
<td>-0.05</td>
<td>0.142</td>
<td>0.762</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right central region retention at 60 minutes</td>
<td>0.508 ± 0.271</td>
<td>0.607 ± 0.217</td>
<td>-0.090</td>
<td>0.012</td>
<td>0.137</td>
<td>0.248</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right central region retention over 60 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right central region retention over 120 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right whole lung retention at 60 minutes</td>
<td>0.479 ± 0.271</td>
<td>0.607 ± 0.217</td>
<td>-0.070</td>
<td>0.018*</td>
<td>0.205</td>
<td>0.157</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right whole lung retention over 60 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
<td>0.092</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right whole lung retention over 120 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HH = heated humidifier, HME = heat and moisture exchanger.

Table 6.4: Results of mucociliary clearance scans expressed as retention (proportion remaining of originally deposited activity). Primary outcome shown in bold.
Figure 6.12: Retention at 60 minutes right central region for mucociliary clearance scans showing relationship of clearance to penetration index.
Figure 6.13: Mucociliary clearance scans from right central lung regions of study two participants showing effect of penetration index (PI) on retention.

HH = heated humidifier, HME = heat and moisture exchanger.
PI = Penetration index.
Chapter 7 Airway Secretion Cytokine Levels

In this chapter I will describe the measurement of inflammatory cytokine levels from airway secretions under the two different treatments and the results of those measurements. For these studies I measured the cytokines interleukin-1beta (IL-1β), interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNFα). These cytokines were chosen due to their association with neutrophilic lung inflammation and their use in a previous study assessing airway secretion inflammation in children with tracheostomies (199).

7.1 Methodology

7.1.1 Sample Collection

Airway secretion samples were collected as described in Section 4.1.2. Suctioning of secretions from the tracheostomy was performed according to a standardised technique. The HME was removed and the external lumen of the tracheostomy tube wiped clean with sterile gauze. A size 8g French suction catheter with thumb trap (Triflo suction catheter with control port, Allegiance Healthcare Corporation) suction catheter was inserted down the tracheostomy tube lumen to a predetermined depth of 1 cm beyond the terminal end of the tube. Suction was applied at 100 mmHg and the suction catheter slowly withdrawn until it was at the tracheostomy lumen. Gentle swirling of the catheter occurred during withdrawal. The catheter was then reinserted, rotated 90 degrees and suctioning repeated. The catheter was then completely withdrawn and the HME replaced. Secretions were collected in the thumb trap of the suction catheter and scraped with a 20 gauge needle into a 0.5 mL pre-weighed microcontainer with a screw top lid and airtight O-ring seal suitable for cryostorage (Sarstedt AG & Co 72.730.106). Samples were transported on ice to
Labplus, Auckland City Hospital where they were re-weighed to calculate the sample weight and then stored at -80°C.

7.1.2 Sample Preparation

Samples were thawed on ice and resuspended in sterile phosphate-buffered saline (PBS) at a final concentration of 100 mg sputum/mL PBS. The samples were ultracentrifuged at 90,000g for 1.5 hours at 4°C (Beckman L70 Ultracentrifuge using a type 50.4 Ti ultracentrifuge rotor). Supernatants were aliquoted in sterile 1.5 mL eppendorfs (at least four aliquots). Samples were stored at -80°C until required for ELISA analysis.

7.1.3 Cytokine Analysis IL-8 ELISA

IL-8 was analysed using a PeproTech human IL-8 ELISA kit, catalogue number #900-K18; supplied by Abacus ALS (NZ). Samples were thawed on ice and diluted 1/10 with PBS for analysis (a small proportion of samples fell outside the standard curve and these were re-assayed using a 1/15 dilution; this assay demonstrated good linearity upon dilution). Human IL-8 ELISA analysis was carried out according to the manufacturer’s instructions. One day prior to conducting the assay, the IL-8 antibody was diluted with PBS to a concentration of 0.5 microgram per mL (µg/mL) and 100 microlitres (µL) added to each ELISA plate well. The plate was sealed and incubated overnight at room temperature. The antibody solution was aspirated from the wells and the plate was washed four times using 300 µL of wash buffer (0.05% Tween-20 in PBS) per well. After the last wash the plate was blotted on a paper towel, following which 300 µL blocking buffer was added to each well and the plate incubated for 1 hour at room temperature. The blocking buffer was aspirated and plate washed four times.
Standards at 100 μL volume provided by the kit or sample were added to each well in duplicate and the plate was incubated at room temperature for two hours. For detection, samples and standards were aspirated and the plate washed four times. The detection antibody was diluted in the diluent provided to a concentration of 0.25 μg/mL and 100 μL was added to each well. The plate was incubated at room temperature for two hours and then washed four times. Avidin-Horseradish Peroxidase (HRP) conjugate was prepared by diluting 5.5 μL of avidin-HRP conjugate 1:2000 in diluent to a total volume of 11 mL and 100 μL was added to each well. Plates were incubated for 30 minutes at room temperature and washed four times. After incubation, 100 μL of substrate solution was added to each well and incubated at room temperature for colour development. Colour development was monitored with an ELISA plate reader (Biotek Synergy 2 Microplate Reader, Biotek Instruments Inc, Vermont, USA) at 405 nm with wavelength correction set at 650 nm. A standard curve was plotted and sample concentrations in pg/mL were derived from the standard curve.

7.1.4 Cytokine Analysis IL-1β ELISA

IL-1β was analysed using a Biosciences OptEIA™ IL-1β ELISA kit, catalogue number #557966. Samples were thawed on ice and diluted 1/15 with PBS for analysis. Analysis was carried out according to the manufacturer’s instructions. All reagents, standards and samples were brought to room temperature prior to use. All standards and samples were run in duplicate and then 100 μL of each standard and sample was pipetted into the provided wells pre-coated with the capture antibody. The plate was sealed and incubated for two hours at room temperature. Contents were aspirated, the wells washed five times with 300 μL wash buffer and the plates blotted on absorbent paper to remove any residual buffer. The detection well were prepared by adding 100 μL of the detection
antibody to each well and then incubating the wells for one hour at room temperature following which the wells were washed five times with wash buffer.

The enzyme working reagent was prepared by pipetting 48 μL of enzyme concentrate into 12 mL of enzyme diluent. Enzyme working reagent (100 μL) was added to each well and the plates incubated for 30 minutes at room temperature. Following washing seven times with 300 mL of wash buffer, 100 μL tetramethyl benzidine one-step substrate reagent was added to each well and incubated for 30 minutes at room temperature in the dark. Next, 50 μL of stop solution was added to each well and the absorbance read on the plate reader (Biotek Synergy 2 Microplate Reader) at 450 nanometres (nm) within 30 minutes of stopping reaction with a wavelength correction of 570 nm. A standard curve was plotted and sample concentrations in pg/mL were derived from the standard curve.

7.1.5 Cytokine Analysis TNFα ELISA

TNFα was analysed using a PeproTech human TNFα ELISA development kit, catalogue number #900-K25; supplied by Abacus ALS (NZ) and according to the manufacturer's instructions. Samples were thawed on ice and used undiluted for analysis. One day prior to conducting the assay, the TNFα antibody was diluted with PBS to a concentration of 1 μg/mL and 100 μL added to each ELISA plate well. The plate was sealed and incubated overnight at room temperature. The antibody solution was aspirated from the wells and the plate was washed four times using 300 μL of wash buffer (0.05% Tween-20 in PBS) per well. After the last wash the plate was blotted on a paper towel. 300 μL blocking buffer was added to each well and the plate incubated for 1 hour at room temperature. The blocking buffer was aspirated and plate washed four times.
100 μL of standards provided by the kit or sample was added to each well in duplicate and the plate was incubated at room temperature for two hours. For detection, samples and standards were aspirated and the plate washed four times. The detection antibody was diluted in the diluent provided to a concentration of 0.25 μg/mL and 100 μL was added to each well. The plate was incubated at room temperature for two hours and then washed four times. Avidin-HRP conjugate was prepared by diluting 5.5 μL of avidin-HRP conjugate 1:2000 in diluent to a total volume of 11 mL and 100 μL was added to each well. Plates were incubated for 30 minutes at room temperature and washed four times. Next, 100μL of substrate solution was added to each well and incubated at room temperature for colour development. Colour development was monitored with an ELISA plate reader (Biotek Synergy 2 Microplate Reader) at 405 nm with wavelength correction set at 650 nm. A standard curve was plotted and sample concentrations in pg/mL were derived from the standard curve.

7.2 Results

We aimed to obtain samples from the 15 children in the short-term study at three different assessment points in each period (Tables 7.1-7.4) and samples from 14 children in the long-term study at baseline and at the end of each treatment period (Tables 7.5 and 7.6). Samples in younger children were often difficult to obtain and frequently of inadequate volume for analysis. This was particularly a problem for baseline measurements in the short-term study which were taken after a four-hour period of no treatment. For two children in the short-term study samples could not be located in the storage facility despite being registered there.

Cytokine levels will depend on the method of collection and whether dilution of the sample results. In a study in a similar population, Asada et al found TNFα
levels in the range 4.7 – 125 pg/mL, IL-1β 100 – 21000 pg/mL and IL-8 754 – 50000 pg/mL (199). In our samples, TNFα was in the range 1 – 437 pg/mL, IL1β 3 – 4000 pg/mL, and IL-8 50 – 24 366 pg/mL. As compared to our participants, those in the Asada study were assessed during an acute exacerbation of respiratory difficulties and would be expected to have higher cytokine levels.

For the short-term study there were no significant period or treatment effects for any of the cytokines measured (Table 7.4), although Figure 7.1 suggests increasing inflammation during HME treatment compared to HH at 20 hours for both IL-8 and IL-1β.

For the long-term study there were no significant treatments or period effects for any of the log transformed cytokines (Table 7.6, Figure 7.2). Post hoc analysis of untransformed IL-8 levels in the long-term study showed a significant treatment difference between HH and HME (p = 0.03) which was confirmed with non-parametric analysis.
<table>
<thead>
<tr>
<th>Participant</th>
<th>0 hours</th>
<th>HH 2 hours</th>
<th>20 hours</th>
<th>0 hours</th>
<th>HME 2 hours</th>
<th>20 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1858</td>
<td>12202</td>
<td>1331</td>
<td>826</td>
<td>2258</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>511</td>
<td>-</td>
<td>669</td>
<td>4392</td>
<td>2254</td>
<td>2218</td>
</tr>
<tr>
<td>3</td>
<td>1361</td>
<td>1244</td>
<td>688</td>
<td>2100</td>
<td>864</td>
<td>2496</td>
</tr>
<tr>
<td>4*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>3712</td>
<td>827</td>
<td>78</td>
<td>568</td>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>8870</td>
<td>2280</td>
<td>-</td>
<td>-</td>
<td>1253</td>
</tr>
<tr>
<td>7</td>
<td>9800</td>
<td>1208</td>
<td>3537</td>
<td>2056</td>
<td>6138</td>
<td>3079</td>
</tr>
<tr>
<td>8</td>
<td>4107</td>
<td>-</td>
<td>1128</td>
<td>929</td>
<td>581</td>
<td>1211</td>
</tr>
<tr>
<td>9</td>
<td>466</td>
<td>-</td>
<td>9035</td>
<td>58</td>
<td>915</td>
<td>15904</td>
</tr>
<tr>
<td>10</td>
<td>182</td>
<td>412</td>
<td>5293</td>
<td>225</td>
<td>327</td>
<td>24366</td>
</tr>
<tr>
<td>11</td>
<td>251</td>
<td>786</td>
<td>127</td>
<td>56</td>
<td>-</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>7203</td>
<td>5014</td>
<td>2885</td>
<td>60</td>
<td>1778</td>
<td>466</td>
</tr>
<tr>
<td>13</td>
<td>673</td>
<td>561</td>
<td>-</td>
<td>-</td>
<td>3313</td>
<td>1432</td>
</tr>
<tr>
<td>14</td>
<td>596</td>
<td>1370</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11155</td>
</tr>
<tr>
<td>15*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- = insufficient sample for analysis.
* = Samples collected but unable to be located in storage.

Table 7.1: Interleukin-8 (IL-8) levels in airway secretions for individual participants in short-term study. Levels in pg/mL.
<table>
<thead>
<tr>
<th>Participant</th>
<th>HH</th>
<th>HME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>1</td>
<td>435</td>
<td>3601</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>466</td>
<td>852</td>
</tr>
<tr>
<td>4*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>786</td>
<td>233</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>2211</td>
</tr>
<tr>
<td>7</td>
<td>1434</td>
<td>265</td>
</tr>
<tr>
<td>8</td>
<td>943</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>347</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>11</td>
<td>154</td>
<td>257</td>
</tr>
<tr>
<td>12</td>
<td>636</td>
<td>1043</td>
</tr>
<tr>
<td>13</td>
<td>1599</td>
<td>444</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>15*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- = insufficient sample for analysis.
* = Samples collected but unable to be located in storage.

Table 7.2: Interleukin-1beta (IL-1β) levels in airway secretions for individual participants in short-term study. Levels in pg/mL.
<table>
<thead>
<tr>
<th>Participant</th>
<th>HH 0 hours</th>
<th>HH 2 hours</th>
<th>HH 20 hours</th>
<th>HME 0 hours</th>
<th>HME 2 hours</th>
<th>HME 20 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>424</td>
<td>89</td>
<td>24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>210</td>
<td>31</td>
</tr>
<tr>
<td>4*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>2</td>
<td>14</td>
<td>143</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>37</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>129</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>17</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>169</td>
<td>-</td>
<td>32</td>
<td>-</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>204</td>
<td>-</td>
<td>-</td>
<td>183</td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>35</td>
<td>14</td>
<td>110</td>
<td>175</td>
<td>378</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>16</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>437</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- = insufficient sample for analysis.
* = Samples collected but unable to be located in storage.

Table 7.3: Tumor necrosis factor-alpha (TNFα) levels in airway secretions for individual participants in short-term study. Levels in pg/mL.
Baseline Two Hours Twenty Hours

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Two Hours</th>
<th>Twenty Hours</th>
<th>Overall study p Value Period Effect</th>
<th>Overall study p Value Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH</td>
<td>(mean ± standard deviation)</td>
<td>(mean ± standard deviation)</td>
<td>(mean ± standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HME</td>
<td>(mean ± standard deviation)</td>
<td>(mean ± standard deviation)</td>
<td>(mean ± standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>2560 ± 3113</td>
<td>1127 ± 1381</td>
<td>3249 ± 4134</td>
<td>1850 ± 1820</td>
<td>2459 ± 2705</td>
</tr>
<tr>
<td>IL-1β</td>
<td>582 ± 525</td>
<td>543 ± 666</td>
<td>904 ± 1149</td>
<td>689 ± 586</td>
<td>716 ± 986</td>
</tr>
<tr>
<td>TNFα</td>
<td>44 ± 57</td>
<td>61 ± 61</td>
<td>123 ± 190</td>
<td>72 ± 94</td>
<td>48 ± 63</td>
</tr>
</tbody>
</table>

HH = heated humidifier, HME = heat and moisture exchanger.

Table 7.4: Inflammatory cytokines levels in airway secretions from children with tracheostomies in the short-term study. All cytokines were log-transformed for analysis which was conducted using a general linear model with repeated measures.
Figure 7.1: Mean treatment differences for inflammatory cytokines for children in the short-term study. Negative values favour heated humidifier.

HH = heated humidifier, HME = heat and moisture exchanger.
Table 7.5: Inflammatory cytokine levels in airway secretions for individual participants in long-term study. Levels in pg/mL.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Baseline</th>
<th>HH</th>
<th>HME</th>
<th>Baseline</th>
<th>HH</th>
<th>HME</th>
<th>Baseline</th>
<th>HH</th>
<th>HME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( \xi )</td>
<td>-</td>
<td>-</td>
<td>3288</td>
<td>-</td>
<td>-</td>
<td>1114</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>2 ( \xi )</td>
<td>-</td>
<td>650</td>
<td>2462</td>
<td>-</td>
<td>58</td>
<td>561</td>
<td>-</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>3*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>775</td>
<td>728</td>
<td>763</td>
<td>336</td>
<td>309</td>
<td>146</td>
<td>-</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>4832</td>
<td>126</td>
<td>674</td>
<td>1511</td>
<td>-</td>
<td>147</td>
<td>88</td>
<td>324</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td>584</td>
<td>1734</td>
<td>1095</td>
<td>263</td>
<td>943</td>
<td>470</td>
<td>16</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>3931</td>
<td>431</td>
<td>935</td>
<td>767</td>
<td>256</td>
<td>336</td>
<td>269</td>
<td>526</td>
<td>212</td>
</tr>
<tr>
<td>8</td>
<td>18106</td>
<td>6827</td>
<td>9004</td>
<td>3469</td>
<td>3711</td>
<td>850</td>
<td>369</td>
<td>69</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>1930</td>
<td>352</td>
<td>2854</td>
<td>467</td>
<td>76</td>
<td>382</td>
<td>89</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>505</td>
<td>-</td>
<td>1534</td>
<td>192</td>
<td>-</td>
<td>430</td>
<td>29</td>
<td>-</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>2017</td>
<td>145</td>
<td>-</td>
<td>187</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>4530</td>
<td>743</td>
<td>7282</td>
<td>456</td>
<td>579</td>
<td>1328</td>
<td>18</td>
<td>-</td>
<td>128</td>
</tr>
<tr>
<td>14</td>
<td>4988</td>
<td>2844</td>
<td>5125</td>
<td>3213</td>
<td>370</td>
<td>4000</td>
<td>422</td>
<td>-</td>
<td>394</td>
</tr>
</tbody>
</table>

*Withdraw from study
- Insufficient sample
\( ^\xi \) Collection method changed after study commenced so baseline result not available
Table 7.6: Inflammatory cytokines levels in airway secretions from children with tracheostomies in the long-term study. Analysis conducted on log transformed data conducted using a general linear model with fixed subject effects.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Baseline (mean ± standard deviation)</th>
<th>HH (mean ± standard deviation)</th>
<th>HME (mean ± standard deviation)</th>
<th>Treatment Difference (95% confidence limits)</th>
<th>p Value Period Effect</th>
<th>p Value Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>4465 ± 5449</td>
<td>1645 ± 2015</td>
<td>2930 ± 2826</td>
<td>-1389 (-3031 - 253)</td>
<td>0.526</td>
<td>0.206</td>
</tr>
<tr>
<td>IL-1β</td>
<td>1186 ± 1285</td>
<td>721 ± 1154</td>
<td>817 ± 1076</td>
<td>-181 (-1463 – 1101)</td>
<td>0.789</td>
<td>0.535</td>
</tr>
<tr>
<td>TNFα</td>
<td>162 ± 166</td>
<td>139 ± 205</td>
<td>99 ± 116</td>
<td>72 (-53 – 197)</td>
<td>0.279</td>
<td>0.661</td>
</tr>
</tbody>
</table>

* P <0.05

HH = heated humidifier, HME = heat and moisture exchanger.
Figure 7.2: Mean treatment differences for inflammatory cytokines for children in the long-term study. Negative values favour heated humidifier. Error bars indicate 95% confidence intervals for the mean treatment difference.
For the short-term study a strong correlation was seen between IL-8 and IL-1β levels taken at baseline for the first treatment period (0.673, p = 0.023) (Table 7.7). No correlation was seen between IL-8 and TNFα levels and a moderate negative correlation was seen between IL-1β and TNFα levels (-0.600, p = 0.208).

For all the cytokines, there was a poor correlation between baseline levels and levels at other assessment times and the baseline assessment term was dropped from the linear model. For the long-term study a very strong correlation was seen between baseline IL-8 and IL-1β levels (0.950, p < 0.001), a strong correlation between IL-8 and TNFα levels (0.667, p = 0.071) and a very strong correlation between IL-1β and TNFα (0.833, p = 0.010) (Table 7.8).

<table>
<thead>
<tr>
<th>Spearman Correlation Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prob &gt;</td>
</tr>
<tr>
<td>Number of Observations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IL-8</th>
<th>IL-1β</th>
<th>TNFα</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>1.000</td>
<td>0.673</td>
<td>-0.086</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.673</td>
<td>1.000</td>
<td>-0.600</td>
</tr>
<tr>
<td></td>
<td>0.023</td>
<td>0.023</td>
<td>0.208</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>TNFα</td>
<td>-0.086</td>
<td>-0.600</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>0.872</td>
<td>0.208</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 7.7: Spearman correlation co-efficients for differing inflammatory cytokines from first period baseline values in short-term study.

<table>
<thead>
<tr>
<th>Spearman Correlation Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prob &gt;</td>
</tr>
<tr>
<td>Number of Observations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IL-8</th>
<th>IL-1β</th>
<th>TNFα</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>1.000</td>
<td>0.950</td>
<td>0.667</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.950</td>
<td>1.000</td>
<td>0.833</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>TNFα</td>
<td>0.667</td>
<td>0.833</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>0.071</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 7.8: Spearman correlation co-efficients for inflammatory cytokines from baseline values in long-term study.
Chapter 8 Qualitative Interviews

In this chapter I will describe the methods and results for qualitative interviews conducted with a selection of parents of children participating in the long-term study. This chapter is written in a different style from other chapters, incorporating, as it does, methodology from qualitative research which is distinct from the usual scientific paradigm of quantitative research. So, for example, the literature review forms a part of the results in qualitative research and is therefore presented in this chapter rather than in Chapter 2. The data in this chapter has been published in a peer-reviewed journal (399).

Qualitative research is increasingly employed in health as a method of exploring participants' experience and understanding of treatments (400, 401). It is often now included as a component of randomised controlled trials (402-404). In terms of study design, qualitative methods are usually incorporated into controlled trials as a sub-study or nested study within the quantitative study. This may be as a "serial" design, in which the quantitative phase follows the qualitative phase or vice versa such as with either a pilot or a follow-up qualitative phase. Alternatively, the study design may be "parallel", as embedded in the current study with a qualitative sub-study of a sample from the study population proceeding at the same time as the quantitative study.

The current study is a mixed-method study incorporating a nested, parallel qualitative phase. Grounded theory (GT) was selected as the qualitative methodology for this study. GT was described by Glaser and Strauss (405) as a formalised method for the collection and analysis of data in order to generate theory from either qualitative or quantitative data. GT is not a theory in itself but is a method for developing theory and is most commonly used to develop
substantive or “middle-range” theory that is “grounded” in data, but may also be used to develop grander formal theory. In GT research, theory is developed through induction from the data rather than by logical deduction from a set of a priori principles and is experienced by the researcher as “emerging” from or being discovered in the data. The features of a GT-based theory are that it describes underlying social or psychological processes that predict and explain the experiences (phenomena and consequences) of individuals within the scope of the setting of the study. GT usually describes a central concern of the participants and a process by which that concern is resolved. Either the central concern or the resolving process may be identified as the “core category”.

The aim of the qualitative phase of this study was to explore the experiences of parents in relation to the two humidification techniques being tested in children with tracheostomies and to explore how these parents chose whether or not to use an assistive technology such as humidification.

8.1 Method

As children completed the RCT phase of the study, parents were invited to participate in the qualitative phase. We intended to interview at least 10 participants or until theoretical saturation was reached. Mothers were selected through a process of purposive sampling aimed at capturing a range of experiences. Therefore recruitment was focused on:

1) Mothers with a declared preference for either the HH, or HME treatment
2) Mothers whose child was withdrawn from the RCT due to concerns with either treatment
Nurses caring for children with tracheostomies also had experience in using HME and HH treatment during sleep periods, so it was decided to ensure a complete understanding of the experience to include hospital and homecare-based nurses in the sample.

Using the GT qualitative method (Table 8.1), data was collected through individual semi-structured interviews with the mothers as the main caregivers and the nurses experienced in caring for children with tracheostomies. Results from the different subject group interviews were pooled and not analysed separately. Interviews were conducted by an experienced qualitative interviewer (AD) or by the principal researcher (DM) an experienced medical practitioner trained in this method. While one of the interviewers (AD) had no previous relationship with the participants, the other had been involved in the children’s care in some cases as a member of the medical team. Table 8.2 shows the initial questions asked in the interview, however in keeping with the principles of Theoretical Sampling these were adjusted to sample emergent concepts of interest. The initial comparison questions were maintained for consistency and because of their apparent utility in exploring participant’s experiences, but were shortened with regard to participant and interviewer burden. Supplemental questions pertaining to the properties of emergent categories and hypothesised relations between categories were added to the guide. Interviews were recorded on a tape recorder and were transcribed by an experienced medical transcriptionist who was familiar with the terminology of medical technology. Typed notes of the interviewer’s impressions were made after each interview. The transcripts were reviewed for accuracy in conjunction with the audio recordings by one of the researchers (DM). All the printed transcripts were then analysed.
1. Identify a field of interest

2. Start literature review in non-related fields

3. Enter the field to collect data
   - Observation of incidents (or reported incidents in interviews)
   - Meaning of incidents derived from participant interviews
   - Further observation guided by continual theoretical sampling

4. Substantive coding (first analytical stage)
   - Starts while theoretical sampling ongoing
   - Open coding
     - Reading and re-reading
     - Line by line analysis
     - Identify incidents with open codes (indicator labels)
     - Generate categories simultaneously with open codes
     - Code incidents for as many categories as possible
   - Memoing
     - Memo emergent concepts/categories
     - Repetitive cycle of identifying and re-grounding of emergent concepts
     - Once sufficient incidents collected, delimit theory by discarding non-relevant concepts
     - Identify candidates for core category
     - Further memoing until empirical descriptive model with good fit
   - Selective coding until theoretical saturation

5. Theoretical Coding (second analytical stage)
   - Starts toward end of substantive coding
   - Model substantive concepts with abstract concepts
   - Model relationships between concepts with theoretical codes
   - Sorting of memos to generate final model of theory

6. Literature review
   - Starts when core category identified
   - Identify useful relevant concepts and abstract concepts
   - Relate final theory to previous literature

7. Write-up and publication

8. Testing, verification, and modification of theory by subsequent research

| Table 8.1: Stages in grounded theory analysis as performed for this study. References: (405-408) |

Analysis was performed as described by Glaser using a process of constant comparison with ongoing theoretical sampling. The stages we followed are listed in Table 8.2. We aimed to achieve a parsimonious theory that fulfilled the validity criteria for GT, that is the theory works, has fit, is relevant, and is modifiable (406).
Please think about the time during the study when you were just using the Swedish nose* for your child's tracheostomy

How well did the Swedish nose work for your child?
How did the Swedish nose affect the amount of care your child needed?
How did using the Swedish nose affect your child overall?
How much did you worry about your child when you were just using the Swedish nose?
How much could you leave your child with another person?
What was the overall effect on you?
What things were difficult about using the Swedish nose?
What things were easy about using the Swedish nose?

Please think about the time during the study when you were using the heated humidifier at night for your child’s tracheostomy

How well did the heated humidifier work for your child?
How did the heated humidifier affect the amount of care your child needed?
How did using the heated humidifier affect your child overall?
How much did you worry about your child when you were using the heated humidifier?
How much could you leave your child with another person?
What was the overall effect on you?
What things were difficult about using the heated humidifier?
What things were easy about using the heated humidifier?

"Swedish nose" is the lay-term for a heat and moisture exchanger.

Table 8.2: Original semi-structured interview questions which were subsequently progressively modified to sample incidents and concepts of interest (theoretical sampling).

The initial stage of analysis was open coding. The analyst read the data line by line in order to identify incidents (events, phenomena or participant experiences) and assign them open codes which were concepts or labels describing or explaining the incidents. Similar open codes were then clustered to identify concepts which could serve as categories. Categories were concepts to which
multiple incidents applied and therefore had proven relevance. Each incident was coded into as many categories as possible (405). Memoing took place while coding was ongoing.

Memoing is a process of conceptualisation by which codes and concepts identified in the study are developed into theoretical categories. This process consisted of making notes about codes and categories describing the characteristics of the concepts, the codes and the categories indicated. Memoing also served to relate the concepts and the categories to each other and through this process the core category emerged. The core category is the over-arching concept of the study while the other categories become indicators for the core category. We employed specified criteria for identifying the core category (406):

- The core category was a central component of the theory
- Had multiple connections to other categories
- Recurred frequently in the data
- Took more time to saturate than the other categories
- Related meaningfully to the other categories
- Had implications for formal theory
- Assisted the analyst through the analysis
- Was completely variable
- Was also a dimension of the basic problem

Once the core category was identified selective coding commenced. During this process the researcher samples for incidents related to the core category and memoing concentrated on the core category.
The memos generated during analysis were then sorted to define the relationships between the categories and concepts. The relationships between the categories were then theoretically coded. Theoretical coding is the process of modelling the relationships between the categories using abstract theoretical concepts derived from formal sociological theory or from other GT studies. This process is analogous to using mathematical distributions such as the normal or poisson distributions to model data for statistical analysis. The theory developed during the study was thereby related to theories developed in related fields.

The emergent theory was compared back to the original data to ensure "goodness of fit" and in describing the theory was compared to the relevant literature. The literature in the current scope of the study was incorporated as a source of comparison for additional incidents, for additional concepts and for points of difference and similarity. The literature therefore served as a further source of data to be analysed and incorporated into the theory (406).

Transcripts were initially open coded with pen and paper and then re-coded using AnSWR 6.4.189 software (Analysis Software for Word-based Records, Centre for Disease Control) designed for the analysis of qualitative data. Once selective coding had commenced, all coding took place with pen and paper. Memoing took place with pen and paper or by word processor. Sorting of memos took place by hand.

8.2 Results

Interviews were conducted with nine mothers of children with tracheostomies with fathers also present during three interviews. The demographics of the children and final preference of the family are given in Table 8.3. In order to further saturate categories and in the interests of theoretical sampling we included one
mother who was recruited from outside the trial, whose preference for the HME was known. Four nurses from the hospital (n = 1) and homecare service (n = 3) were also interviewed. The interviews with the parents and the nurses were pooled and analysed together.
<table>
<thead>
<tr>
<th>Respondent</th>
<th>Child’s age at interview</th>
<th>Child’s age at tracheostomy</th>
<th>Duration of tracheostomy</th>
<th>Child’s gender</th>
<th>Child’s principal diagnoses</th>
<th>Respondent ethnicity</th>
<th>Respondent age</th>
<th>Partner at interview</th>
<th>Family preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 months</td>
<td>3 months</td>
<td>8 months</td>
<td>Male</td>
<td>Pierre Robin sequence</td>
<td>Pacific Island</td>
<td>44 years</td>
<td>No</td>
<td>HH</td>
</tr>
<tr>
<td>2</td>
<td>14 months</td>
<td>5 months</td>
<td>9 months</td>
<td>Female</td>
<td>Tracheomalacia</td>
<td>European</td>
<td>38 years</td>
<td>Yes</td>
<td>HH (did not tolerate HME)</td>
</tr>
<tr>
<td>3</td>
<td>2 years</td>
<td>14 months</td>
<td>1 year</td>
<td>Male</td>
<td>Caustic ingestion</td>
<td>European</td>
<td>39 years</td>
<td>Yes</td>
<td>HME</td>
</tr>
<tr>
<td>4</td>
<td>5 years</td>
<td>8 months</td>
<td>4 years</td>
<td>Male</td>
<td>Tracheomalacia</td>
<td>European</td>
<td>30 years</td>
<td>No</td>
<td>HME</td>
</tr>
<tr>
<td>5</td>
<td>3 years</td>
<td>2 years</td>
<td>1 year</td>
<td>Male</td>
<td>Laryngomalacia</td>
<td>European</td>
<td>32 years</td>
<td>No</td>
<td>HH (did not tolerate HME)</td>
</tr>
<tr>
<td>6</td>
<td>2 years</td>
<td>2 years</td>
<td>8 months</td>
<td>Female</td>
<td>Crouzon syndrome</td>
<td>European</td>
<td>45 years</td>
<td>No</td>
<td>HH</td>
</tr>
<tr>
<td>7</td>
<td>4 years</td>
<td>1½ months</td>
<td>4 years</td>
<td>Male</td>
<td>Subglottic stenosis</td>
<td>Pacific Island</td>
<td>31 years</td>
<td>No</td>
<td>HME</td>
</tr>
<tr>
<td>8</td>
<td>15 years</td>
<td>4 months</td>
<td>15 years</td>
<td>Male</td>
<td>Tracheomalacia</td>
<td>European</td>
<td>45 years</td>
<td>No</td>
<td>HH</td>
</tr>
<tr>
<td>9</td>
<td>2 years</td>
<td>4 months</td>
<td>2 years</td>
<td>Female</td>
<td>Subglottic stenosis</td>
<td>European</td>
<td>32 years</td>
<td>Yes</td>
<td>HH (did not tolerate HME)</td>
</tr>
</tbody>
</table>

Table 8.3: Participant demographics for qualitative interviews.
8.2.1 Core Category

The core category that emerged from the study was that mothers were engaged in “Managing the child’s care” (Figure 8.1). Mothers confronted with problematic health states attempted to resolve issues by employing management strategies. This core category of “managing” was modelled on examples of theories of process management from business literature (409-411). In these business and management theories participants who “manage” are confronted with constraints to which they respond by measuring and assessing, setting goals, acquiring new knowledge and skills, mobilising and pacing the supply of resources, employing others, and assessing progress.

In our study mothers were confronted by a set of constraining health and care states to which they responded by monitoring, adapting, learning new skills, burden sharing, and balancing. The concept of managing goes beyond performing “work” or a set of technical tasks (eg managing the HH and HME treatments) and includes the use of knowledge to make judgements, taking responsibility for outcomes, and planning for the future.

The ability to successfully manage the child’s care was affected by the child’s health trajectory and was dependent on a set of intrinsic skills possessed by the mothers which included organisational skills, advocacy skills, a stable and supportive household, and the mothers’ own health.
8.2.2 Problematic and Constraining States

Mothers collectively referred to being "in the fog" when managing a set of problematic health and care states. The reward for successfully managing was to convert them to a state of running smoothly.

8.2.3 In the fog vs Running smoothly

"In the fog" describes the experiences of mothers when their child initially received a tracheostomy. In this period, when the child was unwell and required frequent traumatic procedures, mothers felt distressed, confused, lacking in knowledge and dependent on hospital staff to the point of being too afraid to even touch their medically fragile and
technology-dependent child. With time, acquisition of knowledge and skills, improvement in the child’s health, and experience, mothers progressed to a state of "running smoothly". "In the fog" was used to refer to subsequent periods when a child was doing poorly or when mothers were not coping well. "In the fog" and "running smoothly" represent the extremes with each family at any time sitting on a continuum. The individual states that emerged were "living worried", "getting up in the night", "frequent illness" and "bearing the responsibility".

8.2.4 Living worried

Mothers in this study were in a state of constant worrying or "living worried". They resolved their worries by acquiring knowledge, adapting to problems and establishing routines. The main worry was “What if?"; what if something happened to their child without them knowing or what if their child died in the night.

“Just that the secretions would get too dry, that he would block up through the night and that I would wake up in the morning and he wouldn’t be alive. I think that scared me the most. That was the hardest part for us.” – Respondent 5.

Worry was increased by changes in the care routine and by problems that were new, unpredictable or not understood.

“We don’t cope when we don’t know … If it’s in our field of knowledge we can cope with it, we can handle it and it’s all good. It’s when it falls outside of that and we don’t know when to be worried.” – Respondent 9.
8.2.5 Getting up in the night

Getting up in the night was a frequent issue for mothers, and when very frequent, resulted in exhaustion and poor health. The two main causes were to suction and/or to manage equipment.

“It’s just you go into coping mode, lack of sleep, constant deprivation, yeah you just go into survival mode rather than, you exist as opposed to live I think is probably a better way of putting it.” – Respondent 9

Increased need for night-time suctioning occurred with thick secretions the child was unable to clear independently by coughing. This became a problem when the child was becoming unwell or when humidification therapy was not effective. Mothers also described getting up to manage equipment - to replace a HH mask or HME, to untangle nasogastric tubes from humidifier hosing, to clear condensate from the HH hosing, or to address equipment alarms. Mothers expressed resentment of having to get up in the night to manage equipment rather than their child’s health needs. The consequence of constant getting up in the night and interrupted sleep was exhaustion and mothers returning to being "in the fog". Successful resolution meant that mothers only needed to get up in the night for routine checking rather than frequent, unplanned, emergent events.

8.2.6 Frequent illness

The state of frequent illness is common early in the child’s trajectory with initial tracheostomy cannulation and recurs if the child goes through a phase of recurrent aspiration or LRTI. The chief consequence of frequent illness was being in hospital. This resulted in isolation of the mother and child and subsequent disruption of family life.
“In the beginning it was very stressful and [my daughter] was having lots of surgery and that. I worried a lot about [my other child], him being without me for so long. Overall it wasn’t a very happy experience. Toward the end it was just really boring and tedious waiting to go home.” – Respondent 6.

The opposite of being in hospital is a state of doing normal things. When the child is well the mothers can concentrate on being mum rather than the carer with this and other children in the family.

“I can play with [with my other child] more, have more time to spend together. It just gets to be a more normal day to day. We can take her out; it’s great when we take her out.” – Respondent 6

8.2.7 Bearing the responsibility

Bearing the responsibility describes the burden of duty as mothers take responsibility for not only the health and safety of their child, but also ensuring adequate supplies were ordered and delivered, and clinic appointments attended. This could become a heavy burden.

“It just sucks being in a situation where your kid’s life is in your hands, you know. It is just bullshit. It’s just wrong.” – Partner of Respondent 9.

Most mothers expressed positive attitudes to their children and seemed to accept the responsibility of their care.
“I mean, I am really lucky with [my son] because he has, even though he is non-verbal, he has got great personality and you know, he’s cheeky and he likes life.” – Respondent 8.

As part of bearing the responsibility, mothers have to perform frequent traumatic procedures on their child such as nasogastric tube insertion, tracheostomy tube changes, and deep or prolonged suctioning. The mothers reported that it fell to them to perform these tasks as the fathers felt too uncomfortable to perform them. The transition from traumatic procedures to routine cares was chiefly determined by the child’s health. Families also had additional costs; power, home modifications, and repairs to the house with wheelchairs and equipment causing damage. Having professional caregivers in the home caused some negative consequences, although mothers did not feel that this changed the way they felt about their home.

“Well I still feel like it's definitely our home and everything. It's, there's more wear and tear happening, even already. So that I get a bit annoyed about that, but not really how I feel about it.” – Respondent 6.

8.2.8 Management Strategies

In response to these constraining states which confronted them, mothers employ a set of management strategies which are modelled on the theoretical codes of the underlying basic psycho-social processes. These strategies are: constant checking, becoming the expert, family pulls together, and electing to use preferred technology.
8.2.9 Constant checking (Monitoring)

Constant checking was modelled on a process of assessing, diagnosing, responding, re-assessing, and taking preventative actions. Mothers monitored their child for signs of ill-health.

“But it is normal for me to wake up every six times to see him. I think I get used to it. I always wake up and check his nappy and see how well he is” – Respondent 1.

They also monitored the tracheostomy tube, airway secretions, the equipment, supplies, and other carers. Mothers engaged in preventative measures checking on their child if they were awake in the night or refilling the humidification chamber in order to prevent disturbance from sleep.

“Sometimes you would just get up because you woke up in the night so you thought I will just go and check.” – Partner of Respondent 2.

Constant checking also describes the way in which mothers supervised other carers. Some mothers felt unable to trust any caregivers outside the immediate family.

“The only time that me and my husband feel that he is in safe hands, is either one of us is with him at all times.” – Respondent 7.

Mothers felt obliged to stay with their child in hospital to ensure constant observation and to support their child emotionally in the unfamiliar and/or stressful environment.
8.2.10 Becoming the expert (Adapting & Learning)

Becoming the expert describes how mothers progressed from a state of feeling ignorant about the care of a child with a tracheostomy to a state of independent, expert practice. Mothers manage this by gaining knowledge and skills, becoming practiced at cares, developing routines, and eventually knowing more about their child’s care than healthcare professionals. Having become experts, mothers then became a source of knowledge and expertise for other parents.

“The hospital there, I know more about the medical procedures than they do because they have never seen a kid with a gastrostomy, a trachey tube. You know, no disrespect to them, but they would have a heart attack if I took her up and said ‘Can you do this?’ “ – Respondent 2.

Following training and learning the care routines in hospital, mothers must then adapt these routines to suit themselves and their lifestyles. Routines were particularly important for coping with the technology that supported the child.

“We just made it routine; we went and got the pyjamas, we turned the humidifier on. So, it was a piece of cake really.” – Respondent 4.

8.2.11 Family pulls together (Burden sharing)

Most of the burden of caring for the child fell to the mother as the usual main caregiver, but the burden was shared with other family members at times. Some fathers contributed becoming involved in their child’s care and supporting the mother.
“Especially if he is off in the weekends then he tries to take over while I get a break.” – Respondent 7.

When the child was admitted to hospital accompanied by the mother, the burden of managing the house other children fell to the father or siblings. Caregiving then became a shared experience with the family supporting each other through tiredness and/or difficult times.

8.2.12 Electing to use preferred technology (Balancing)

This strategy explained the principal concern of the researchers; how families choose which technology to use. In order to explore this further we also needed to ask mothers’ experiences with these and other technologies beyond HH and HME. Mothers balanced the perceived effectiveness of the device (overall comfort and happiness of the child) against the difficulties of using the device (ease of use, reliability, maintenance, and portability). These factors were also balanced against the positive or negative effects of the treatment on the problematic states which mothers had to manage.

Mothers assessed effectiveness of a device or treatment principally by the child’s overall level of comfort. Trauma to the child was negatively associated with perceived effectiveness, and mothers balanced the trauma of the treatment against the improvements gained from its use.

“What is more effective for her health wise is going to have much better benefits for all of us, regardless of simpleness of ease and all the rest of it. Because if she is happy; we are happy. She is settled; we are settled. Yeah, she is not traumatized; we don’t get stressed.” – Respondent 9.
Effectiveness was also judged by the need to perform suctioning with mothers favouring the option that led to less time suctioning. Some children had more LRTIs while on the HME and these mothers expressed a strong preference for the HH. Most children in this study had thinner secretions which they were able to clear themselves in the night while using the HH. However, some mothers found that their child needed no overnight suctioning while on the HME but needed one or two routine suctions while on the HH so preferred to continue with HME. Other children had no infections on either treatment and maternal preference was therefore determined by other factors.

Ease of use and feelings of frustration were important factors in determining mothers’ preferences. Ease of use was principally related to “fiddly” adjustments, difficulties threading tubing, and time. Reliability and maintenance issues also affected preferences, improved if there was regular access to a regular maintenance service. Portability of the devices was also important.

Both devices used in this study presented frustrations as reported by these families and the nurses. Regarding the HH:

- Some children found the heat uncomfortable and kept moving the mask
- Condensation would form in the tubing and produce gurgling noises
- Water in the hosing would run back into the humidifier chamber, cooling the water and triggering alarms
- The humidifier hosing would get tangled in nasogastric tubes and mothers would have to get up to untangle their child
- Most mothers had difficulties with the lack of portability of devices
Regarding the HME:

- Some children continually pulled the devices off
- Some children appeared uncomfortable with increased work or rate of breathing
- Secretions would collect in the HME if the child coughed in the night so that mothers would have to suction and change the HME
- Mothers would have to carry several devices with them and had difficulty sourcing adequate quantities
- Three of the children failed to tolerate HME devices because of thick secretions or LRTIs

8.3 Discussion and Comparison With The Literature

In the qualitative phase of this study, our aim was to explore the experiences of mothers in relation to the two humidification techniques being tested in children with tracheostomies and to explore how these mothers chose whether or not to use an assistive technology such as humidification. As the study progressed we also asked about mothers’ experiences with other technologies. From this we have developed a GT which shows the range of strategies employed by the parents confronting a set of problematic health states to manage their child’s care. In refining and theoretically modelling this theory, the theory developed for this study has been influenced by previous literature, particularly literature related to theories of stress and coping. During the development of this theory we have compared it to previous GT in this field of study.

Caregivers have been recognised as performing the “work” of care in chronic illness (412, 413) and as the experts and managers of their child’s care (414-418). “Managing it” was a core category found in parents dealing with exacerbations of their child’s asthma (419) - managing was described as an active and dynamic process, not merely
coping. Wilson et al (1998) developed a core concept of “Absolute involvement” in which parents of children with tracheostomies employed strategies to manage constraints and resources in caring for their child. We, in a similar group of children, have also described a core category as one of “managing” based on examples from the business management literature (409-411). In comparing the studies, Wilson et al described resources such as personal support systems or hospitalisation that may at times become constraints whereas in our study constraints and resources were distinct categories. Wilson et al also maintained a distinction between specific strategies and basic processes whereas we have attempted to integrate these in our theory (Figure 8.1).

Similarly, previous studies have found that parents are the ones bearing the responsibility for their child’s care rather than the health professionals (418, 420, 421). This responsibility may not be welcomed by parents, but they feel obligated as they love their child (422). Parents also feel pressured by professionals who assume that parents will be willing to take on responsibility and perform all the complex and uncomfortable cares for their child (423, 424).

In our study, mothers were generally the prime caregivers and in some cases did not trust their partners to look after the child. This finding that the ‘mother does it all’ or ‘carries the burden’ is a common theme in the literature (425, 426). Some siblings were recruited to assist with the care of the child. This strategy of sharing the burden of domestic or health care tasks with other children has been described previously (427).

The concept of families of children with chronic illness progressing through stages of coping with their child’s health management is well described (418, 422, 428, 429).
Jerrett (1994) reported parents progressing from “turmoil and confusion” to “taking charge”. Carnevale et al (2006) compared families where family life was stable or “under control” to those who were unstable and “on the verge of unravelling”. Knafl and Deatrick (2003) described five family management styles or typologies; “floundering”, “struggling”, “enduring”, “accommodating”, and “thriving. In our study families were seen to start in the fog, a state akin to “floundering” and progress to running smoothly akin to “thriving”. When the child’s health deteriorated and mothers were plunged back in the fog, they described themselves as “surviving” or enduring “day to day”.

Anxiety and worry are commonly described in studies of parents caring for chronically ill or technology-dependent children (426, 430, 431). The level of worry and stress described by parents in previous studies has caused symptoms of anxiety and depression severe enough to warrant psychiatric evaluation or treatment in up to 50% of mothers (22, 23, 27, 432-434). Stress and worry have also been found to affect the parents’ relationship (22, 435-438). The concept living worried used in our study was described by Monsen in a study of parents of adolescents with spina bifida (439). For those parents worrying began at the child’s birth and was ever present. The parents’ chief concern was constant worry about the future; worry about their child’s future care, independence, and normalcy. We have enlarged the concept “living worried” to embrace worries about the present, principally the worry “What if?” which is the fear that something will happen to the child or the child will die in the night. Like the participants in our study, parents in other studies of chronically ill children reported worrying about their child dying and a need for constant vigilance without respite (420, 422, 436-438, 440). In our study, parents who were “in the fog” were preoccupied with fears of their child dying, whereas those parents who were "running smoothly" had worries about the future and issues of normalisation for their child.
Uncertainty and unpredictability increased the levels of worry for parents in our study and have been associated with increased stress in previous studies (438, 441-446). Uncertainty may be one of the factors that contributes to the development of post-traumatic stress disorder in parents (447). Parents in previous studies have used the acquisition of knowledge and the development of routines to reduce uncertainty and to manage their stress (417, 418, 420, 442, 445, 448-450). Likewise in our study parents utilised "becoming the expert" or adapting and learning to manage their child and their stress. This suggests that instability or uncertainty may be a consequence as well as a cause of poor coping.

In our study, parents becoming the managers of their child’s care was a gradual process of adopting a new role or identity. There was initial loss of the role of competent carer at the time of tracheostomy insertion which was gradually regained through "becoming the expert" and adapting and learning. There was also the loss of the child's identity or potential identity as normal and healthy. Parents then gradually took charge until they reached a point of independent expert care of their child at home with all the responsibilities and duties of the chief manager of the child’s health care. Parents remained open to health professional advice and during acute changes in the child’s state were willing to hand responsibility back to the professionals. However, if the professionals did not provide care of an adequate quality to satisfy the expectations of the parents then the role of manager would be taken back.

Frequent waking in the night resulted in exhaustion for parents in our study. Tiredness and fatigue are commonly described in the literature on caring for a chronically ill child (425, 426, 430). Parents suffer from broken sleep due to frequent interruptions (31, 451)
especially when frequent illnesses increase the burden of direct medical and nursing cares parents perform (22-25, 27, 31, 434, 440, 451). These interruptions may be due to anxiety and insomnia, equipment or monitor alarms, episodes of care, acute illness, or to normal childhood awakenings. Similar to our study, Heaton et al identified problems with blocked and kinked feeding tubes and with false alarms (452). In that study, parents were only able to get a full night’s sleep if equipment was not used for the night or if there was some form of respite such as an overnight carer or the out of home care.

Fatigue may also relate to the constant unrelenting demands of care and the need for constant vigilance even in the night (420, 438-440, 442). This combination of sleeplessness and vigilance may lead to exhaustion and burnout (436, 437, 453, 454). Tiredness and the demands of caring may force mothers out of employment or create difficulties for them at work (25, 427). Respite serves as an important resource for these families, providing an opportunity for recovery from exhaustion and a period of normalcy for the rest of the family (452, 454).

"Frequent illness" describes the episodic deteriorations that affect the child and the fluctuating and unpredictable health states of chronic illness where good days may be followed by bad days (455). Although episodic deteriorations may result in hospitalisation it also increases the burden of direct medical and nursing cares that parents perform. The burden of care imposed on parents fluctuates with the health state of the child. In previous studies, parental coping and family well-being have been found to be inversely related to the time or intensity of burden of care (22-25, 27, 434, 440). Parents describe increased worry and stress at critical times such as acute illness and hospitalisation (438, 456). These episodes are unpredictable and disruptive and increase the levels of uncertainty with which parents have to contend.
Prolonged hospitalisation and difficulties with discharge planning were common in descriptions of technology-dependent children, particularly those who are dependant on ventilators, with children spending months in hospital after they are medically stable (457, 458). However, despite the stressors of caring for the child at home most parents prefer home care and feel that their child does better at home than in hospital (459). Hospitalisation is a time of uncertainty and increased stress for parents (442, 460). Hospitalisation also disrupts the family routine, puts pressure on the family budget, and may increase difficulties in dealing with professionals (420). In the current study, children suffered prolonged hospitalisation when there were difficulties arranging adequate home care support or when their child went through a period of frequent illness. These parents experienced frustration and boredom.

In our study, resolution of the problems of "frequent illness" and being in hospital meant the ability to do normal things with the child and as a family. Normalisation, i.e. attempting to provide a normal family life or home, has been described in previous studies as a major strategy employed by parents to manage childhood chronic illness (422, 428, 439). However, for children who are severely disabled, medically fragile, or technology-dependent, “normalcy” is not possible (420, 448, 461-463). Some studies have described parents as struggling to define a new meaning of “normal” within the constraints of the differences imposed by the child’s condition (450, 462, 463). Normalcy applies not just to doing normal things but also to the child appearing normal and fitting in. In the current study, most parents reported that their child’s condition was generally not noted in public as the tracheostomy tube is relatively discreet. Oxygen tubing or nasogastric tubes were more likely to attract comment as were performing cares such as suctioning and adjusting feeding pumps. Previous studies have noted that the
differences in a child’s appearance, behaviour or the way that parents provide care, particularly normal parenting care such as disciplining their disabled child in public can attract unwanted stares or comments and be stressful (439, 461).

In previous studies, parents have struggled with relationships with professionals (426, 430, 431, 464). Parents may feel that they have been thrown into a web of unwanted relationships with a multitude of professionals (465). Parents have expressed fears about upsetting professionals and compromising the care of their child or have been forced to develop strategies in order to get along with professionals (420, 440). Parents have also expressed a need for partnership and recognition of their status as experts in the care of their own child (416-418, 442). Parents have a special level of knowledge and care because of their continuous and emotional relationship with their child (418, 421, 466, 467). When there is overnight or full-time professional care in the home, the role of the parent and the professional need to be negotiated and continuously revised as parents gain new skills or have new stressors imposed on them by changes in their child’s needs (468). Some parents have reported managing carers who come into their homes by setting and enforcing rules (420, 461). Similarly to our study where parents felt the need for "constant monitoring" of carers and always being there, parents have also expressed concerns about the skills of staff assigned to look after their child, with some carers lacking basic necessary competencies, and parents, therefore, feeling unwilling to leave the child in their care (28, 416, 417, 459, 461).

Although having caregivers come into the house is a welcome relief, studies have generally shown that parents experience an invasion of their privacy (421, 469-471). Some authors have interpreted this invasion as a constant reminder to parents that their child is not normal (421, 470). Unlike our study, several studies have reported that
parents experience a change in the meaning of their home and that it has become a mini-hospital or place of work rather than a place of comfort and security (421, 471).

In shifting the care of the technology-dependent child from hospital to the home there has been a shift in the financial burden from the health system on to parents (430). Financial stress is one of the major burdens described in previous studies of technology-dependent children, usually exceeding the physical burden of caring for the child (459). Inconsistencies in funding are common, with many families having to pay for some items and costs themselves (25, 459). These costs include not just specific care costs but also increased electricity costs, travel costs, and phone bills which may not be covered by any funding source (22, 25, 438, 459). This is at a time when one parent may no longer be able to work because of the demands of caring for the child, putting further pressure on family finances. Financial stress leads to significant distress and even psychiatric symptoms in parents (26, 432, 459).

As in our study where parents expressed frustration with the hassles of dealing with fiddly or unreliable equipment, significant inconveniences due to the malfunction of equipment are also commonly reported in previous studies with families unable to leave the house while waiting weeks for replacement wheel chairs (422). Parents feel that they constantly struggle with suppliers and funders to service and maintain equipment (28). The delivery of supplies often needed to be re-organised by parents following discharge (427). Stress is not just related to underfunding and the lack of support but the continual need to advocate to obtain sufficient support (28, 435).

The difficulties of lack of support also extend to obtaining carers for the home or for respite (28). Funders may not support the way in which parents need or want to use
respite, particularly if the mother is trying to remain in employment (427, 472). Parents can feel that they are dumped into the community with no support and left to fend for themselves (459, 473). Even when there is funding, appropriately trained carers may not be available and parents report hiring and training their own formal and informal carers (25, 420, 435). The end result of lack of funding and support is social isolation of the family as they are unable to maintain social ties due to the time demands of their child’s care (22, 25, 422, 438, 459). This means loss of social support which is an important protective factor in coping with the stress of caring for a child with a chronic illness (27, 433, 434, 440).

Performing traumatic procedures on one’s own child turns around the usual expectations parents have of loving and protecting their children and means taking on a new role and identity as nurse as well as parent (421, 468). However, in most studies parents report rapidly getting used to this aspect of care and performing procedures because it has to be done. Learning to perform the medical care for a child can also be a source of feelings of mastery and improve parents’ perceptions of coping (27, 28, 474). The need to perform traumatic procedures on one’s own child was less of an issue in this study than in previous studies of children with chronic illness (421, 468, 475). This is likely to be because most of the children in the current study were advanced on their trajectory, were accustomed to suctioning and had gastrostomies rather than nasogastric tubes. None of the children in the study was currently requiring regular blood tests or intravenous treatments.

We also wanted to specifically investigate factors which determine the mothers’ choice whether or not to use an assistive technology, such as humidification. The responses showed that mothers engaged in a process of balancing the effectiveness of the
technique versus the difficulties of using the device to decide their preference. Here, the effectiveness was measured by the overall outcome that using humidification had on the child’s health. This included the level of comfort for the child, the need to perform traumatic procedures, the need to get up in the night to manage the child's secretions or the equipment, the level of parental worry of something happening to the child in the night, and the risk of the child developing an acute illness. Issues decreasing the acceptability of a device were related to ease of use, reliability, ease of maintenance and portability.

The cross-over design of the RCT allowed the mothers in our study to have the opportunity to try both treatments. After the first weeks, all mothers appeared to form differing but strongly held preferences for one or other treatments. Three children had recurrent LRTIs or very thick secretions to the point of failing treatment on the HME and, unsurprisingly, these mothers had a very strong preference for the HH. Two additional families preferred the HH as it decreased the thickness of secretions and the need for suctioning during the night. However, four mothers preferred the HME at night as they felt any benefit from using the HH was outweighed by the increased difficulties of use. We found that mothers used their own experience and judgement as the experts in their child’s care rather than relying on the recommendations given by medical and nursing staff in determining which treatment they preferred for their child.

In conclusion, we found that caregivers are the managers and experts in their child’s care and bear the responsibility of treatment decisions. The choice whether or not to use an assistive technology, such as a HH versus an HME overnight in children with tracheostomies, took place within the overall context of how caregivers managed their
child’s care. The stated preference for one device over the other had balanced the perceptions of positive and negative factors within the family context rather than relying solely on the recommendation from health professionals. In this way, the choice should therefore not be viewed as being non-adherence, but an active decision by caregivers to improve their own coping and the care of their child.
Chapter 9 Discussion

For this thesis I have conducted two randomised cross-over studies comparing overnight treatment with a HH to treatment with a HME for conditioning the gases inspired by children with tracheostomy tubes in situ. The short-term study compared 20 hours of treatment following a four-hour wash-out period while the long-term study compared eight weeks of treatment following a two-week wash-in period. The two studies differ in that for the short-term study all assessments were conducted with the assigned treatment applied whereas for the long-term study assessments were conducted at the end of the treatment period and while participants were wearing the HME device irrespective of treatment allocation.

For this chapter I will summarise the results for each outcome measure on a chapter by chapter basis. I will then discuss limitations of the study. Finally, I will discuss possible future research directions.

9.1 Clinical outcomes from the short-term study

Participants in the short-term study were assessed for clinical examination findings, airway secretion characteristics and overnight events. On clinical examination participants were found to have a lower summary respiratory examination score (p < 0.001), with lower respiratory rate (p = 0.038), less retractions (p = 0.011) and less wheeze (p = 0.020) when treated with HH compared to HME. Oxygen saturations were also improved to a statistically, but not a clinically, significant level. The observed improvement in clinical examination findings may represent the result of improved conditioning of inspired gases. Improved conditioning or humidification of inspired gases may reduce mucus inspissation and lung atelectasis and thereby work of breathing.
There may be an acute effect of inadequate humidification on airway inflammation and wheeze similar to the effects of breathing cold dry air in asthma which may have resulted in acute changes in work of breathing.

On the other hand, the respiratory rate and work of breathing may also have been increased by a direct mechanical effect of the HME. The addition of a HME imposes increased dead space and airway resistance. In adults spontaneously breathing through tracheostomies the use of a HME has not been found to significantly affect work of breathing (317). However, in adult patients ventilated for respiratory failure the additional load of a HME has been shown to result in either a small decrease in ventilation or a compensatory increase in work of breathing (300, 301, 310-313). Adults spontaneously ventilating via a tracheostomy have usually undergone laryngectomy for cancer and are less likely than tracheostomised children to have lung disease and, therefore, are less likely to be affected by the additional mechanical load of a HME. In addition, the increase in dead space imposed by the addition of a HME to the airway may be relatively greater in an infant or small child compared to an adult, especially given that adults and children all wear the same size and volume HME. Potentially, the increased work of breathing related to the mechanical load of a HME may not be clinically significant. However, the increased respiratory rate and effort will increase the energy required for respiration, resulting in increased utilisation of calories from nutrition. This may in turn affect weight gain, resulting in failure to thrive. Prolonged increased work of breathing may also potentially have an effect on neurocognition similar to that seen in the obstructive sleep apnoea syndrome. This is a disorder characterised by prolonged periods of increased work of breathing against increased upper airway resistance and has been shown to be associated with deficits in neurocognition (476).
No difference was found between treatments in assessing the characteristics of suctioned airway secretions. This may be explained by the lack of observed variability in airway secretions between treatments and over time. In addition, approximately half the samples were of small or no volume so there may have been inadequate volumes to appraise some of the secretion characteristics such as colour and thickness. When secretions become dehydrated the amount of secretions obtained on suctioning may decrease in volume as well as increase as they may be retained in the distal airway.

Overnight there was no difference noted in terms of mean oxygen saturation, mean pulse rate, or numbers of time suctioned with and without saline. There were no tracheostomy occlusions on either treatment requiring an emergency tracheostomy change. The duration of treatment may have been too short to demonstrate a difference in these outcomes as the effects of inadequate humidification increase with time (272). In previous studies in adult ICU patients endotracheal tube occlusions have also been a relatively infrequent event and so a larger or longer study might be needed to demonstrate a difference in overnight events (333, 334, 340, 341).

9.2 Clinical outcomes from long-term study

In the long-term study a significantly smaller proportion of participants experienced a major clinical event when treated with HH as compared to HME. As shown in Figure 5.2, there were also trends toward decreased acute admission for any cause and acute respiratory admissions, chest infections, decreased emergency tracheostomy change or occlusion, and decreased treatment failure or study withdrawal. Indeed, no participants experienced treatment failure while on treatment with HH. The two participants who withdrew from the study both did so while on treatment with HME; however their stated reasons for withdrawal were not related to treatment. In a secondary analysis a
significant decrease in time-to-event was shown for the outcomes of time to a first major clinical event and a trend toward decreased time to acute admission, chest infection and treatment failure or study withdrawal. The decrease in clinical events while on treatment with HH is consistent with our early anecdotal experience which resulted in the initiation of this research. While the ICU literature suggests decreased ETT occlusion events with the use of a HH compared to HME in ventilated adult patients (333, 334, 340, 341), a reduction in episodes of pneumonia has not been consistently demonstrated, although participants with thick airway secretions were excluded from all the reviewed trials in a meta-analysis (354). Previous studies in spontaneously ventilating tracheostomised adult patients have generally compared no treatment to humidification via HME and only one previous study has assessed the occurrence of clinical events over a prolonged period (358). In that study there was a decrease in the occurrence of pneumonia with the use of humidification.

The chief weakness of this aspect of our study was the inability to recruit the intended number of subjects with resultant small sample size. The long-term study was planned and designed partly on the basis of an increasing number of children with tracheostomies, particularly children who had had tracheostomies in place for a number of years. However, there was an increase in the rates of tracheostomy decannulation or death for children with tracheostomies under the care of the Starship Children’s Hospital ENT team during the years 2003 and 2004 (Figure 9.1). This resulted in a decrease in the available population of children with tracheostomies during the study recruitment period.
Figure 9.1: Graph of number of children having tracheostomies inserted per year under the care of Starship Children's Hospital and number of children having tracheostomies decannulated, dying or turning 18 years old per year. Results derived from a database maintained by the Starship Children's Hospital ENT team.

If the observed trend toward decreased clinical events is a real effect, a larger sample size may enable statistical significance to be reported. Retrospective power calculations suggest that at an alpha level of 0.05 and power level of 80% and utilising the McNemar test, the study would require: 36 participants for the outcome of all major events, 29 participants for the outcome of acute admission, 39 participants for the outcome of acute respiratory admissions, 55 participants for the outcome of chest infection, 163 participants for the outcome of tracheostomy tube occlusion or emergency tracheostomy change and 20 participants for the outcome of treatment failure or study withdrawal. These sample sizes are larger than the sample sizes for the significant results in the
current study as the McNemar test is less powerful than the statistical tests used for this study and sample size calculators are not available to account for ties in the data.

A Type I error must also be considered for the observed trends in major clinical events which may not be present in a larger sample due to the small sample size and the possibility of over-representation of events. In addition, analysis of this section is complicated by the cross-correlation of results which may result in a form of Type II error. For example, treatment failure resulting in cessation of treatment during one of the periods may prevent the observation of chest infections or hospital admissions in that period thereby biasing results. In addition, participants withdrawing completely from the study during the first period do not contribute data to the second period. This is more significant for the time-to-event data where withdrawal in the first period resulted in censoring of all outcome events in the second period for two of the participants. In addition, for many of the participants data for an outcome was censored at the end of the period if they did not experience a particular event. If the participant was censored in both periods for a particular event this resulted in their data being "undefined" and not able to be utilised for the planned analysis (367). This suggests that time-to-event analysis may not be suitable for relatively short-term duration studies, although Feingold and Gillespie (367) did propose an alternative less powerful analysis which makes full use of the data irrespective of censoring. As the author of the textbook on the statistical analysis of cross-over studies (363, 477) does not specifically recommend this test it was not considered for the current study. The results from our study may also have been biased by participant baseline preference, particularly with respect to the outcome of treatment failure. This may have resulted in parents interpreting thick secretions as treatment failure while on HME even if the treatment might have been tolerated if continued for the full treatment course. A further source of bias was that treatment failure
while on HH was not a measurable outcome as HH was regarded as standard treatment and treatment failures were returned to HH treatment. All participants had tolerated HH treatment prior to recruitment. For a future study "treatment intolerance" should be substituted for treatment failure as this outcome could be measured for both treatments.

We also found a decrease in retrospectively recalled chest infections but not other events during treatment with HH in our study. However, the retrospectively recalled data for other outcomes was not completely consistent with the prospectively recalled data (the primary outcome) and these results should therefore be interpreted cautiously. The recall of events could have been improved by the use of a diary to record daily symptoms and events. This was not performed for the current study as we were keen to balance achieving the study with the degree of additional burden imposed on participating families.

On clinical examination there were no observed differences between treatments for any of the measurements performed. The lack of difference on examination is in contrast to the short-term study where significant differences between treatments were seen. This is most likely because for the long-term study all participants were wearing the HME at the time of assessment for the purposes of partial treatment concealment. This suggests that the difference observed in the short-term study is the result of the airway resistance and dead-space imposed by the HME rather than an effect of humidification. However, it may also be that after prolonged periods of treatment with HME participants habituated to the decreased humidification capacity of this device. From the qualitative interviews discussed in Chapter 8, some parents reported that their child's secretions and breathing improved over a time period of years and the results may also be explained by the child
no longer requiring the increased humidification from the HH. However, this last explanation is not supported by the data on major clinical events.

Similar to the short-term study, in the long-term study we did not find a difference between treatments in examination of the characteristics of suctioned airway secretions, and there was surprisingly little variability between treatments in this outcome. This may be due a true lack of treatment difference or masking of any difference by the participants wearing the HME at the time of assessment. In the short-term study we did not observe a treatment difference in assessment of airway secretions over the time period of the study so it would seem that masking of a difference through the use of the HME on the morning of assessment is an unlikely explanation. The assessment measure used had previously demonstrated a treatment difference in a study of adults in ICU by Branson et al (339). The volume of airway secretions obtained in the study we conducted were likely to be much smaller than that obtained from adult patients by Branson et al. In addition, the technique for assessing airway secretion thickness by aspiration of fluid through the catheter may not have been performed identically to the Branson study as they did not describe the volumes of fluid used. The size of the catheter may also have had an important effect as we used smaller diameter suction catheters to suction the smaller lumens of the children’s tracheostomies. It would have been useful to perform an objective measurement of the secretions such as mucus viscoelasticity in addition to the subjective visual assessment thereby demonstrating any deficiencies in the visual assessment. Unfortunately the planned measurement of mucus viscoelasticity was unable to be performed during the study period.

We also assessed the effects of the two overnight treatments on parental reports of their own health-related quality of life (HRQOL) via the SF26v2 questionnaire and of parental
and parent-reported child HRQOL via the Pediatric Tracheostomy Health Survey Index (PHTSI). As expected due to the known stresses of caring for a child with a tracheostomy, parents of children in the study reported significantly lower HRQOL than the general national population in the SF36v2 domains of general health, energy and vitality, social functioning and emotional health. The mean mental component summary score was also significantly lower than that of the national population \((p = 0.008)\). This difference was not seen for the physical component summary score \((p = 0.355)\) or the domains of physical functioning, physical role and bodily pain. These results were similar to previous studies of caregivers of adults and children with tracheostomies or on home ventilation where high levels of stress, fatigue due to broken sleep and social isolation have been reported. These results were also consistent with the findings of the qualitative interviews described in Chapter 8.

We did not find a difference between treatments for any of the domains of the SF36v2. Figure 5.5 demonstrates the slightly higher mean parental HRQOL scores across all domains during treatment with HH as compared to HME. However, the mean difference was below the generally recognised minimal clinical significant difference of five points. The figure also shows the wide variability in the domains of mental and social health which suggests that a larger sample would be needed to demonstrate any effects of treatment on parental HRQOL using this measure.

We modified one of the domains of the PTHSI questionnaire and changed the overall reporting time frame of the questions for this study, so we are unable to compare results from our study population directly to previously reported studies utilising this questionnaire. Furthermore, the previous studies have included children on home ventilation via tracheostomy which would be expected to have a greater impact on the
parents’ and child’s HRQOL than tracheostomy alone. In assessing correlations a weak correlation is defined as being between 0.2 and 0.39, a moderate correlation between 0.4 and 0.59, a strong correlation between 0.6 and 0.79 and a very strong correlation between 0.8 and 1.0 (478). Utilising baseline responses we found good internal consistency with a Cronbach’s alpha statistic greater than 0.8 in three of the four domains; health/hospital visits, child stress and parent stress. In the remaining domain of child physical health the internal consistency was moderate at 0.57. Between domains there was moderate agreement between the domains of child physical health and health visits (Pearson correlation co-efficient 0.67, p = 0.02), child physical health and parental stress (0.51, p = 0.09) and parental stress and health visits (0.54, p = 0.07). Correlation between the domain of child stress and all the other domains was poor. This is likely to be due to this domain being a proxy report of another individual’s HRQOL status and proxy reports may not correlate well with the individual’s own report, particularly for non-observable domains such as psychologic and social domains (479). In developing the PTHSI, Hartnick et al reported within domain Cronbach’s alpha scores of 0.66 to 0.87 (370). They also found a moderate correlation between the PTSHI domain of parent stress (referred to as caregiver burden in that paper) and the SF12 summary mental component score but no strong correlations between the PTHSI domains and the SF12 physical component summary scale (32). For the baseline results from the current study, moderate to strong negative correlations between the PTHSI domain of parental stress and the SF36v2 domains of vitality (-0.73, p = 0.007), mental health (-0.74, p = 0.006) and the mental component summary scale (-0.584, p = 0.046) were found. There was also a moderate to strong negative correlation between the PTHSI domain of health visits and the SF36v2 domain of general health (-0.65, p = 0.021) and a moderate relationship between child physical health and parental general health (-0.61, p = 0.035) suggesting an effect of the child’s physical health on the general health of the parent.
We did not find a correlation between PTHSI measures of the child’s health and the SF36v2 domain of parental social functioning (-0.08, p = 0.80). This suggests that beyond the effect of the child having a tracheostomy the child’s level of health might not contribute strongly to social isolation. Due to the small sample size these correlations should be interpreted cautiously.

In comparing treatments there were no significant differences in any of the domains of the PTHSI. Figure 5.6 also does not suggest any consistent trends in terms of health or stress despite the observed difference in major clinical events including acute hospital admissions.

Compliance with the HH device during the treatment period appeared to be excellent with a mean use of 11.8 hours per day on days used. However, this measurement only records the time that the HH was switched on and is not able to measure if the device was attached to the child’s tracheostomy or not. While the result implies good compliance, the device could have been removed by the child for prolonged portions of the night, or parents may have left the machine switched on without applying it to the child’s tracheostomy. While no parents reported this, one parent did report leaving the HH running overnight during the HME phase of the study as they found it useful to apply during suctioning.

The difference between the amount of HMEs used per day during the two treatment periods was surprisingly small – an individual treatment difference of 0.6 HMEs per day (CI90% 0.1 to 1.1). The overall number of HMEs used in each group was higher than expected and may represent the number of HMEs filled with secretions or, more prosaically, thrown on the floor by the child during the day. Although HMEs are
expensive, costing the health service approximately NZ$4 each at the current time, the small difference in numbers of HMEs used between groups has shown that using a single HH humidification device overnight does not appreciably decrease the number of HMEs used in the day. In addition, the use of sterile water in the humidification chamber of the HH is a significant ongoing cost and there is also an additional cost to families in terms of power usage. The use of a HH during sleep would reduce HME costs by NZ$876 per year but would cost NZ$1395 for the hospital to purchase the HH and NZ$358 per year for sterile water (2-3 bottles per week at $2.75 each) at a net cost of NZ$877 per patient per year. We followed the manufacturer’s recommendation to use sterile water in the humidification chamber rather than tap water which would result in corrosion of the hot plate. However, using tap water rather than sterile water and replacing the damaged chambers would be significantly cheaper (NZ$91 per chamber each six to twelve months) and clinically safe. Assuming the use of sterile water, and that the results of the eight-week long-term study can be averaged over a twelve-month period, this would equate to a net cost of NZ$45 per acute hospital admission prevented or NZ$13 per chest infection prevented. In order to perform a formal economic analysis a twelve-month study would need to be conducted in order to test these assumptions.

More parents expressed overall satisfaction with the HH rather than the HME at the end of the study (p = 0.018). There also appeared to be trends towards an increased overall effectiveness but decreased convenience with the HH compared to the HME (Figure 5.3). Although there was a definite trend toward overall preference for using HH overnight compared to HME, this was not statistically significant possibly due to the small sample size (p = 0.070). These results were confirmed in the qualitative interviews where parents expressed that they perceived that the HH was more effective but that it was very inconvenient, especially for travel. In the interviews some parents expressed
that the perceived difference in effectiveness between the two humidification devices disappeared over a period of years as the child grew larger and healthier.

### 9.3 Clearance of mucus from the airways

For the long-term study we attempted to measure the clearance of mucus from the airways under the two different humidification techniques utilising measures of CBF and MCC. In a pilot study of six adults with tracheostomies we took cytology brush sample specimens for the analysis of CBF from the proximal trachea just distal to the end of the lumen of the tracheostomy tube. We obtained poor quality samples using this technique with moderate to copious amounts of stratified epithelium rather than ciliated epithelium and moderate to copious amounts of mucus. The numbers of strips of ciliated epithelium were inadequate for good quality measurement. There was a trend for poorer quality samples to have a lower CBF (Figure 6.1). Although the adult volunteers in that pilot study reported an acceptable level of discomfort, we observed quite forceful coughing as a result of the procedure and perceived the procedure as too distressing to apply to children without general anaesthetic. We then obtained samples under general anaesthetic from five children with tracheostomies from the middle to distal trachea. These samples gave adequate numbers of strips of ciliated epithelium in all cases with less mucus and stratified epithelium than those from the proximal trachea in the adult participants. The difference may be explained by findings from the literature where the presence of a tracheostomy resulted in damage to the respiratory epithelium just distal to the end of the canula (193, 194, 197, 480). However, the difference may also result from differences in sampling technique with samples from the children obtained under direct vision via a rigid bronchoscope as compared to samples from the adults which were obtained blindly via the tracheostomy lumen. Furthermore, the depth to which the cytology brush could be inserted may have been limited by elicitation of the cough reflex.
We did not obtain sufficient numbers of samples from the children to compare the effects of the two different treatments. As the measurements of CBF are performed in vitro in a preparation and microscope stage at standardised temperature, it is possible that the preparation itself reversed any potential observed difference between treatments under measurement conditions. A comparison of the proportions of ciliated and unciliated cells or an electron microscopy assessment of acquired ciliary defects may be more likely to demonstrate a difference between treatments but this was not done.

We also performed measures of MCC utilising a radioaerosol technique. Between MCC scans on individual children there was a wide variation in the penetration index which is a measure of the pattern of initial radioaerosol deposition. This had a highly significant effect on measured MCC. Radioaerosol scans were developed in the 1970s to assess mucus clearance, particularly to assess the effects of smoking and environmental pollution (481, 482). While initial scanning techniques were able to demonstrate differences between affected subjects and healthy controls, there was wide intra- and inter-subject variability principally due to the variability in deposition (382). The development of specific breathing patterns during inhalation enabled improved consistency of deposition and the targeting of central airway deposition as alveolar deposition results in excess noise in the signal-to-noise ratio of measured clearance (398, 483). We could not control the pattern of breathing for the children in the current study due to their age and/or developmental delay and instead we attempted to increase central regional deposition through the use of larger droplet size than previously described. As early studies using MCC scans had demonstrated effects of disease states despite the lack of controlled breathing patterns we felt that we would be able to demonstrate a treatment effect. In our study, a strong signal was deposited on the walls
of the tracheostomy tube itself suggesting that in some cases the larger particles we intended for the central lung region were being deposited on the upper airway.

Unexpectedly, in some of the scans there was an increase rather than a decrease in measured retention at serial time points. This was particularly the case for measurements of the peripheral region. This increase in retention may be explained by retrograde mucus flow or by subject movement. Retrograde flow of mucus (that is the movement of mucus in a distal rather than proximal direction) has been previously observed during MCC scans in patients with conditions associated with decreased mucus clearance (484). As patients with tracheostomies have loss of cilia in the trachea this was likely to occur in our study participants. Movement during mucociliary clearance scans may generate "clearance artefact" possibly due to rotation between images (485). As our participants were allowed to mobilise between scans this may have occurred in our study. In addition, we did not employ an initial transmission scan which has been used in previous studies to define the limits of lung anatomy and define the peripheral regions. A transmission scan would have entailed performing an additional scan in the restraining cradle prior to nebulisation and would have decreased the tolerability of the procedure for young children. In addition, the initial scans we performed on adult volunteers showed the lung anatomy to be well defined by the initial deposition of the radioaerosol. It may be that we underestimated the size of the lungs and thereby did not accurately define the peripheral regions resulting in artefactual increases in signal especially during movement between serial scan images.

Cough or suctioning during the scan procedure causes step-like changes in measured clearance (486). If frequent images are taken a correction may be performed for these discontinuities in calculation of the MCC curves. In our study images were captured
infrequently in consideration of tolerability of the procedure in young children and we were not able to perform this correction. Coughing has also been found to normalise total clearance in patients with primary ciliary dyskinesia, a condition of severely impaired or absent mucociliary clearance (487). This suggests that the result of the frequent coughing observed in our study may have reduced any observable treatment differences.

There was also a significant period effect on the results of the MCC scans – an effect of factors other than treatment such as the above described factors of penetration index, subject movement and cough. In addition, the ten-week time duration between measurements is long enough to potentially impact the results. It may have been that growth or physiological maturity between measurement points affected the results. Changes in season may have also affected results with children less likely to be recovering from an upper respiratory tract infection in summer than in winter. Respiratory viruses, which are more common in winter than in summer, have previously been shown to have profound and prolonged effects up to several weeks in duration on the ciliated epithelium (488). This is pertinent to the long-term study as the ten-week treatment period is close to the length of one season.

In addressing the above weaknesses of the study, I would recommend that future studies utilising this technique take measures to further reduce the mobility of children between scans and that these scans be performed under sedation. Although sedation does carry risks to the participants, and may affect the results of the scans if the medications used decrease MCC, this would enable the performance of more frequent acquisition of images for each child (as in previous studies in adults) and allow correction for step-wise changes in clearance due to coughing or suctioning. It would
also allow the performance of transmission scans to more accurately define the lung regions, particularly the limits of the peripheral region. For children with tracheostomies, it would be helpful to reduce the deposition on the tracheostomy tube lumen by performing nebulisation through a catheter, the tip of which would be advanced to the end of the tracheostomy. In studies enrolling adults participants where there has been targeting of central deposition, subjects are instructed to breathe at fixed tidal volume and rate and in a controlled pattern in order to minimise the variability in the penetration index between scans. This is not possible in children unless ventilation is controlled. It may be better to use smaller radioaerosol droplets that do not concentrate in the central regions but give a more even pattern of deposition. The repeatability of targeting central deposition as opposed to even deposition using smaller droplets should be compared in this study population. Lastly, due to the inability to control coughing during the scanning process in this population, it may be that this technique is not appropriate in children with tracheostomies as cough will reduce treatment differences.

9.4 Inflammatory Cytokines

The inflammatory cytokines IL-8, IL-1β and TNFα were assessed in both the short-term and long-term studies conducted for this thesis. For the short-term study no statistically significant differences between treatments in any of the inflammatory cytokine levels were observed. Despite this lack of significant differences higher mean levels of all the cytokines were observed at the end of treatment on HME compared to HH. Mean cytokine levels increased from baseline (after four hours of no humidification treatment) to after two hours of active treatment. This result was unexpected as cytokine levels were expected to decrease with both active treatments and may reflect the time course of evolution of inflammatory cytokines levels in airway secretions. The cytokine levels in airway secretions collected at the site of the tracheostomy may have been produced
several hours prior to collection and slowly moved proximally through mucociliary or
cough clearance. Alternatively, cytokines may take several hours to be produced being a
result of complex interactions between triggers of inflammation, resident inflammatory
cells and migration of inflammatory cells to the site of initial injury as seen in the late-
response in asthma (489). This study was complicated by the difficulty in obtaining
adequate sized samples for analysis and as a result there was a large proportion of
missing values particularly for TNFα. In the long-term study there were also no
statistically significant differences observed between treatments when performing the
planned analysis with log-transformed cytokine levels. In a post hoc analysis, using non-
log transformed measures or non-parametric analysis, a significant difference was found
for levels of IL-8. A similar pattern of inflammation was observed in a study of children
with tracheostomies comparing airway secretion cytokine levels during respiratory
exacerbations to during well periods (199). That study found elevated levels of IL-8 but
not IL-1β or TNFα during exacerbations.

Analysis of cytokine levels was performed using commercial ELISA kits which can be
assumed to be accurate. Quality control measures are contained in the analysis process
involving the checking of curves through serial dilutions with samples showing high
variability being excluded from analysis. The chief weakness for this set of outcomes
was in the volume of secretions obtained for analysis with insufficient volumes obtained
in many cases. The small volumes raises concerns about the accuracy of dilutions for
sample weight performed and the accuracy of the performed correction factors. This
concern could be avoided in future studies by the use of alternate collection techniques
which obtain larger samples. A strong correlation was found between cytokine levels in
the long-term study whereas there was a lack of correlation between IL-8 and TNFα
levels in the short-term study. This may be a consequence of the small number of
adequate samples for TNFα assessment but also may indicate that the samples were too small to provide consistent results. Larger volume samples may have been obtained by performing broncho-alveolar lavage under general anaesthetic However, this would entail the risk of anaesthesia to the child. For future studies in awake children, I would suggest aspirating fluid through the catheter to obtain the sample in a mucus trap rather than attempting to scrape the sample from the thumb trap as performed for this study. I would also recommend routinely instilling saline into the trachea prior to suctioning in order to encourage coughing and the loosening of secretions from distal airways.

9.5 Qualitative Interviews

For this thesis I performed a qualitative sub-study with the aim of exploring parents' preferences for using either the HH or the HME treatment over night. The use of qualitative methods within this study has allowed us to describe the experiences of caregivers using two humidification treatments and to generate a GT to explain how they choose whether or not to use a prescribed assistive technology. This adds an experiential perspective to the RCT arm of the study and allows for the development of comprehensive clinical practice recommendations. From the qualitative interviews I developed a GT of parents managing their child's health by employing management strategies in confronting problematic or constraining health states. This GT was similar to previously described models of caregiving in the literature. I also found that parents employed a process of balancing in electing to use or not use a prescribed treatment. Parents balanced the positive effect of the treatment on the health of the child’s state against any negative effects on the child that might affect their coping such as having to wake more in the night and also against factors such as ease of use, reliability, ease of maintenance and portability.
The main limitations of the qualitative phase of this study are the study size, with only nine mothers and four nurses interviewed, and that data saturation was not reached in all of the categories. We did not perform follow-up interviews with participants to confirm findings or do triangulation as described in other qualitative study methodology as this would not be consistent with the GT method (407). We also did not address issues of interviewer bias or reflexivity, a decision based on the original description of the method (407). However, lack of reflexivity in GT is generally a criticism of studies using this method (490). Although we followed the GT method described by Glaser, we did employ some variation. Firstly we used semi-structured interviews rather than completely unstructured interviews. This was to enable systematic comparisons of the incidents of using each of the two treatments. Secondly, as with many other GT studies in health research, we taped interviews and performed open coding from transcripts (491). We do not feel that this approach deviates significantly with GT methodology, particularly as the interview guide was continually modified for the purposes of theoretical sampling.

We found that caregivers are the managers and experts in their child’s care and bear the responsibility of treatment decisions. The choice whether or not to use an assistive technology, such as a HH versus an HME overnight in children with tracheostomies, took place within the overall context of how caregivers managed their child’s care. The stated preference for one device over the other had balanced the perceptions of positive and negative factors within the family context rather than relying solely on the recommendation from health professionals. In this way, the choice should therefore not be viewed as being non-adherence, but an active decision by caregivers to improve their own coping and the care of their child.
9.6 Summary of findings

In the studies conducted for this thesis children were found to have increased abnormalities on clinical examination such as increased respiratory effort and respiratory rate when wearing the HME device as compared to the HH device. However, these differences were not seen in the long-term study in which participants wore the HME at assessment for both treatment periods. This suggests an acute treatment effect which may involve small airway narrowing or an effect of the increased airway resistance and/or dead-space imposed by the use of the HME. During the long-term study participants were more likely to experience a major clinical event such as hospital admission or treatment failure infections when being treated by HME when asleep and awake compared to when being treated with HH asleep and HME awake. Trends were observed toward an increase in hospital admissions and chest infections. In a secondary analysis there was a shorter time-to-event for all major events and a trends toward shorter time to acute hospital admission or chest during this treatment period.

Parents of children with tracheostomies reported a lower baseline HRQOL than the general population but I did not find statistically significant differences between treatments in any of the measures of parental or parent-reported child HRQOL. I also did not find any statistically significant differences in terms of inflammatory cytokine levels between treatments in either the short-term or the long-term study.

I attempted to demonstrate effects of treatment on measures of MCC. For logistic reasons the planned numbers of bronchial brushings for the measurement of CBF were not performed as participants did not undergo the routine laryngoscopy and bronchoscopy expected despite this being recommended in the local ENT clinical
protocol. We were also unable to have airway secretions analysed for mucus viscoelasticity via microrheometer as planned. No difference between treatments was observed in results of the nuclear medicine radioaerosol MCC scans. This was probably due to the fact that any potential changes in MCC between treatments, if they existed, were within the variation seen with the technique of measurement. This may also be a result of cough clearance decreasing any measured treatment difference.

Lastly, I performed qualitative interviews in a selection of parents. These interviews confirmed the decreased HRQOL of parents caring for children with tracheostomies and highlighted the stressful and difficult role that parents find themselves in as carers of these technology-dependent children. The interviews confirmed the overall study findings that children experienced less clinical events on HH and that most parents preferred using the HH overnight. However, as children became older some parents reported that they found the use of the HH no longer necessary although all families retained the HH for use when the child became unwell.

The children recruited for the these studies came from a heterogeneous population with children in the long-term study ranging in age from 0.4 to 15.3 years and the duration of tracheostomy ranging from 0.17 to 15.6 years. The indications for tracheostomy in this group were tracheomalacia, subglottic stenosis, Pierre Robin sequence and craniofacial abnormalities. These different pathologies may have affected many of the outcomes for the study, impacting in different ways on airway mechanics, risk of infection, risk of chronic aspiration, risk of tracheostomy occlusion and MCC. While a more homogenous population would have been desirable this would have further reduced recruitment. Furthermore, the use of a cross-over design and within-subject contrasts was employed to reduce the effects of the heterogeneous population.
While some statistically significant benefits from the use of the HH as compared to the HME were found in these studies, the small sample sizes of the short-term and long-term study indicate a risk of both Type 1 and Type 2 errors. Further study comparing these treatments is indicated to confirm these findings and larger study populations are needed to confirm non-significant the trends observed.

9.7 Suggestions for future research

In summarising and discussing the results I have attempted to make suggestions above for how the individual measures used could be improved for any future study. In this section I will discuss how the overall planning, design and conduct of a future study could be improved based on the experience gained in this study.

I experienced difficulty recruiting participants to the long-term study and this was due to a combination of two factors. The number of tracheostomies performed at our institution has decreased following the employment of paediatric sleep physicians and the increasing use of continuous positive airway pressure (CPAP) as an alternative to tracheostomy for the management of airway malformations (Figure 9.1). The duration of tracheostomy has also decreased which greatly limited the numbers of participants for a long-term study. In order to recruit a sufficient population for a long-term study a multi-centre study would be required. One of the weaknesses of this study was that the researchers and most of the parents of participants had a strong bias favouring the HH as more effective than the HME. This may have resulted in calling treatment failures when participants experienced thickened secretions or chest infections on the HME. In a future study it would be preferable to conduct the study in a population that was naïve to the use of the HH and where HME was the usual treatment as is the current clinical
practice in Australian centres. This would reduce the bias in favour of the HH for the outcome treatment failure.

Recruitment to the short-term study was more efficient. This was due to the greater availability of participants having relatively shorter duration of tracheostomy. Participant availability was also increased by performing the study during a period when participants were in hospital for a sufficient time period to complete the study. This also improved the ease of overnight assessment and monitoring for any safety concerns. This early period when children first have a tracheostomy is a particularly important time to study as secretions are increased and children are potentially more vulnerable to adverse events from inadequate humidification treatment. A further short-term study in participants with newly inserted tracheostomy tubes, assessing changes in mucus characteristics or a measure of MCC, is recommended prior to the conduct of a further long-term study.

In conducting this study I selected a cross-over design. This design had the advantage of utilising within-subject differences which was important given the heterogeneous nature of the study population. The cross-over design is statistically more powerful than a parallel group study thereby compensating for the small size of the available study population. However, there is controversy as to the appropriate statistical analysis of these studies, In addition, the cross-over design increases burden on participants, and when two participants withdrew from the study this resulted in loss of most of the available data on these subjects as within-subject differences could not be ascertained. There are also difficulties with the measurement of time-to-event data in cross-over studies due to the cross-correlation of outcomes. For a future short-term study a cross-over design appears to be appropriate as it has greater power than a parallel study design. However, for a long-term study, if a more homogenous population can be
recruited, then a parallel design may be more preferable in order to better utilise time-to-event data. If only a heterogeneous population is available, as was the case in our studies, then a cross-over design is still the recommended option but incorporating larger numbers. For a future cross-over study time-to-event data should only be utilised for outcomes such as chest infection and hospital admissions where there will not be a high rate of censoring at the end of the observation period for each treatment.

Lastly, I excluded nebuliser devices from this study. Nebulisers, such as those manufactured by DeVibliss, are in use in some countries for providing humidification for children with tracheostomies and their clinical effectiveness is unknown. A trial comparing a HH to a nebuliser for overnight conditioning of inspired gases could be performed.

9.8 Clinical recommendations from the study

In this study we found a decrease in the risk of major clinical events during overnight humidification treatment with HH set to deliver conditioned gases at 37°C and 44 mmHg as compared to the HME. While the study population is small and further study is recommended, the results of these studies confirm anecdotal observations made at our institution that use of the HH overnight appears to be more effective than use of HME alone in providing humidification. The use of HH has become accepted clinical practice at our institution and the results of these studies suggest that this should continue, particularly in children with thick secretions, frequent chest infections or requiring frequent hospital admissions. However, further comparisons could be performed in a population naïve to the use of the HH before introducing the treatment as standard clinical practice in other centres.
The HME used in the study is the standard HME device used at our institution for clinical practice and is widely used world-wide. A review of the literature suggests that it may not perform according to current clinical recommendations (3) for long-term use. More effective devices such as hygroscopic foam HMEs are available but are currently not affordable for long-term use. Further research on the in vivo performance in terms of delivered temperature and humidity of gases for the HME device used in this study should be performed. HME devices that perform according to guidelines and are affordable for long-term use should be developed as children will continue to require HME use for daytime mobility even with the use of the HH overnight.

Following the commencement of this study the HH device has been modified by the manufacturer, although we continued to use the original design for all participants in this study. One modification has been the replacement of the tracheostomy mask with a direct tracheostomy connection. This modification addresses concerns expressed by parents about the discomfort of warm moist air blowing on the neck of the child and about the development of a moist infection-promoting environment around the child’s neck. The heated hosing conducting the conditioned gases to the patient has been made more permeable thus decreasing condensate in the tubing which was another concern of parents in this study. Other modifications have improved the portability and ease of use of the device. None of these changes has affected the heating and humidification characteristics of the device. This suggests that a future study employing the modified device would likely find greater parental preference for HH versus HME as the issues parents most raised about using the device have now been addressed or improved.
Lastly, the qualitative interview conducted for this study confirmed parents as the managers and expert in their child’s care. The expertise of parents in the care of their individual child needs to be given a greater respect by the health professionals caring for children with tracheostomies in hospital. We also found high levels of stress and difficulties with coping with inadequate provision of respite and other support services in the community. In New Zealand tracheostomy is not recognised as a disability whereas in the United States disabilities involving the airway are recognised as the highest-level of disability (492). Tracheostomy in children should be recognised as a disability in order that parents receive adequate support and that this support is equitable across different regions in our country.

9.9 Conclusions

For this thesis I conducted a short-term and a long-term study comparing treatment with a HH compared to HME for conditioning the gases inspired by children with tracheostomy tubes. I demonstrated a short-term effect on clinical examination findings which may be explained in part by imposition of increased airway resistance and dead-space through the use of a HME. In the long-term study children were at reduced risk of experiencing a major clinical event during the period they were treated with the HH. No differences were found in measures of mucociliary clearance probably but there were technical difficulties with the test employed. In addition no differences were found in the assessment of airway inflammation. The use of HH during sleep in children with tracheostomies has become routine at our institution and the results of this study indicate this should continue. While a larger multi-centre study would be preferable prior to widespread adoption of the HH as routine clinical practice in other centres, we would still recommend its use for children with thick secretions, repeated chest infections or frequent hospital admission based on the results of this trial. Until such a trial is
conducted, HH devices should be available for children with particularly thick secretions as this has been an exclusion factor in previous studies of humidification.
Chapter 10 Personal Reflections

I commenced this research at the beginning of my advanced clinical training in paediatric respiratory medicine. The research continued throughout my training and indeed shaped it in many ways. My interest in children with tracheostomies and the difficulties they face commenced with two individual patients. This led to my keenness to develop research with these children. In turn this sparked an interest in children with airway abnormalities generally and in supportive technology which later led me to seek further training in clinical sleep medicine which I undertook in 2007 at the Sleep Medicine Unit, Sydney Children’s Hospital, Australia.

Many of the assessments performed for this research involved an objective assessment of respiratory physiology. However, I also wanted to assess the personal impacts of treatment on patient's lives. The investigation of patient satisfaction and quality of life through questionnaire and lived experience was strongly complementary to the physiological measures, broadening my concepts of how I measure the effects of illness or treatment on a patient and their families.

Performing the research for this thesis has allowed me to spend longer periods of time with individual children and their families and given me the opportunity to visit families in their homes. This has enabled me to observe how families integrate healthcare technology into their homes and into their lives. An example of this was observing the amount of storage space that is required to accommodate supplies such as suction catheters, replacement tubing and bottles of sterile water. This made me realise the burden that falls on the whole family as they reorganise their practical lives to accommodate the needs of a technology-dependent child. We asked parents to use a
relatively burdensome treatment that we believed would improve the health of their child. Whether the parents thought that burdensome treatment was worthwhile did not depend upon changes in measures which I assessed, but in changes that the parents perceived to be important – usually regarding the child’s and the family’s overall well-being and functioning.

While I have gained greatly from the positive experiences of conducting this research I have also learnt from the disappointments. I experienced difficulties in recruitment for the long-term clinical study due to both the prolonged time-frame of the study and also in scheduling visits for patients around their ongoing commitments. Furthermore, consent could not be obtained in some cases as a proportion of children who would otherwise have been eligible for recruitment were under the care of government agencies or we felt that their parents were mentally unwell and unable to provide informed consent, further demonstrating the intense demands placed on these families as some failed to cope. In contrast, the short-term study placed much lighter demands on parents as it was conducted while the children were in hospital and there was more rapid recruitment and generation of data. In retrospect, this format may have been more suitable as the larger study for this thesis.

Conducting the research for this study enabled me to observe the interaction between the well-being of the child and that of the family as distinct entities and as a single unit. I have observed how a child’s ill-health can cause disruption to all aspects of a family’s life. I have observed the consequences of difficulties in coping and maintaining an organised family life in terms of recurrent illness and hospital admissions. I have also observed how an effective treatment that improves a child’s health can enable a family under pressure to re-attain a sense of normal functioning. As paediatricians and
scientists we are unable to apply our skills and knowledge unless we can understand a child’s health in relation to the functioning of the whole family and learn what it is that parents perceive as the significant facets of family well-being.
References Cited in This Thesis


<table>
<thead>
<tr>
<th>Page</th>
<th>Reference</th>
</tr>
</thead>
</table>


321. Bell GT, Martin KM, Beaton S. Work of breathing in anesthetized infants increases when a breathing system filter is used. Paediatric Anaesthesia. 2006;16(9):939-43.


APPENDIX A: Health-Related Quality of Life Questionnaire for Long-term Study
HUMIDIFICATION FOR CHILDREN WITH TRACHEOSTOMIES STUDY: PARENT QUESTIONNAIRE SHEET

Thank you for agreeing to take part in this survey.

All your answers will be kept confidential.

We would like to know how you and your child are doing and how you feel about things. This is not a test, so there are no right or wrong answers. We are interested in your impression of things. If you are unsure about what to answer please choose the one that seems the best.

Many of the questions ask you to make a choice from a selection. The choices are in a scale. For example:

How good a sleep did you have last night? (Please circle one number)

<table>
<thead>
<tr>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

If you did not get any sleep at all you would select 1 If you had a great sleep you would select 5.

An interviewer will sit with you to help you answer the survey. Some of the questions may be repeated. Please answer all the questions.
Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this questionnaire!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

**QUESTIONS 1 -11 DELETED FOR COPYRIGHT PURPOSES.**

The following questions ask about your child’s general health and quality of life

12) In general, would you say your child’s health is currently: (please circle one number)

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

13) How would you describe your child’s current overall quality of life?

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

14) Since the last time you completed this questionnaire, how would you describe any change in your child’s health or overall quality of life compared to before the tracheostomy was inserted?

If this is the FIRST time you are answering this survey how would you describe any change in your child’s health or overall quality of life compared to before the tracheostomy was inserted?

<table>
<thead>
<tr>
<th>Much better now</th>
<th>Somewhat better now</th>
<th>About the same</th>
<th>Somewhat worse now</th>
<th>Much worse now</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Section B) Child’s Physical Symptoms

Please circle ONE number per question.

How often over the past 4 weeks has your child

15) Awakened in the middle of the night?

<table>
<thead>
<tr>
<th>Never</th>
<th>Once a week</th>
<th>2-3 times/week</th>
<th>4-5 times/week</th>
<th>Every night</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

16) Gasped or choked during sleep?

<table>
<thead>
<tr>
<th>Never</th>
<th>Once a week</th>
<th>2-3 times/week</th>
<th>4-5 times/week</th>
<th>Every night</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

17) Needed assistance to breathe during sleep?

<table>
<thead>
<tr>
<th>Never</th>
<th>Once a week</th>
<th>2-3 times/week</th>
<th>4-5 times/week</th>
<th>Every night</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

18) Had difficulty breathing during waking hours?

<table>
<thead>
<tr>
<th>Never</th>
<th>Once a week</th>
<th>2-3 times/week</th>
<th>4-5 times/week</th>
<th>Every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

How true do you think the following statements are?

19) My child seems to be less healthy than other children I know.

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

20) My child has never been seriously ill.

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

21) I worry about my child's health more than other people worry about their child's health.

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Section C) Medical Visits

22) Approximately how many visits to see a doctor did your child have for breathing or tracheostomy related problems during the last 2 months?

<table>
<thead>
<tr>
<th>None</th>
<th>1 visit</th>
<th>2 – 3 visits</th>
<th>4 – 5 visits</th>
<th>6 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

23) Approximately how many chest infections did your child have during the last 2 months?

<table>
<thead>
<tr>
<th>None</th>
<th>1</th>
<th>2 – 3</th>
<th>4 – 5</th>
<th>6 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

24) Approximately how many hospitalizations did your child for breathing or tracheostomy related problems during the last 2 months?

<table>
<thead>
<tr>
<th>0 visits</th>
<th>1 visit</th>
<th>2 visits</th>
<th>3 visits</th>
<th>&gt; = 4 visits or in chronic care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

25) How often do you feel you need a nurse to visit you at home?

<table>
<thead>
<tr>
<th>One visit a month</th>
<th>2 - 3 visits per month</th>
<th>about once per week</th>
<th>about 2 -3 times per week</th>
<th>4 times a week or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

26) How often do you receive a nurse to visit you at home?

<table>
<thead>
<tr>
<th>One visit a month</th>
<th>2 - 3 visits per month</th>
<th>about once per week</th>
<th>about 2 -3 times per week</th>
<th>4 times a week or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

27) How often do you feel you need respite care for your child (for example Carer Support, Family Options, or other family members looking after your child)?

<table>
<thead>
<tr>
<th>Less than once a week</th>
<th>One day a week</th>
<th>2 - 3 days a week</th>
<th>4 - 5 days a week</th>
<th>6 – 7 days a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

28) How often do you receive respite care for your child (for example Carer Support, Family Options, or other family members looking after your child)?

<table>
<thead>
<tr>
<th>Less than once a week</th>
<th>One day a week</th>
<th>2 - 3 days a week</th>
<th>4 - 5 days a week</th>
<th>6 – 7 days a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Section D) Stress and Coping/ Care-givers’ view of child’s perspective

The questions in this section ask how stressed or bothered your child is by having a tracheostomy.

How difficult or bothered does your child find:

29) Not being able to communicate as well as other children?

<table>
<thead>
<tr>
<th>Not difficult/bothered at all</th>
<th>Mildly difficult or bothered</th>
<th>Moderately difficult or bothered</th>
<th>Very difficult or bothered</th>
<th>Extremely difficult or bothered</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

30) Not being able to play in the same way as other children?

<table>
<thead>
<tr>
<th>Not difficult/bothered at all</th>
<th>Mildly difficult or bothered</th>
<th>Moderately difficult or bothered</th>
<th>Very difficult or bothered</th>
<th>Extremely difficult or bothered</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

31) Not being as independent as other children the same age?

<table>
<thead>
<tr>
<th>Not difficult/bothered at all</th>
<th>Mildly difficult or bothered</th>
<th>Moderately difficult or bothered</th>
<th>Very difficult or bothered</th>
<th>Extremely difficult or bothered</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

How difficult or bothered does your child find:

32) Being in hospital?

<table>
<thead>
<tr>
<th>Not difficult/bothered at all</th>
<th>Mildly difficult or bothered</th>
<th>Moderately difficult or bothered</th>
<th>Very difficult or bothered</th>
<th>Extremely difficult or bothered</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

33) Medical procedures?  (e.g. suctioning, nasogastric tubes, tracheostomy changes, iv lines)

<table>
<thead>
<tr>
<th>Not difficult/bothered at all</th>
<th>Mildly difficult or bothered</th>
<th>Moderately difficult or bothered</th>
<th>Very difficult or bothered</th>
<th>Extremely difficult or bothered</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
Section E) Stress and Coping/ Caregivers

We are now going to ask some questions about how YOU are doing.

34) How would you describe your overall quality of life?

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

35) How often are you able to perform activities to manage your home?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

How often are you worried or concerned about your child's safety:

36) When you perform a tracheostomy change?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

37) When you suction the tracheostomy?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

38) With regards to your child's overall ability to breathe?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

39) How often over the past week have you been able to take your child out of the house (i.e. to run errands for recreation)?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

During the past 4 weeks, how often have you been worried or concerned about:

40) Your child's physical health?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

41) Your child's emotional well-being or behavior?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
During the past 4 weeks, how often have you been limited in fulfilling your own needs because of:

42) Your child's physical health?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

43) Your child's emotional well-being or behavior?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

During the past 4 weeks, how often has your child's condition:

44) Affected your health?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

45) Affected your emotional state?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

46) Affected your sleep?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

47) Affected your relationships?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

48) Interrupted various everyday family activities? (eating meals, watching TV, going out)

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Over the past four weeks, how often did you:

49) Need help from skilled medical personnel?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
50) Get help from skilled medical personnel?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

COMMENTS (optional):
Is there anything you would like to add about your child's physical health?

__________________________

__________________________

Is there anything you would like to add about your child’s stress or emotional health?

__________________________

__________________________

Is there anything else you would like to add or say about your own stress or coping?

__________________________

__________________________

F) Specific Items
These questions ask about what your child’s tracheostomy suctions were like when you suctioned your child’s airway this morning. Please circle ONE number per question.

51) What colour were your child’s airway secretions this morning?

<table>
<thead>
<tr>
<th>Clear (watery)</th>
<th>White</th>
<th>Yellow or green</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

52) How much secretions did your child have this morning

<table>
<thead>
<tr>
<th>None or a small amount</th>
<th>A moderate amount</th>
<th>A large amount or copious secretions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

53) How would you describe the thickness or stickiness of the secretions from your child's tracheostomy tube this morning?

<table>
<thead>
<tr>
<th>Thin</th>
<th>Moderate</th>
<th>Thick</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
54) This morning how difficult was it to insert the suction catheter into your child’s tracheostomy tube?

<table>
<thead>
<tr>
<th>Easy or not at all difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

During a typical day over the past week, how often

55) Did your child’s tracheostomy need to be suctioned during the day?

<table>
<thead>
<tr>
<th>Less than 8 hourly</th>
<th>4 to 8 hourly</th>
<th>2 to 3 hourly</th>
<th>Every hour</th>
<th>More than every hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

56) Did your child’s tracheostomy need to be suctioned at night?

<table>
<thead>
<tr>
<th>Less than 8 hourly</th>
<th>4 to 8 hourly</th>
<th>2 to 3 hourly</th>
<th>Every hour</th>
<th>More than every hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

57) Did saline need to be instilled into your child’s tracheostomy to assist with suctioning?

<table>
<thead>
<tr>
<th>Never</th>
<th>Once a day</th>
<th>2 to 3 times a day</th>
<th>4 to 5 times a day</th>
<th>6 or more times a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

During the past 2 months how many times (please write the number of events in the box)

58) Has your child had a chest infection?  
59) Had a course of antibiotics?  
60) Has your child’s Swedish nose become blocked with secretions?  
61) Has your child’s tracheostomy tube become blocked?  
62) Have you had to perform a tracheostomy tube change as an emergency?

How much do you agree or disagree with the following statements

63) I find the Swedish nose is effective in humidifying the air my child breathes in

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral or don’t know</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
64) I find the Swedish nose is convenient to use

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral or don’t know</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

65) Overall, how satisfied are you with using the Swedish nose?

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Satisfied</th>
<th>Neutral or don’t know</th>
<th>Dissatisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

How much do you agree or disagree with the following statements

66) I find the Heated Humidifier is effective in humidifying the air my child breathes in

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral or don’t know</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

67) I find the Heated Humidifier is convenient to use

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral or don’t know</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

68) Overall, how satisfied are you with using the Heated Humidifier?

<table>
<thead>
<tr>
<th>Very Satisfied</th>
<th>Satisfied</th>
<th>Neutral or don’t know</th>
<th>Dissatisfied</th>
<th>Very Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

69) Overall, which way of humidifying your child's airway would you prefer?

<table>
<thead>
<tr>
<th>Heated Humidifier during sleep and Swedish nose when awake</th>
<th>No preference</th>
<th>Swedish nose awake and asleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
70) What things do you dislike about using the Swedish Nose?

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

75) What things do you dislike about using the Heated Humidifier?

________________________________________________________________________

________________________________________________________________________

YOU HAVE FINISHED.

THANK YOU VERY MUCH FOR TAKING THE TIME TO COMPLETE THIS SURVEY.
APPENDIX B: Clinical Examination Guide for Short-term and Long-term Studies
**HCT Study CLINICAL EXAMINATION SCORE SHEET**

Please circle the appropriate number

**SUCTION SAMPLE**

**Difficulty Inserting Suction Catheter**

<table>
<thead>
<tr>
<th>Easy or not at all difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Colour Of Secretions**

<table>
<thead>
<tr>
<th>Clear</th>
<th>White</th>
<th>Yellow or Green</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Volume Of Secretions**

<table>
<thead>
<tr>
<th>None or a small amount</th>
<th>A moderate amount</th>
<th>Copious secretions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Thickness Of Secretions**

<table>
<thead>
<tr>
<th>Thin</th>
<th>Moderate</th>
<th>Thick</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Thin*: The catheter is clean after suctioning  
**Moderate**: there are secretions adherent to the catheter after suctioning but they are cleared by suctioning with water  
**Thick**: there are secretions attached to the catheter after suctioning and they cannot be cleared by suctioning with water.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Height</th>
<th>Resp Rate</th>
<th>(measure over 1 full minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pulse Rate</td>
<td>(measure over 1 min and take representative reading)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SaO2</td>
<td>(measure over 1 min and take representative reading)</td>
</tr>
</tbody>
</table>
**CLINICAL EXAMINATION**

**Dyspnoea**

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*None*: Normal feeding, vocalisation and activity  
*Mild*: One of: difficulty feeding, decreased vocalisation, increased coughing after play, or agitated  
*Moderate*: Two of: difficulty feeding, decreased vocalisation, increased coughing after play, or agitated  
*Severe*: Stops feeding, no vocalisation, stops playing, or drowsy or confused

**Retractions**

<table>
<thead>
<tr>
<th>None</th>
<th>Intercostal</th>
<th>Intercostal and subcostal</th>
<th>Intercostal, subcostal and supraclavicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Wheeze**

<table>
<thead>
<tr>
<th>Normal breathing, no wheeze present</th>
<th>End expiratory wheeze only</th>
<th>Expiratory wheeze</th>
<th>Inspiratory and expiratory wheeze OR decreased breath sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Crackles (Crepitations)**

<table>
<thead>
<tr>
<th>Normal breathing, no crackles present</th>
<th>End inspiratory crackles in one area only (focal)</th>
<th>Bilateral inspiratory crackles</th>
<th>Widespread crackles</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
APPENDIX C: Overnight Event Record for Short-term Study
Overnight Suction Record
Study of Overnight Humidification in Children with Tracheostomies

Please fill in this chart from 2000h to 0800h or for your 12 hour shift. Each time you suction please record Time, Volume of secretions, Colour of secretions, Thickness of secretions and whether saline was needed.

Please record overnight oximetry for a printout using a Masimo oximeter and download and save under the child's name and date eg filename “jayden131005” on the computer in the morning.

Please try not to alter oxygen flow through the night. It has been preset to a level that should be safe, please do not try to wean. If an increase in oxygen is needed please record.

<table>
<thead>
<tr>
<th>Brand of Trache</th>
<th>Type of humidification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Trache</td>
<td>Starting Oxygen flow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygen flow</th>
<th>Volume</th>
<th>Colour</th>
<th>Thickness</th>
<th>Saline needed?</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a change occurs</td>
<td>0 = none</td>
<td>0 = none</td>
<td>0 = none</td>
<td>“Yes” or “No”</td>
<td>In case I can’t read your writing</td>
</tr>
<tr>
<td>1 = small</td>
<td>1 = clear</td>
<td>1 = thin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = moderate</td>
<td>2 = white</td>
<td>2 = moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = copious</td>
<td>3 = yellow or green</td>
<td>3 = thick or tenacious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>O₂ Flow</td>
<td>Volume</td>
<td>Colour</td>
<td>Thickness</td>
<td>Saline?</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*continue on back of page if needed*

Please record the time of any other events, Eg Swedish nose change, emergency trache change etc.

<table>
<thead>
<tr>
<th>Time</th>
<th>Description of Event</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Thank you very much for your help in filling out this form*
<table>
<thead>
<tr>
<th>Time</th>
<th>O₂ Flow</th>
<th>Volume</th>
<th>Colour</th>
<th>Thickness</th>
<th>Saline needed?</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>