THE EVALUATION OF STRATEGIES FOR PRODUCING OPTIMAL INHALANT THERAPY IN PRESCHOOL CHILDREN (2-6 YEARS) WITH CHRONIC ASTHMA

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DECLARATION

The work presented in this thesis was performed by the author, unless otherwise acknowledged.

Chapters Two and Three: After the initial methodology was developed, and breathing patterns were recorded, the bench testing was performed by research assistants from the Aerosol Research Group, Department of Paediatrics and Child Health, University of Western Australia. The recorded breathing patterns were processed with software purposely developed by Guicheng (Brad) Zhang.

Chapter Two has been submitted as a manuscript to the Journal of Aerosol Medicine and Pulmonary Drug Delivery. Estimated author contributions were as follows:

André Schultz	50%
Timothy J Le Souëf	5%
Kevin Looi	5%
Guicheng Zhang	5%
Peter N Le Souëf	15%
Sunalene Devadason	20%

Chapter Four: The methodology for the clinical trial was originally developed by Peter le Souëf, Sunalene Devadason and Peter Sly. The author made various ammendments to the clinical trial design before the trial commenced, including the addition of electronic adherence monitoring, quality of life measurements, and breathing recording. The author had the assistance of a study nurse/ research assistant (Nicole Shaeffer, Trudi Mackenzie and Jane Jones) during all study visits. The research assistants also co-ordinated the day-to-day running of the clinical trial.

The author performed all data analysis except for the generalized estimating equations, which was performed by Guicheng Zhang.

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ABSTRACT

Background:

The dose of inhaled medication reaching a patient is dependent on drug formulation, method of delivery, output and correct use of the delivery device and frequency of use. The most commonly used aerosol drug delivery device in preschool children is the pressurised metered-dose inhaler (pMDI) -spacer. This study evaluated strategies for improving the delivery of inhalation therapy in preschool children by focusing on factors affecting the optimal use of pMDI-spacers and on the frequency of their use as determined by adherence to prescribed drug regimes.

The study was divided into two parts. Part 1 examined the number and type of breaths needed for efficient drug delivery through a pMDI-spacer in preschool children. Part 2 was a randomised, controlled, prospective clinical trial in which a comparison was made between an incentive spacer device and a small volume spacer with respect to adherence, correct device use (spacer technique) and clinical outcome.

Overall aims:

- To determine how many tidal breaths are required to effectively inhale medication from different types of spacer/ valved holding chamber devices, and to determine the efficacy of a single maximal inhalation for drug delivery in young children.

- To investigate the relationship between factors that determine dose delivery of inhaled asthma maintenance therapy and symptom control in preschool asthmatic children.

- To determine the influence of an incentive inhalation delivery device on drug delivery and clinical outcome in preschool asthmatic children.

Part One (Chapters Two and Three):

Background: The pMDI-spacer combination is currently the most commonly used method of drug delivery to preschool asthmatics. A patient's competence in using a pMDI-spacer is an important part of drug delivery. Preschool children are instructed to breathe normally (tidally) through spacer devices. There is little evidence on the number of breaths required for optimal drug delivery. Whether the single maximal breath technique has a place in spacer use in preschool children also remains unclear. Due to a lack of data, authors of asthma guidelines have been unable to give evidence-based instruction on how a preschool child should breathe through a spacer.

Aims: To determine the optimal method of breathing through a spacer for preschool asthmatic children to ensure effective drug delivery.

Hypothesis: Based on technical data on *in vitro* spacer performance and knowledge of tidal flow patterns in young children the hypothesis is that a limited number of breaths would be sufficient for efficient drug inhalation via spacer in preschool children.

Methods: A method for reliably recording and simulating breathing of patients using pMDI-spacer devices was designed, constructed and validated. Breathing flow patterns were recorded in preschool children inhaling placebo from spacers. The breathing patterns were reproduced by a breathing simulator which was connected to spacer devices. Breathing patterns previously recorded using each specific type of spacer, were simulated with the corresponding spacer type. To estimate delivery, the mass of salbutamol was measured on a filter interposed between the spacer and the simulator. Four different spacer devices, the Aerochamber Plus®, Funhaler®, Volumatic® and a modified 500ml plastic soft drink bottle were tested with a salbutamol pMDI. The effect of different numbers of tidal breaths and that of a single maximal breath on drug delivery were compared.

Results: Drug delivery via the Funhaler® mean (95CI) was 39% (34-43) and 38% (35-42) of total dose recovered from filter, pMDI and spacer, for two and nine tidal breaths respectively. Drug delivery via the Aerochamber Plus mean (95CI) was 40% (34-46) and 41% (36-47) for two and nine tidal breaths respectively.   There was no significant

difference in drug delivery after three tidal breaths mean (95CI) 40% (36-44%) and nine tidal breaths nine tidal breaths; mean (95CI) 37% (33-41) for the Volumatic®. With the (unvalved) modified soft drink bottle, there was no significant difference in drug delivery between two, five or nine tidal breaths.

Inhalation volumes were almost double the expected tidal volumes. The inhalation volume means (SD) of subjects using the Aerochamber Plus®, the Funhaler®, the Volumatic® and the modified soft drink bottle were respectively 393ml (247), 432ml (225), 384ml (185), 445ml (167) during tidal breathing and 515ml (164), 550ml (239), 503ml (213), 448ml (259) for the single maximal breath manoeuvre.

100% of seven year old children, 84% of six year olds, 76% of five year olds, 38% of four year olds and 20% of three year olds could perform a single maximal breath manoeuvre. Nine tidal breaths resulted in significantly greater drug delivery to filter than single maximal inhalation for both the Funhaler® (p=0.04) and the Volumatic® (p=0.01). There was no significant difference in drug delivery to filter between single maximal inhalation and nine tidal breaths with both the Aerochamber Plus® and the modified soft drink bottle.

Conclusion: In preschool children, two tidal breaths were adequate for drug delivery through small volume valved spacers and a 500ml modified soft drink bottle. For a large volume spacer, three tidal breaths were adequate for drug delivery.

Part Two (Chapters Four and Five):

Background: Drug delivery by pMDI-spacer is determined by many different factors, including spacer technique and adherence to prescribed medication. The effect of both spacer technique and adherence on clinical outcome has been demonstrated in older asthmatics. In this part of the thesis the influence of these factors on clinical outcome in preschool asthmatics was firstly investigated. Thereafter, the additional influence of an incentive spacer device on adherence, spacer technique and clinical outcome was also assessed.

 Aims:

- To investigate the effect of proficiency in spacer technique, as measured by deposition of drug inhaled onto a filter, on clinical outcome in preschool asthmatic children.

- To investigate the effect of adherence to prescribed inhaled asthma medication on clinical outcome in preschool asthmatic children.

- To investigate the influence of the use of an incentive spacer device on inhaled drug dose, adherence to prescribed treatment and clinical outcome in preschool asthmatic children.

Hypothesis:

- Proficiency in spacer technique correlates positively with improved clinical outcome.

- Good adherence to prescribed medication regimens correlates positively with improved clinical outcome.

- Use of an incentive spacer device, the Funhaler® , improves both competency in spacer technique and adherence to prescribed medication and thereby improves clinical outcome in preschool children with asthma.

Methods: A prospective randomised, controlled clinical trial was performed. Subjects were two to six year old children who had doctor-diagnosed asthma and were on daily maintenance therapy with inhaled corticosteroids. Maintenance therapy was delivered by Funhaler® in the study group and Aerochamber Plus® in the control group. Subjects were assessed for the following outcomes at three-monthly intervals for one year:

(1) Proficiency in spacer technique was measured at each study visit by measuring the drug dose deposited on a filter interposed between the subject and the spacer.

(2) Adherence was monitored using an electronic monitoring device (Smartinhaler)

(3) Asthma symptoms were monitored using diary cards.

(4) Quality of life (QoL) was measured using the PedsQL questionnaires.

(5) Lung function was monitored using the forced oscillation technique.

The Funhaler group was then compared with the Aerochamber Plus group in terms of determinants of drug delivery and markers of clinical outcome.

Results: One hundred and thirty two subjects were included in the study. One hundred and eleven patients (84%) completed the study. By the six month follow-up, significantly more subjects in the Funhaler group had dropped out of the study (p=0.04).

Throughout the clinical trial, there was large intra-subject variation in proficiency in spacer technique, as measured by drug dose deposited on filter. Individual patient drug doses recovered from the filters ranged from zero to 136μg (calculated as the mean of five 100μg pMDI actuations). There was no significant correlation between proficiency in using the delivery device and any measure of asthma control ($p > 0.05$). Correcting for age, gender, and adherence to prescribed medication did not influence the results.

Inter subject variability in adherence to prescribed medication was extremely high throughout the study. Adherence to prescribed medication ranged from 1% to 99%. There was a significant correlation between adherence to prescribed medication and nights without wheeze, throughout the study period ($r = 0.01$; $p = 0.01$). The correlation between adherence to prescribed medication and nights without wheeze remained after correcting for age, gender, proficiency in spacer technique, and the number of nights without wheeze at the baseline visit ($r = 0.01$; $p = <.01$). There was also a significant correlation between adherence to prescribed treatment and (daytime) days without wheeze ($r = 0.01$; $p = 0.01$). The correlation ceased to be significant after correcting for age, gender, proficiency in

spacer technique, and (daytime) days without wheeze at the time of the baseline visit. There was a significant correlation between adherence to prescribed medication and bronchodilator free days (r = 0.01; p = 0.02) throughout the study. After correcting for age, gender, proficiency in spacer technique, and bronchodilator free days at baseline, the correlation between adherence to prescribed medication and bronchodilator free days remained significant (r = 0.01; p = 0.01). There was no significant correlation between adherence and other markers of clinical outcome.

After correcting for age and gender, the Funhaler group demonstrated significantly higher proficiency in spacer technique as determined by filter dose (p = 0.05). The improved proficiency in spacer technique in the Funhaler group was limited to subjects who were younger than 4 years of age at the baseline visit (p < 0.01).

There was no significant difference in adherence to prescribed medication between the Funhaler group and the Aerochamber Plus group (p = 0.93). Correcting for age and gender did not influence the results.

At the start of the clinical trial (baseline visit), the Funhaler group reported significantly less days without wheeze (p = 0.03), and significantly less bronchodilator free days (p = 0.02) than the Aerochamber Plus group in the seven days before the baseline visit. The Funhaler group also scored lower than the Aerochamber group in terms of QoL scores at the time of randomisation (p = 0.05). Where needed, various measures were used to correct for the significant differences at baseline, between the Funhaler group and the Aerochamber Plus group. There was no significant difference between the Funhaler group and the Aerochamber Plus group in terms any of clinical outcome measures used. Correcting for age, gender did not influence the results.

Discussion: Use of the Funhaler® therefore appeared to specifically improve drug delivery in those subjects who, with a conventional spacer, would have inhaled very low doses of medication. The Funhaler® was therefore partially successful as an incentive device, as its use positively influenced drug delivery in a specific sub-group of preschool children.

Proficiency in spacer technique did not translate to improved clinical outcomes. Various reasons for the lack of association between proficiency in spacer technique and clinical

outcome, including the inevitable inherent limitations in design in a clinical study, are discussed.

Results suggest that adherence to prescribed medication regimens correlates positively with improved clinical outcome in preschool children with asthma. Use of the Funhaler® did not improve adherence to prescribed medication, or clinical outcome, in preschool children with asthma. Funhaler® therefore failed as an incentive device to improve long term adherence, and clinical outcome, in preschool asthmatic children. Future design for an incentive device will need to consider providing feedback that is of more ongoing interest to the child.

As the large variation, as observed in this study, in proficiency in spacer technique, and adherence to prescribed medication, is likely to influence results of clinical trials, an awareness of the variation in spacer technique and drug delivery may contribute towards the accurate interpretation of results in future studies.

Finally, the wide variation in both proficiency in spacer technique, and adherence to prescribed medication, both factors that determine drug delivery to patients, highlight the importance of pursuing ways to improve inhalation drug delivery to preschool children in order to eliminate the variability in prescribed medication that eventually reaches patients. The delivery to the lungs of a constant, reliably repeatable inhaled drug dose should be a continuing aim for aerosol scientists and physicians.

LIST OF ABBREVIATIONS

AC+…………………………………… Aerochamber Plus

CFCs………………………………... Chlorofluorocarbons

cm…………………………………… Centimetre

DPI………………………………….. Dry powder inhaler

eNO…………………………………. Exhaled nitric oxide

f…………………………………... Frequency

$FEV_{0.5}$…………………………………. Forced expiratory flow at 0.5 second

$FEV_{0.75}$…………………………………. Forced expiratory flow at 0.75 second

FEV_1…………………………………. Forced expiratory flow at 1 second

FH…………………………………… Funhaler®

FOT……………………………….. Forced oscillation technique

GEE…………………………………. Generalized Estimating Equations

HFAs……………………………….....Hydrofluoroalkanes

HR-QoL……………………….……...Health Related Quality of Life

Hz………………………………….....Hertz

I : E……………………………….......Inspiratory: expiratory ratio

kg……………………………………..Kilogram

kPA……………………………….…..KiloPascal

LPM………………………………….Litres per minute

μg…………………………………….Microgram

mg…………………………………...….Milligram

ml…………………………………......Millilitre

MMAD……………………….…….Mass median aerodynamic diameter

NO………………………………......Nitric oxide

PEF…………………………….……..Peak expiratory flow

PIF…………………………………………....Peak inspiratory flow

pMDI………………………………….…...Pressurised metered dose inhaler

Q……………………………………….…...Flow

QoL……………………………...………Quality of life

Rint……………………………......……..Interrupter resistance

RR……………………………...………Respiratory rate

Rrs…………………………..…………Respiratory system resistance

Rrs6…………………………......……Respiratory system resistance at six Hz

Rrs8……………………….…………Respiratory system resistance at eight Hz

RSS……………………………………Really Simple Syndication

s…………………………………..……..Second

Ti……………………………….……Inspiratory time

VHC……………………………………Valved holding chamber

Vt………………………………………Tidal volume

Xrs…………………………………..Respiratory system reactance

Xrs6…………………………………Respiratory system reactance at six Hz

Xrs8…………………………………Respiratory system reactance at eight Hz

Zrs…………………………………..Respiratory system impedance

1 CHAPTER ONE: Literature review

1.1 Inhalation treatment for asthma in preschool children

Asthma is the most common chronic disease in preschool children in developed countries. It places an immense financial burden on health care systems. Young asthmatic children consume three times more inpatient resources per capita than older children and adults [1], with rates for emergency department visits and hospitalisations more than double that of older children [1, 2]. Asthma fluctuates in severity, with episodic acute exacerbations leading to morbidity and mortality. Inhalation drug delivery is the primary mode of asthma therapy in children. Acute asthma is generally managed with inhaled beta agonists and systemic steroids. Inhaled steroids are the most effective and most widely used maintenance therapy for asthma. Throughout most of the developed world pressurized metered dose inhalers (pMDIs) used in combination with valved holding chambers (VHCs) or spacers are the preferred method for delivering asthma preventers in preschool children [3-5]. The regular use of inhaled steroids has been shown to reduce the frequency and severity of asthma symptoms [6]. Although asthma preventers have been shown to reduce asthma symptoms, asthma related morbidity still remains high. Reasons for the continued high asthma related morbidity could be ascribed partly to inadequate inhalation drug delivery.

Targeted medical treatment to the airways enables us to provide higher drug doses to the lungs while sparing other organs from unnecessary drug exposure. The science of delivering therapeutic drugs to the lungs is still being perfected: Even with the best delivery systems available, a significant fraction of aerosolized drug does not reach the lungs and either goes to waste in the atmosphere, deposits onto the delivery device [7] or deposits in other sites in the upper airway [8] [9]. A fraction of inhaled drug is absorbed into the systemic circulation via these sites [10], and even via the lungs [11].

Reliable delivery of inhaled medication to children is important [12]. Accurate dosing of inhaled corticosteroids is especially important, as side effects can be caused by excessive dosing[13], and sub-optimal dosing can lead to treatment failure. Drug delivery to a patient is determined by drug characteristics, the delivery system used, and patient related factors

[14]. Factors that determine aerosol drug delivery, related to the drug and delivery systems, include drug formulation, delivery device and prescribed medication dose. Patient-related factors that influence aerosol drug delivery include an individual's airway anatomy, expertise in using the delivery device and adherence to prescribed medication. Before drugs and delivery systems can be discussed, it is important to understand certain basic principles of aerosol behaviour in relation to the airways.

1.2 Basic principles of aerosol behaviour

Whether aerosol particles are inhaled into the lungs or deposited in the upper airways is determined by the inertial characteristics of the particles [14-16]. Particle deposition onto the airway surface during inhalation, depends upon the method of inhalation, the characteristics of the aerosol particles and physical characteristics of the subject inhaling the particles [17, 18]. Therapeutic aerosol particles are designed to be deposited on the surface of small to medium airways. Whether a fraction of an aerosol that reaches the lungs is deposited onto the airway surface or simply exhaled again is determined by sedimentation, due to gravitational forces [19], and impaction due to inertia.

An aerosol particle's inertial characteristics are mainly determined by its size, density and shape [14]. Aerosols generally consist of particles with a range of sizes, densities and shapes, and therefore accurately describing the particle characteristics of an aerosol can be challenging. To make description and comparison possible, aerosols are often described in terms of mass median aerodynamic diameter and the associated geometric standard deviation. Aerodynamic diameter is defined as "the diameter of a sphere of unit density which has the same settling velocity in air as the aerosol particle being measured" [14]. The measurement of an aerosol's aerodynamic diameter and geometric standard deviation is especially important for "particle sizing", which is discussed below.

During inhalation, therapeutic aerosol particles do not always follow airstream lines, as mechanical and electrostatic forces influence particle movement: Electrostatic forces can play a role in aerosol delivery outside the body [20], but as the external surface of the airways is generally not electrostatically charged, mechanical forces are of more importance in determining the movement of an aerosol particle in the airways. The forces that act on an aerosol particle are diffusion (Brownian movement), sedimentation (gravitational transport) and inertia [17, 21]. The specific type of mechanical force that

most influences the movement of a particle is determined by the size and density of the particle, as well as by time, as described below:

Diffusion: Diffusion is the random motion of small particles suspended in a gas as a result of random thermal agitation that leads to the intermingling of molecules. Microfine particles with a diameter smaller than 0.1μm are transported by diffusion [21, 22]. Diffusional movement is not influenced by particle density, but is influenced by time and particle size [14]. As diffusional transportation is time dependent, it follows that during breathing, lung deposition by diffusion occurs in parts of the lung with the longest residence time i.e. the small airways and alveoli. If the residence time is not long enough, i.e. when a patient's respiratory rate is very fast, a significant fraction of inhaled microfine particles can be exhaled before deposition of the particles onto the surface of the airways occurs [22, 23].

Sedimentation: Sedimentation is also known as gravitational transport. As particles increase in size, the influence of sedimentation on particle movement increases and the influence of diffusion on particle movement decreases [14, 19, 21]. When a unit density particle exceeds a diameter of one micrometer, diffusion has a negligible effect on particle movement [21], and the influence of sedimentation is paramount. Movement by sedimentation is, like movement by diffusion, time dependent. Lung deposition as a result of sedimentation therefore also mostly occurs in smaller airways, where air movement is slower [19, 21].

Inertia: Inertia is the property of a particle that causes it to resist changes in speed or direction (velocity). Aerosol particles of unit density larger than two micrometers are primarily deposited by inertia [14, 22]. Inertial transport is velocity dependent. Airways branch, and change direction frequently. Larger particles, which are mainly transported by inertia, are therefore deposited onto airway surfaces of the larger airways[22, 23], where air flow is greater than in the smaller airways.

Under laminar flow conditions, particles larger than five micrometers in diameter will mostly impact on larger airways [22] and will therefore not be inhaled into the lungs. Under turbulent flow conditions, particles larger than three micron will mostly not be inhaled past the nasopharyngeal bend [22]. As mentioned above, particles smaller than half a

micrometer in aerodynamic diameter do not deposit in the lungs under normal breathing conditions and are therefore mostly exhaled [24]. Aerosol particles are therefore most suitable for inhalation if they have an aerodynamic diameter between one and five micrometers [25]. Pharmaceutical preparations generally have MMADs (mass median aerodynamic diameters) of one to five micrometers [24, 26]. As described above, particles with a diameter larger than one micrometer are mostly submitted to inertial and to a lesser extent, to gravitational forces. Drug delivery to the lung will therefore mostly be determined by particle size, inertial and to a lesser extent, gravitational forces, with drug delivery increasing due to gravitational forces during breath holding manoeuvres

The main asthma drugs used in preschool children will be discussed below, followed by a discussion on delivery devices. Emphasis will be placed on drug formulations and delivery devices suitable for use in preschool children, and their effect on aerosol characteristics and drug delivery.

1.3   Inhaled asthma drugs

Asthma pathophysiology includes bronchoconstriction, airway inflammation with mucous secretion and airway remodelling. The standard drug treatment for asthma consists of bronchodilators and corticosteroids. Leucotriene antagonists are also used in selected patients for preventive therapy.

1.3.1   Bronchodilators

In the preschool age group, mostly short acting β-stimulants (e.g. salbutamol) and to a lesser extent anticholinergics (e.g. ipratropium bromide) are used as asthma relievers or bronchodilators. Beta-stimulants have a wide therapeutic index, are relatively inexpensive and are only used for treating acute asthma symptoms, making accuracy in dosing less important. The need for repeated high doses of bronchodilators during acute asthma exacerbations makes fast, effective drug delivery a priority. Long acting β-stimulants (e.g. salmeterol) are used in conjunction with inhaled corticosteroids as asthma controllers. For delivery of β-stimulants, drug formulations with larger particles, in the upper range of one to five micrometers may be more desirable, as regional targeting of bronchodilators to the proximal airways have been shown to be more effective for bronchodilation than distal alveolar drug deposition [27].

1.3.2 Corticosteroids

Inhaled corticosteroids are used for the secondary prevention of airway inflammation and mucous secretion. Where inhaled steroids are used to treat asthma, particles within the lower range of 1-5µm are more desirable, as inflammation in the distal lung can exceed that in the large airways [28]. Inhaled steroids are generally prescribed for daily or twice daily use as asthma preventers. The medium to long term need for the daily- or twice daily administration of inhaled steroids makes a rapid, effective delivery mechanism preferable. A fast, effective delivery mechanism is especially preferable in preschool children who are known to often be resistant to being treated. Fluticasone, budesonide, beclomethasone and more recently ciclesonide are commercially available inhalation steroids.

Beclomethasone was the first commercially available inhaled corticosteroid. Since the initial introduction of beclomethasone dipropionate to the market, the drug has been reformulated as an extra fine aerosol [29] with a MMAD of one micrometre. The small particle size allows for improved lung deposition. The extra fine beclomethasone formulation also has high systemic bio-availability, due to absorption through the pulmonary vasculature [30]. Fluticasone propionate currently is one of the most widely used corticosteroids. Fluticasone is a potent inhalation corticosteroid with low gastro-intestinal bioavailability [31]. Budesonide, an older formulation, is widely used in dry powder inhalers and nebulisers. Budesonide is less potent than fluticasone, which has higher corticosteroid receptor binding affinity [32]. Budesonide has relatively low bio-availability due to low gastro-intestinal absorption and its tendency to bind with plasma proteins. Budesonide is highly protein bound in plasma, reducing the effect of absorption through the airway mucosa or gastrointestinal system. Ciclesonide is the most recent development in inhalation steroids. Ciclesonide is unique as an inhalation steroid, in that it is inhaled as a pro-drug, and converted to its active metabolite in the airways [33]. The use of ciclesonide, therefore, theoretically should reduce the chance of developing systemic side effects to a minimum [34].

1.3.3 Dose-response relationship between inhaled corticosteroids and asthma control in preschool children

Although the efficacy of inhaled steroids is well known in older children and adults with asthma, the dose-response relationship of inhaled steroids in preschool children is currently still not entirely clear [35]. Interpretation of data on preschool children is made difficult by a large variation in age groups being studied, various definitions used for asthma and wheezing disorders [35] and the difficulty in obtaining objective physiological data.

In a four month long double blind parallel trial [36], where the effect of budesonide 400μg per day was compared with that of placebo, in 41 "young wheezy children" aged 0.7-6.0 years, budesonide had no significant effect on acute episodes of wheeze. The results of this study should, however, be interpreted in the light of the relatively low subject numbers, the short duration of the study, and the inclusion of very young infants.

In a clinical trial comparing 200μg fluticasone per day, 100μg fluticasone per day, and a placebo, in 237 asthmatic children aged 12 to 47 months, exacerbation rates were inversely related to inhaled steroid dose [37]. Thirty seven percent of the placebo group had one or more exacerbations during the 12 week study period. In the treatment groups, respectively 37%, 26% and 20% of subjects in the placebo, 100μg and 200μg groups experienced asthma exacerbations.

Guilbert el al [38] compared the effect of long term inhaled fluticasone to that of placebo on 285 two- to three-year old children at high risk of developing asthma. Over a two year period, the treatment group (fluticasone 88μg bi-daily) demonstrated a greater proportion of symptom-free days, a lower rate of asthma exacerbations, and a lower rate of supplementary use of controller medication.

1.3.4 Side effects of inhaled steroids

Adverse local and systemic effects caused by the use of inhaled corticosteroids have been well described [39-41]. Inhaled corticosteroids have been shown to have a suppressive effect on linear growth and may cause suppression of the hypothalamic-pituitary axis. Cases of adrenal crises leading to significant morbidity and mortality have been well documented in children using high doses of inhaled corticosteroids. Because of the potential for side effects with the use of regular inhaled corticosteroids, accuracy in dosing should be a priority. Unfortunately, accuracy in dosing when delivering inhaled

corticosteroids has remained an elusive goal, as many different factors influence the inhaled drug dose delivered.

1.3.5   Delivery of inhaled asthma medication in preschool children

Fast and effective delivery systems are preferred for delivery for both bronchodilators and inhaled steroids. Reliability and consistency in dosing should be a priority when delivering inhaled steroids. The efficiency and accuracy of drug delivery is greatly influenced by the choice of delivery device, which will be discussed below.

1.4   Delivery devices

1.4.1   Pressurised metered dose inhalers

Pressurised metered dose inhalers (pMDIs) used with valved holding chambers (VHCs) or spacers are considered to be the method of choice for delivering aerosolized medication to preschool children [29, 42]. pMDIs, when used correctly, are an effective means of delivering medication to the airways and are relatively inexpensive and quick to use. Isolation and pressurization of contents protects against colonisation of the drug formulation by pathogens. For very young children a major benefit of using pMDIs and spacers is that inspiratory effort from the patient is not essential in order for the metered dose to be dispensed. Guidelines for the most effective use of pMDIs will be discussed later in theis thesis.

pMDI design: The pMDI is a complex configuration for delivering medication. A pMDI consists of a canister that contains propellants and a drug, a metering valve, and a sleeve/actuator. Each component plays a role in determining the characteristics of the aerosol being dispensed [43].

Canister: The drug formulation is contained within the canister. The canister acts as a reservoir for the drug, propellants and excipients which make up the drug formulation. The canister must be able to withstand high pressures generated by the propellant and is usually made of aluminium. Chemical interaction of the drug and the material of which the canister is made may be prevented by coatings on the internal container surface of the canister [44].

<u>Drug formulation</u>: In a pMDI the physicochemical properties of the drug formulation play an important role in determining the characteristics of the aerosol produced [44]. The drug used, propellants, and surfactants all play a part in contributing to the characteristics of a drug formulation.

<u>Propellants</u>: Propellants in pMDIs are highly volatile substances that are in liquid form when compressed in pMDI canisters, but change into the gaseous phase at atmospheric pressure [43]. When exposed to room temperature and atmospheric pressure, propellants immediately boil, thereby atomizing the drug, which is suspended in or dissolved with the propellant.

Hydrofluoroalkanes (HFAs) have largely replaced chlorofluorocarbons (CFCs) as propellants in pMDIs. CFCs have traditionally been used as propellants, but are in the final stages of being phased out by international agreement because of their detrimental effect on the ozone layer [45]. HFAs do not have a damaging effect on the ozone layer [46]. HFAs are greenhouse gases, although their potential to contribute to global warming is a tenth of the potential of CFCs [46]. Both HFAs and CFCs are still being used as propellants in pMDIs and there are still CFC propelled pMDIs available on the market [42].

Vapour pressure must be constant throughout the usage life of a pMDI to ensure consistent dosing. Within a closed pMDI canister, the propellant forms a two phase system made up of liquid and vapour. A dynamic equilibrium exists between the liquid and vapour phases, giving a constant vapour pressure. The constant vapour pressure is maintained irrespective of whether the canister is full or nearly empty. The pressure inside a pMDI canister is typically 300-500kPa (three to five atmospheres) [43].

<u>Drugs</u>: Drugs in pMDIs can be formulated to take the form of either particulate suspensions or solutions. Most HFA pMDIs (with a few exceptions) and all CFC pMDIs are formulated as suspensions. A difference in density between drug particles and propellants will cause drug particles to separate from the suspension if the pMDI is left standing. The drug particles will either rise to the liquid surface or sink under the influence of gravity [47, 48]. Suspension formulation pMDIs therefore need to be shaken immediately before use to ensure uniform mixing of drug particles in the propellants to

make dosing reproducible [48]. Shaking may not be as important for HFA formulations [49].

Aerosol droplet size for suspension formulations is reduced if the formulation has a high vapour pressure, a small drug particle size, or a low drug concentration [50]. For HFA solution formulations aerosol particle size is influenced by the initial droplet size, the concentration of the non-volatile components in the droplet and, to a lesser extent, the ambient conditions [43, 51].

Surfactants and excipients: Surfactants (such as oleic acid or sorbitan trioleate) are used in suspension (mostly CFC) formulations to reduce particle aggregation and to lubricate the valve mechanism. Ethanol is used as a co-solvent/ excipient in some HFA formulations (especially in solution formulations) to solubilise the surfactants or to solubilise the drug itself [42, 43].

Metering valve and metering chamber: The metering valve is the most important determinant of drug dose delivered by a pMDI. The metering valve functions as a measuring device that delivers a reproducible amount of the liquid phase of a drug formulation. The volume of the metering chamber may range from 25 to 100μL [43, 51]. Before actuation of the pMDI, there is an open channel between the body of the container and the metering chamber. The open channel allows for the metering chamber to be filled. On actuation of the pMDI this channel closes, and another opens, connecting the metering chamber to the atmosphere. The drug formulation, which is under pressure, is rapidly expelled into the valve stem and an expansion chamber. As soon as the propellant is exposed to atmospheric temperature and pressure, it begins to boil. After actuation, a spring returns the valve stem to the resting position and the metering chamber refills. In some devices the valves are surrounded by a retaining cup that contains the next few doses of the drug [43].

Actuator: A pMDI canister is fitted into a plastic actuator. The nozzle of an actuator is critical to formation of the aerosol spray [52]. The actuator's nozzle diameter greatly influences aerosol particle size [44, 50]. The length of the actuator nozzle also influences aerosol particle size [53]. The final atomization process of the drug formulation occurs as follows: When the drug dose leaves the actuator nozzle, the liquid components are

separated by aerodynamic forces to form a spray of liquid droplets [43]. Evaporation of the propellant cools the droplets. The term "cold-freon effect" has been used to describe the cold pMDI plume that may impact on a patient's oropharynx, thereby momentarily altering a patient's inhalation [54]. The cold-freon effect is less important in HFA powered pMDIs.

Determinants of the aerosol plume: For a CFC pMDI, the plume velocity at the start of pMDI actuation is around 30m/s and the plume duration is typically 100-200ms [43, 52]. The plume may be as long as 32cm [55]. Both spray force and temperature reduction appear to be less pronounced with some, but not all HFA formulations [54, 56]. Actuator orifice diameter is the most important factor determining spray force [54]. The size and velocity of the aerosol plume that is expelled from a pMDI influence oropharyngeal deposition. A breath actuated plume-control pMDI, which reduces the size and velocity of the aerosol plume significantly, has recently been designed [9]. The plume control pMDI increases drug delivery to the lung and decreases oropharyngeal deposition markedly. Oropharyngeal deposition of aerosol can be greatly reduced by the use of spacers [42].

1.4.2   Spacers and holding chambers

Spacers and VHCs have also been called add-on devices, accessory devices, extension devices, and holding chambers. Both the names "spacers" and "valved holding chambers" are in common use today. Technically speaking, a spacer with a valve is a holding chamber. The two terms are often used interchangeably.

Spacers are attachments to pMDI actuators. Spacers perform several functions: By placing distance between the point of aerosol generation and the patient's mouth, they reduce oropharyngeal deposition and (especially in children) increase lung deposition. Spacers were initially developed to improve drug delivery with pMDIs in adult patients with coordination problems [57]. Valved spacers simplify pMDI use by reducing the need for coordination between actuation and inhalation [43]. Valved spacers prevent the actuated dose from being blown out of the chamber by exhalation, when actuation of the pMDI is not synchronised with the beginning of inhalation.

Spacers are generally made out of metal or plastic. Over time, plastic spacers build up an electrostatic charge which reduces drug output significantly [58, 59]. Electrostatic build-up

can be reduced for two to four weeks by rinsing spacers in detergent and leaving the detergent on [58, 60]. Spacers made from charge-dissipative material have been made commercially available and appear to be more effective for drug delivery [20, 61-63].

Successful commercially available spacers range from 100 mL to 750 mL in volume [42]. Spacers can be classified as small volume and large volume. There is no formal agreement on the cut-off point between small volume and large volume spacers, but spacers with volumes of less than 250ml will be referred to as small volume spacers in this thesis. Small volume spacers are generally used in young children, while large volume spacers are used in older children and adults.

In young children, who may have difficulty coordinating inhalation with the actuation of the pMDI, it is desirable to use spacers. If exhalation precedes inhalation, valved spacers prevent the drug in the holding chamber from being blown into the atmosphere before it can be inhaled. In certain developing countries, plastic cold drink bottles are converted into unvalved spacers. These hand made spacers have been shown to be effective in children older than five years of age. A more recent publication [64] argued that a modified soft drink bottle spacer is as efficient as a conventional spacer for delivery of bronchodilator therapy in younger children. The methodology of this particular study could be questioned; however, as the study population (median age (25th–75th centile) was 12 (6–25) months) was unlikely to have demonstrated a marked response to bronchodilator therapy *per se*.

Different combinations of pressurized metered dose inhalers and spacers may result in considerable differences in dose output [65-69]. Several studies have demonstrated that the behaviour of an aerosolized drug with a spacer device is specific to the drug and spacer combination being used [10, 55, 68, 70-72]. For accuracy in drug delivery, a strong case can be made for using only a specified spacer with a specific drug formulation where the output for the specific spacer-drug combination is known [73]. However, in practice, the likelihood is that different drugs and spacers will be used interchangeably by both health care providers and patients. Testing the influence of all different spacers on the delivery of all different inhaled drug formulations is impractical. Fortunately there are certain generalizations that can be made with regards to drug delivery and spacer size: In small volume spacers, up to the medium sized Babyhaler (350ml), when the electrostatic charge of spacers is reduced, the lung dose appears to be pMDI dependent and spacer independent [69]. At low tidal volumes, large volume spacers deliver lower inhaled doses than small

volume spacers [74]. At high tidal volumes, large volume spacers deliver higher doses than small volume spacers [74].

1.4.3 Breath actuated devices

The first breath actuated inhaler was described in 1971 [75]. Breath actuated inhalers were designed to overcome the problem of synchronizing release of the drug with the start of inhalation [75]. After priming a breath actuated metered dose inhaler, the patient's inhalation triggers actuation of the device. Breath actuated devices improve drug delivery in adults with poor co-ordination [29, 76], but are not recommended for preschool children. Most preschool children are unable to perform the two- to four-second long maximal inhalation required for effective drug delivery through a breath actuated device [77].

1.4.4 Nebulisers

For the delivery of asthma medication in preschool children, nebulised delivery of drugs is inefficient and expensive. Some authors have stated that nebulisers should be reserved for children who are unable or unwilling to use pMDIs and spacers [78]. Traditional nebulisers are expensive, need a power source, are less efficient than pMDI-spacers in delivering drugs to the lungs (more drug required for similar pulmonary delivery, and higher systemic absorption of drug), take longer to use and are more difficult to maintain in terms of safety and hygiene [5, 10, 79-82]. Even in acute asthma attacks delivery of bronchodilators by pMDI-spacer is at least as effective as delivery by nebulizers [5, 83].

Some authors suggest that if a child is very distressed during administration of aerosols by pMDI-spacers, a nebulizer could possibly be a more effective acceptable alternative [84]. However, nebulisers have not been shown to be more efficient in drug delivery in such circumstances and have not been proven to be more effective than pMDI-spacers when used to administer medication to crying children. Hence, in many clinics, particularly in Australia, nebulisers are no longer prescribed for any asthmatics. Nebulisers do play an important role in aerosol medication delivery where the medication is not available in pMDI formulation e.g. antibiotics and enzymes in the management of cystic fibrosis.

Several new generation nebulisers that deliver medication rapidly have been developed [29], for example: Respironics I-neb, Omron MicroAir, the Nektar Aeroneb, and the Pari

eFlow [85]. These devices play a role in delivering expensive medications efficiently where pMDI formulations are not available. However, high cost generally inhibits the use of these devices for the day to day delivery of asthma medication.

1.4.5 Dry powder inhalers

Dry powder inhalers (DPIs), like breath actuated pMDIs, reduce the need for the patient to co-ordinate actuation with inhalation. DPIs are popular amongst patients because they are small, unobtrusive and easily portable and do not produce any greenhouse gases. When using DPIs a forced inspiratory manoeuvre is required for the metered dose to be dispensed [29]. The inspiratory flow determines the total emitted dose and the respiratory fraction. The need for a forced inspiratory manoeuvre prevents the effective use of DPIs in most young children. Most children below the age of six are not able to generate the inspiratory flow through the DPI that is needed to disperse the powder from most of DPIs [86, 87]. The DPIs that are currently commercially available are therefore not recommended for children under the age of six years.

1.4.6 Conclusion

A multitude of different delivery devices are available for aerosol drug delivery. pMDIs, when used correctly, are an effective means of delivering medication to the airways, are relatively inexpensive and quick to use, the contents are protected against colonisation of the drug formulation by pathogens, and high inspiratory effort from the patient is not essential in order for the metered dose to be dispensed. In young children, who may have difficulty coordinating inhalation with the actuation of the pMDI, spacers should be used in conjunction with pMDIs. Nebulisers are still widely used to deliver asthma medication in young children. DPIs are not suitable for use in preschool children, who are generally unable to perform the required forced inspiratory manoeuvre. Traditional nebulisers are less efficient than pMDI-spacers in drug delivery. Because of the advantages of pMDI-spacers mentioned above, pMDI-spacers are considered by most authorities to be the preferred means of delivering asthma medication to preschool children.

There are many variables that influence drug delivery through pMDI-spacers. The next section will focus on drug delivery from pMDI-spacers.

1.5 Testing drug delivery through spacers

1.5.1 Overview

The dosing properties of inhalation devices can be determined by *in vitro* measurements of the quantity and quality of the emitted aerosolized drugs. *In vitro* measurements of aerosolized drugs allow an estimation of the reproducibility of the dose and particle size distribution of the aerosol delivered under optimal circumstances by a given drug formulation-delivery device combination. *In vitro* studies are useful as they isolate the variability of the device from the variability of patient factors in using it, and from the variability of aerosol and drug deposition after the aerosol is inhaled.

When evaluating the *in vivo* performance of an inhalation device, the important parameters to consider are the total dose that reaches the patient and the deposition pattern of the inhaled dose in the airways [88]. The total dose that reaches the patient is a measure of the body's exposure to the drug. The inhaled medication's deposition pattern, which can be estimated by particle sizing, is a measure of the drug distributed between the targeted and non-targeted areas in the body [88]. Total dose delivery and deposition pattern can be seen as different measures of safety and efficacy.

Various *in vitro* and *in vivo* techniques are available to measure the performance of delivery devices. Particle sizing is the main *in vitro* technique, while pharmacokinetics and scintigraphy are the main *in vivo* techniques. Filter studies are used both *in vitro* and *in vivo*.

1.5.2 Pharmacokinetics

The total lung dose of an inhaled drug can be determined pharmacokinetically by measuring drug levels in the blood or urine [89, 90]. Pharmacokinetic studies to determine lung dose can only be accurate if the drug tested is not metabolized in the lung and there is negligible absorption of the drug through the gastro-intestinal system. Charcoal can be used to limit gastro-intestinal absorption of a drug. Pharmacokinetic estimation of lung deposition has been used to determine aerosol characteristics of a range of different drug

formulations [91-94]. There is strong agreement between pharmacokinetically determined lung deposition and scintigraphically determined lung deposition [95].

1.5.3   Scintigraphy

Gamma scintigraphy allows for the measurement of the distribution of an aerosolized drug throughout the delivery device, the patient's body and the exhaled air [88]. In gamma scintigraphy, the drug formulation is labelled with a radio-active isotope. Drug deposition is measured with an external gamma camera [11]. Two-dimensional (planar) scintigraphy is mostly used, but three dimensional imaging by way of single particle emission computed tomography is available in highly specialised laboratories [96].

There are two major criticisms against using scintigraphy to determine the efficacy of aerosol drug delivery. Firstly, gamma-scintigraphy exposes the patient to low doses of radiation. The second major criticism against using scintigraphy for aerosol testing is that the labelling process may alter the formulation being tested. The labelling process usually involves mixing of the drug with the label; however the drug and label are indirectly associated within the aerosol droplets. More sophisticated molecular labelling has also been described (direct labelling) [96]. Concerns about the labelling technique are usually allayed by the validation process: Validation of the labelling process is performed by particle sizing (see below for particle sizing) in order to ensure that the distribution of label within the aerosol droplets closely reflects the drug distribution.

Various techniques have been used to analyze scintigraphic lung images to determine the distribution of the label in different anatomical areas of the lung [97-100]. These methods have had limited success. Because of limited anatomical resolution, scintigraphy generally focuses on whole lung deposition rather than distribution patterns within the lungs [88]. Some assessment of central to peripheral distribution may be made, however this is more feasible with 3-D (SPECT) imaging involving higher doses of radiation than 2-D planar imaging techniques. The radioactivity involved limits this technique to only carefully selected studies with optimal devices and small subject numbers, particularly in young children.

1.5.4 Particle sizing

In vitro measurements of aerosol particle size are used in the development and quality control of pharmaceutical aerosols [11]. *In vitro* particle sizing also has a limited role to play in predicting lung deposition *in vivo* [11, 24].

Several different techniques are available for measuring particle size of aerosols including time of flight, laser diffraction and inertial particle impaction. Each technique has advantages and disadvantages:

Time-of-flight techniques measure the aerodynamic diameter of individual particles following controlled acceleration in a well-defined flow field [24]. Time-of-flight is widely used for the rapid assessment of aerosols from drug delivery devices. The main advantage that time-of-flight techniques offer is rapid measurement times [24, 101]. However, only a single particle can be measured at any given time, and while data on the single particle is being processed, other particles cannot be measured simultaneously. While a single particle is being measured, time-of-flight methods are vulnerable to coincidence effects (accidental coincidence is defined as the erroneous registration of two photons). Time-of-flight techniques are specially vulnerable to coincidence errors when sampling concentrated aerosols; this vulnerability severely limits the usefulness of using time-of-flight techniques for measuring aerosols produced by pMDIs [24]. Another disadvantage of time-of flight methods is that no drug assay is performed. Therefore, the resulting size distribution includes particles that do not contain any medication, e.g. excipients and surfactants that may be present in pMDI formulations [101], thus (generally) underestimating the particle size and hence deposition of drug-containing droplets.

Laser diffraction, also commonly used to estimate the size range of an aerosol cloud produced by aerosol delivery devices, has similar advantages and disadvantages as those mentioned for time-of-flight techniques of particle sizing [11].

Cascade impactors and multi-stage liquid impingers are the most widely used means for the *in vitro* determination of the particle size distribution of aerosols from therapeutic inhalers [102]. Cascade impactors directly measure aerodynamic size using a constant suction flow through the device, and are used to quantify the mass medication in different particle size

ranges, independent of other non-physiologically active components of the formulation [102].

Many aerosols change their aerodynamic characteristics after they are generated, and the measurement technique may have an effect on aerosol particle characteristics [88, 103]. For instance, when one is particle-sizing wet aerosols using cascade impaction, evaporative losses of aerosol droplets, as they enter the impactor at ambient temperature, may give rise to an apparent shift in the particle size distribution, resulting in an artificially reduced mass median aerodynamic diameter (MMAD) [104]. Higher flow generally results in greater drying of particles; cooling of the impactor or humidification of the air stream and surroundings can ameliorate these effects.

Correlations exist between particle sizing data and whole-lung deposition [9], especially for particles smaller than 3µm. However the use of a constant flow through these devices results in an overestimation of drug delivery compared with *in vivo* studies. Agreement between *in vitro* and *in vivo* data may be improved by measuring particle size in ways that more closely mimic clinical use [9]. The use of impactor inlets that simulate the human upper airway anatomy, and the inclusion of breathing simulation in cascade impaction techniques are a move toward *in vitro* conditions that more closely mimic *in vivo* conditions.

1.5.5 Filter studies

The total drug dose delivered to a patient from pMDIs with spacers can be assessed non-invasively by interposing a filter between the delivery device and the patient. The amount of drug delivered to the filter represents the amount of drug that would have reached the patient's mouth. Filter studies can be performed either *ex vivo* [105, 106] or *in vitro*. There is good agreement between *ex vivo* and *in vitro* measurements [107, 108].

Use of filters adds a resistance and dead volume to the inhaler setup. There is often a trade-off between resistance and dead volume (i.e. reducing the dead volume often increases the resistance. These factors introduce a greater error when estimating drug delivery in children as it is harder for them to overcome the additional resistance, and the inspiratory volumes of very young children may be similar to the filter dead volume. If the inspiratory

volume of the child is lower than the dead volume of the filter, rebreathing within the filter occurs, resulting in little or no drug being deposited on the filter membrane.

Filter studies have been used to determine the efficacy of inhalation drug delivery devices and factors influencing drug delivery since the early 1990s [105, 109-112] and are widely used to determine drug delivery using pMDI-spacers (63-65, 67, 108-117).

Filter studies cannot be used to accurately determine the dose delivered to the lungs as the respirable fraction of the drug dose delivered cannot be measured. However, filter studies have specific advantages over other techniques for determining total drug dose delivered to a patient: *In vitro* analysis of the drug deposited on a filter is more time- and labour efficient than the use of particle sizing. *Ex vivo*, filter studies allow for the measurement of the drug dose delivered to a patient without exposing the patient to medication, venepuncture or urine sampling (as in pharmacokinetic studies) and without exposing the subjects to radiation (as in nuclear scintigraphic studies). As mentioned, filter studies are an effective means of determining the total drug dose delivered to a patient.

1.5.6 Breathing simulation

1.5.6.1 Background

In vitro drug delivery by pMDI-spacer, when tested at a constant flow, is different from drug delivery where breathing is incorporated [65, 72]. *In vitro* measurements made at constant high flow rates may not reveal differences in performance that may be clinically significant, and may lead physicians to prescribe devices that under certain conditions may not deliver any drug to small children [113]. Before breathing simulation studies, much of the *in vitro* data available on drug delivery through spacers had been obtained using inhalation flows typical of single breath adult inhalations, and could not be extrapolated to children [72].

Breathing simulation for *in vitro* testing of inhalation drug delivery devices allows for a more accurate assessment of drug delivery through pMDI-spacers than traditional methods.

1.5.6.2   Previous breathing simulation studies investigating aerosol drug delivery using paediatric breathing patterns

Paediatric breathing simulation studies have increased our understanding of the effect of children's breathing on drug delivery through spacers. The contribution of pMDI-spacer related paediatric breathing simulation studies has up to now been greatest in demonstrating the following:

- The sensitivity of pMDI-spacers to changes in breathing patterns

- The critical importance of spacer design for drug delivery in children

- The importance and effect of tidal volume on drug delivery

- The dramatic effect of breathing patterns peculiar to young children on drug delivery

The following is a summary of the contribution made by breathing simulation studies to our understanding of drug delivery through pMDI-spacers to children:

Low inspiratory flow is required for optimal drug delivery through pMDI-spacers [69, 114]. Under low flow conditions, spacer output generally correlates with tidal volume [69], but not for some spacers (Nebuchamber) when the tidal volume exceeds 150ml [115]. Paediatric breathing simulation data have also demonstrated that at low tidal volumes, the high aerosol concentration in smaller holding chambers enhance drug delivery, while at high tidal volumes delivery is greatest from larger holding chambers [74]. This finding has been applied to clinical practice where small volume spacers are generally prescribed for infants and small children and large volume spacers are prescribed for older children and adults. Paediatric breathing simulation studies have further demonstrated that at low tidal volumes, some spacers do not deliver any drug at all [113]. The poor drug delivery at low tidal volumes by these spacers was mostly ascribed to large areas of dead space. In young children spacers with minimal dead space are therefore preferred. Paediatric breathing simulator studies have also demonstrated that spacer output does not necessarily correlate with respiratory rate [69]. However, in line with previous *in vivo* work [114], breathing simulation has demonstrated that lung dose decreases with increased inspiratory flow [69]. Using breathing simulation, Nikander at al (2007) demonstrated that crying reduces the dose that reaches the patient to 1% of the label dose [108] –certainly useful information for clinicians.

Breathing simulation studies have demonstrated that the rate of drug delivery via nebulizers is influenced by the configuration of the simulated breaths, e.g. peak inspiratory flow (PIF), tidal volume (Vt), frequency (f), inspiratory time (Ti) [116]. The shape of the simulated wave forms is more important in pMDIs than it is in nebulizers: With nebulizers, the use of sinusoidal waveforms resulted in similar drug delivery as when square wave forms were used [116]. Data from breathing simulation studies with nebulizers should, however, not be extrapolated to pMDI-spacers. Smaldone et al (2005) demonstrated that drug delivery from pMDI-spacers is more sensitive to changes in breathing pattern than drug delivery through jet nebulisers [117].

As mentioned before, there are significant differences in dose output from different combinations of pressurized metered dose inhalers and spacers [72, 113]. Breathing simulation has shown that, under certain conditions, estimated lung dose is pMDI dependant and spacer independent [69]. Certain spacers (Aerochamber® and Optichamber®) show less age and breathing pattern dependence on fine particle dose [72].

Although the studies described above have advanced our understanding of drug delivery through spacers, there are two important points to make about the breathing patterns used in these studies. Firstly, in all the above breathing simulation studies, breathing patterns were either ventilator produced (sinusoidal or square) wave forms, or simulations of actual recorded paediatric breathing patterns which were recorded on patients breathing through face masks. Both methods have shortcomings in that the breathing patterns used may not be truly representative of children's breathing patterns when the children are inhaling from the type of spacers being tested, as the ventilator produced breathing patters used were based on expected breathing parameters for children. The actual breathing patterns that were simulated were recorded from children wearing masks.

As pMDI-spacers are very sensitive to changes in breathing pattern [117, 118], it is essential that representative breathing patterns be used when breathing is simulated, in order to effectively evaluate the delivered medication dose. External factors like instrumentation can influence a patient's breathing pattern [119]. It would therefore follow that breathing patterns that are used for breathing simulation are representative of breathing patterns that are:

- Recorded in the patient population under investigation

- Recorded on patients while they are using the aerosol delivery device that is being evaluated

- Recorded with minimum interference between the patient and the aerosol inhalation device.

The second notable point about the studies described above is the variation in either the number of breaths simulated, or time of simulation, when pMDI-spacer output is tested i.e. five breaths, six breaths, 30 seconds. In Table 1 all published paediatric breathing simulation studies and the breathing patterns used, are summarised.

Author	Breathing pattern	Spacers & Drugs	Findings	Comments
Everard et al, 1992 [74]	Starling ventilator; Tidal volumes of 25, 50, and 150 ml/ 6 breaths Filter study	750ml Nebuhaler &Aerochamber …with masks Cromoglycate	At lowest tidal volume, high aerosol concentration in smaller chamber enhanced drug delivery. At highest tidal volume delivery greatest from larger chamber	Vt smaller than Vt measured in children breathing through mask [120].
Mitchell, 1997 [113]	Infant Star Vt = 50ml (RR=30/min) Vt = 100ml (RR=26/min) Vt = 200ml (RR=18/min) I/E = 40:60 5 inhalations	Aerochamber (145ml) Vent-170 (170ml) Space Chamber (250ml) salbutamol beclomethasone Face masks	At Vt = 50ml the Vent-170 and SpaceChamber did not deliver any drug	significant differences in dose output from different combinations of pMDIs and spacers
Berg, 1998 [65]	Harvard Animal Respirator 20 breaths/min Vt = 195 mL sinusoidal wave form I:E of 1:2. No. of breaths used not noted	metal Nebu-Chamber 250ml and AeroChamber135 mL with budesonide Babyhaler 350 mL (40 mL dead space) with fluticasone Detergent coated	significant differences in dose output from different combinations of pMDIs and spacers	constant flow higher doses than simulated breathing, less so for Nebuchamber
Finlay, 1998 [72]	Infant: Vt = 0.075L, Q= 4.8 LPM Toddler: Vt = 0.19L, Q= 8.2 LPM Child: Vt = 0.23L, Q = 11LPM Equal inh/exh flow rates 5 breaths	Aerochamber Optichamber Space Chamber E-Z spacer …with masks Beclomethasone & salbutamol	Different formulations behave differently in holding chambers. Aerochamber & Optichamber Showed less age/ breathing pattern dependence to fine particle dose	Vt used to represent infant breaths possibly too small
Barry, 1999 [115]	Pari Sinus Breathing Simulator Vt = 50,100,150,200,300ml RR = 20/min I:E = 40:60 5 simulated breathing cycles	Aerochamber(145ml) Nebuhaler(750ml) metal Nebuchamber(250ml) budesonide	Nebuchamber increases *in vitro* budesonide delivery but delivers a greater percentage of the drug in large particles	Drug delivery increase with increased Vt but not with Nebuchamber when Vt>150ml
Janssens, 2004 [69]	Sinusoidal patterns Vt = 25ml, 50ml, 100ml, 150ml, 200ml RR = 20-80/min 30 sec breathing	Nebuchamber plus budesonide Aerochamber and budesonide plus fluticasone Babyhaler plus fluticasone	Lung dose decrease with increased flow. Spacer output correlated with Vt but not with RR	Lung dose is pMDI dependant and spacer independent
Smaldone, 2005[117]	Breathing patterns recorded on children 30 seconds breathing Pattern 1: Vt = 207ml RR = 37.01/min Duty cycle = 0.41 Pattern 2: Vt = 75ml RR = 25/min Duty cycle = 0.40	Aerochamber Optichamber Nebulizers	Leaks around the facemask reduce drug delivery and for pMDI spacers can negate the beneficial effects of detergent coating.	pMDI-spacers more sensitive to changes in breathing pattern than jet nebulisers
Louca 2006 [63]	Sinusoidal patterns Vt = 155ml Inspiratory time = 0.8sec Total respiratory time = 2.4 sec 3 simulated breathing cycles	Aerochamber Max Optichamber ProChamber …all with face masks	Improved drug delivery with spacers made of charge dissipative materials	Only 3 inhalations per acuation of pMDI
Nikander, 2007 [108]	Human breathing patterns recorded –representative patterns simulated Crying 1year old breathing recorded & simulated Mean Vt = 134ml Duty cycle = 0.26	Aerochamber Plus Optichamber Nebulisers …all with face masks	facemask with a crying breathing pattern reduced the inhaled mass to 1% of the label dose	

Table 1. Previous breathing simulation studies using paediatric breathing waveforms to study drug delivery through spacers. Vt = tidal volume, Q = flow, RR = respiratory rate, I:E = inspiratory: expiratory ratio; pMDI = pressurised metered dose inhaler.

1.6 Patient related factors influencing drug delivery

The interaction between a patient and a drug delivery device is an important determinant of drug delivery. Patient-device interaction can be subdivided into two categories: Firstly, the patient's proficiency in using the device and secondly, the patient's adherence to prescribed medication. As this thesis focuses on preschool asthmatics, the patient's proficiency in using the delivery device will be discussed under the heading of "Spacer technique" with a discussion on adherence following shortly thereafter.

1.7 Spacer technique in preschool children with asthma

1.7.1 The importance of spacer technique

Inhaled asthma drugs should be delivered as effectively as possible to improve asthma control, reduce side effects and offer cost-effective therapy [121]. The method for using a pMDI and spacer is referred to as spacer technique or device compliance. The inability to use inhalers effectively has been shown to adversely affect drug delivery [114, 122, 123]. Poor spacer technique can even render inhalation drug delivery by pMDI totally ineffective, resulting in morbidity [124]. Studies have shown that in many asthmatic children, inhaler technique is too poor to result in reliable drug delivery [125, 126]. Even after instruction in correct inhaler use, incorrect inhaler use is common amongst asthmatic children [127, 128]. To add to the problem, correct inhalation technique deteriorates over time [129]. When using pMDI-spacers with young children and infants, cooperation during administration is the most important determinant of drug delivery [84].

Spacer use with a mouthpiece, as opposed to spacer use with a face mask, will be discussed because of its relevance to this study. The following steps have been shown to be important in using a pMDI and spacer: Firstly the pMDI should be shaken [130]. Shaking ensures mixing of the drug and the propellant inside the canister[131]. Shaking before each actuation may be less important for HFA propelled drug solutions. The next, simple step in pMDI-spacer use is to take the cap off the sleeve of the pMDI. Although taking off the cap seems intuitive, it is not always done. Thirdly, the pMDI needs to be inserted correctly into the spacer. The fourth step for correct pMDI-spacer use is to place the spacer into the

patient's mouth before actuation. Waiting between placing the spacer into a preschool child's mouth and actuating can cause unnecessary delay while a portion of the aerosolised drug will deposit onto the spacers inside wall by sedimentation [58, 132]. A pMDI should only be actuated once in between breaths as multiple actuations reduce drug delivery [58, 132]. Multiple actuations result in aggregation of aerosol particles, larger particle size and subsequently decreased lung delivery [133].

Vodoff and associates [127] found that in children under four years of age, the most common errors in using a pMDI were not shaking the device before use (48% of subjects) and taking two consecutive puffs (28% of subjects). The final step in using a spacer is to breathe through it. Breathing through a spacer is discussed in detail below.

1.7.2 Breathing through a spacer

A patient's breathing is an important determinant of spacer output: Various studies have demonstrated that spacer output and drug delivery to the lung are strongly related to breathing pattern [65, 69, 72, 74, 108, 113, 115, 117, 120, 134, 135]. When a patient inhales aerosolised medication, slow inhalation flow (below 60 litres per minute) results in increased lung deposition when compared with higher inhalation flow [136, 137]. Inhalation rates of 120 litres per minute and higher lead to greatly reduced lung dose and increased deposition of aerosol in the upper airways [138]. As mentioned before, during crying, drug deposition to the lungs is minimal [139, 140].

Two different methods are used to breathe through a spacer: Tidal breathing, and the single maximal breath technique, with or without breath hold.

1.7.2.1 Tidal breathing

Preschool children are instructed to breathe tidally through spacers. There is little evidence on the number of breaths required for optimal drug delivery through a spacer. Advice on the number of tidal breaths required for a preschool child to effectively inhale medication from a spacer is at present arbitrary, based on little evidence. Asthma guidelines worldwide fail to give specific instructions for preschool children on the correct method of breathing through a spacer [141-143].

Gleeson and Price (1988) demonstrated in older children with asthma, that five tidal breaths result in an improved bronchodilator response compared with two single maximal breaths, when inhaling terbutaline from a 750ml Nebuhaler [144, 145]. Pool, Greenough, Gleeson and Price (1988) then went on to examine the efficiency, in two to five year old asthmatic children, of five tidal breaths sufficient to operate the holding chamber valve [144]. Terbutaline delivered via a Nebuhaler using five breaths resulted in a significant improvement in lung function in most of the preschool children studied. The optimal number of breaths required for drug delivery was, however, not studied.

James et al (1999) compared, in children, the bronchodilator effect between tidal breathing and a single maximal breath, administering 200µg of salbutamol through a large volume spacer [146]. They demonstrated that the bronchodilator responses resulting from the two breathing techniques were comparable. However, the subjects' mean age was 10.9 years – significantly older than the preschool age group. In addition, only 21 subjects participated in this randomised cross-over study

Studies investigating spacer use in children have made use of a range of different breathing periods or number of tidal breaths, including 30 seconds of breathing [69, 117, 147], 60 seconds of breathing [120], five breaths [72, 113, 115] and six breaths [74].

When delivering multiple doses or regular doses of inhaled medication to preschool children, the practicality of using a 30 to 60 second period for breathing is questionable. Preschool children do not always cooperate with parents during medication administration [84, 148]. For parents, administering inhalation medication to young children can therefore be difficult at times. It can be postulated that if parents know that only a few breaths will deliver the medication they will be more motivated to adhere to treatment plans. It could therefore, potentially be beneficial to patients if the minimum number of breaths required for effective drug delivery through a pMDI-spacer combination could be defined.

1.7.2.2   The minimum number of breaths required for effective drug delivery through a pMDI-spacer combination

No study has ever specifically been designed to address the issue of the number of breaths needed for preschool children to empty a spacer. Everard et al (1992) used a Starling ventilator to investigate the influence of various design factors on the drug dose inhaled

from spacers at different tidal volumes [74]. As part of their study the authors derived a mathematical equation to predict the dose delivered by a spacer using different tidal volumes (respectively 25ml and 100ml) and different numbers of breaths. Analysis of data from the manuscript suggests that five to 12 breaths would be required for maximum drug delivery from a 150ml valved spacer, whereas 12 breaths would be required for maximal drug delivery from a 750ml valved spacer. However, Everard's study was not specifically designed to determine the number needed for preschool children to empty a spacer of aerosolised drug. Hence, various factors would prevent one from using the data to advise how preschool children should breathe through spacers. Synthetic waveforms were used in the study, with breath parameters that were based on the assumption that children's breathing through pMDI-spacers would not be different from normal tidal breathing. The authors also pointed out that they had made various assumptions with the derivation of the mathematical equation, "This model assumes a zero deadspace from valve to patient, a valve closing and opening efficiently, and complete mixing within the chamber once the valve is closed. It also assumes that taking a breath from the chamber does not affect the rate at which the aerosol settles out".

Berg et al (1998) simulated breathing with a Vt of 200 mL into a 350ml Babyhaler [65]: Although the spacer volume was less than double the Vt used, complete emptying of the spacers required approximately five to six breaths. It took 15 to 20 seconds to complete the five to six breaths, demonstrating that drug delivery via spacer is not necessarily complete when the Vt multiplied by the number of tidal breaths taken exceeds the spacer volume –a fact that was also indirectly illustrated in a study by Barry & O'Callaghan (1999), measuring drug deposited on a filter with breathing simulation studies using sinusoidal breathing patterns [115].

In a review article, Rubin and Fink (2005) stated that it takes three to five breaths for an infant to clear a holding chamber of 145ml [149]. Their calculations were based on a Vt of 7ml/kg for a one year old child with a weight of 10 kilograms. They were however, assuming that a child would breathe at normal tidal volumes when breathing through a spacer, and that a spacer would empty if the Vt multiplied by the number of tidal breaths taken exceeded the spacer volume.

1.7.2.3   Breath hold technique

Whether the single maximal breath technique can be appropriately used in preschool children using small volume spacers is not known. Breath hold appears to be beneficial for lung deposition in adults.   A study in adults with reversible airway obstruction demonstrated that when a β-stimulant is inhaled through a large volume spacer, a seven second breath hold causes a larger bronchodilator response than a four second breath hold [137]. Breath holding may have little benefit for drug delivery in children. With a dry powder inhaler (Turbuhaler) containing terbutaline 0.25mg, breath holding for ten seconds has no benefit over inhalation without breath hold on bronchodilation in children aged eight to 14 years [150].

The age at which a child can perform a single maximal breath with or without a breath hold has not been ascertained. There are no data available as to whether a single maximal breath would be superior to tidal breathing in delivering aerosolised treatment to preschool children using small volume spacers. The efficacy of tidal breathing compared with single maximal inhalation from spacers in preschool children is also unknown.

1.7.3   Interventional strategies to improve spacer technique and the Funhaler®

The concept of altering a child's breathing with incentives is not new. Various incentive devices have been used successfully in young children performing lung function tests [151].   Incentives used mostly include computer programs simulating, for example, blowing out candles or blowing up balloons to facilitate deep inhalation and exhalation. There is no literature on incentive devices being used to improve inhalation through drug delivery devices.

The Funhaler® (Figure 1)is a small volume valved spacer with a spinning disk and whistle on the expiratory arm [152, 153]. The function of the spinning disk and whistle combination is to act as an incentive for young children to cooperate when their inhaled asthma preventer medication is being administered. External factors like instrumentation can influence a patient's breathing pattern [119]. Therefore, use of the Funhaler® may potentially influence spacer technique in young children by influencing inspiration.   To isolate the spinning disk and whistle from the main inspiratory circuit by a valve, the toys

on the Funhaler® are located on the device's expiratory arm, and therefore only exhalation may be influenced. However, inspiration and expiration are interrelated, and therefore it is likely that the characteristics of inspiration (i.e. flow and volume) would be influenced by any factor that may influence the preceding exhalation.

If use of the Funhaler® does influence inhalation, then drug delivery will also be influenced. As discussed in the sections above, an increase in inhalation volume would be expected to correspond with an increase in drug delivery, whereas an increase in inspiratory flow could potentially correspond with an increase in drug depositing in the upper airways, thereby reducing drug delivery to the lungs.

Figure 1. The Funhaler®

1.7.4   Important questions about spacer technique in preschool children

In the sections above, the importance of correct spacer technique, focusing on the correct breathing technique through spacers was discussed. A patient's breathing characteristics through a spacer is one of the most important determinants of drug delivery through a spacer, and there are important questions that need to be answered with regard to the correct breathing technique for preschool children using spacers:

1.   How many tidal breaths are required for a preschool child to effectively inhale

medication from a spacer?

2.   From what age should large volume spacers be used?

3.   From what age is the single maximal breath technique feasible/ useful?

4.   Can the use of an incentive spacer improve drug delivery in preschool children by influencing breathing technique and if so, would it improve clinical outcome?

Questions one, two and three will be addressed in Chapters Three and Four of this thesis. Question four will be addressed in Chapter Five of this thesis.

As mentioned above, inhaled medication dose reaching a patient is dependent on drug formulation, delivery mechanism, the correct use of the delivery mechanism and adherence to prescribed treatment. The first three factors influencing the inhaled medication dose have been discussed. The following section will address adherence to prescribed treatment.

1.8   Adherence to prescribed treatment in preschool asthmatics

1.8.1   Overview

Preschool children are too young to assume any responsibility for adhering to a medication regimen. When preschool children's adherence is discussed in this chapter, it will refer to the behaviour of preschool children's parents/carers that determines whether their children are administered their medication as prescribed by their health care providers. The potential of the preschool child to influence its parents' behaviour will then be discussed.

Preschool children's adherence to prescribed asthma therapy is often sub-optimal The literature reports that preschool children's adherence to prescribed medication ranges from zero to 100% [154-161]. In Table 2, only electronically monitored adherence data are reported, as electronically monitored adherence data are far more accurate than adherence data obtained by other means (see section on adherence monitoring, below).

Author	Year	N	Age	Duration of monitoring	Outcome
Schoni el al[159].	1993	21*	2 months – 14 years	3 – 50 days	Mean adherence was 47.6%
Gibson et al[154].	1995	29	15 months – 5 years	2 months	Full adherence median of 50% of study days (range 0-94%), and 77% of prescribed doses.
Burgess et al[160].	2007	51	18 months – 7 years	1 month	Median adherence was 70.5% (21.4 – 100%)
Burgess et al[161].	2008	47	18 months – 7 years	3 months	Median adherence ranged from 46% - 74% for different groups over 1 month intervals
*children with respiratory illness (10 with diagnosis of asthma)					

Table 2. Published studies where adherence to prescribed inhaled medication was monitored electronically on preschool children.

Poor adherence to prescribed medication regimens leads to poor asthma control and increased hospital admissions for asthma [162, 163]. Poor adherence has been shown to be a major risk factor for near fatal asthma attacks in older children and adults [164].

Improved adherence has a positive effect on asthma control in older children [165]. More adherent asthmatic children and adults are significantly less likely to experience exacerbations than their less adherent counterparts [166]. Very little research has been done on the effect of adherence to medication in preschool asthmatic children.

1.8.2   Specific difficulties in the preschool age group

Preschool children are a unique group as they are totally dependent on their parents for the administration of their asthma treatment. Preschoolers have little insight into their disease or the need for asthma preventers and are notorious for refusing to take inhaled medication [148].

Until now, attempts to improve adherence in this age group (see below) have focused on the parents/ caregivers [167-172].

1.8.3 Barriers to adherence

Factors that prevent patients from being adherent to their prescribed medications are complex. Studies have shown [155] that barriers to adherence include prolonged and complex medication regimens, concerns about adverse effects and cost. Barriers to adherence that relate to the doctor include treatment by one different doctor after another, perceived clinician disinterest, and time constraints [155].

Demographic factors:

Low-income and minority patients report the following barriers to their own adherence to asthma medication: cost, difficulty in obtaining medication, daily life hassles, and a general distrust of the medical establishment [148]. Younger and less educated mothers are more likely to report a barrier to giving their children a required medication [173].

Family influences:

Family dysfunction, dysfunctional parenting and difficulties with time management have been shown to be important contributors to non-adherence [174-176]. A good daily routine has been shown to be a marker for better adherence [177].

Parent specific issues related to adherence:

In preschool children, adherence to prescribed medication is the responsibility of the parent. Parental non-adherence is not always intentional [178]. Parents may have doubts regarding the usefulness of medications [148], and when they misunderstand the role of inhaled steroids, adherence may be reduced [179]. The delayed onset of the action of inhaled asthma preventer medication may lead to its being perceived as ineffective. Asthma patients in general underestimate the severity of their condition and over-estimate how well their asthma is being controlled [180]. In children, both parents and doctors generally overestimate asthma control [181, 182]. Parents of children with asthma may

believe that their children's asthma is under good control and not severe enough to require daily treatment despite high asthma-related morbidity [148, 175, 181].

Parents may have concerns about drug safety and cost [148, 183-185]. Children from low-income families are less likely to adhere to prescribed treatment than children from higher-income families [186].

More specifically for the preschool child: Adherence has been shown to be inversely related to age [187]. Use of day care facilities is also associated with poorer adherence [154].

Child behaviour:

Parent-child conflict over taking medication has been shown to reduce adherence [148]. Asthmatic children are at high risk of behavioural problems that may indirectly contribute to increased asthma morbidity [176]. Behavioural problems in older asthmatic children are related to the severity of their asthma [188]. The earlier in life that there is an onset of asthma, the more risk there is that behavioural problems will increase[189]. A child's behaviour may directly influence its parents' willingness to administer asthma medications, and their effectiveness in doing so, as described below.

Parent-child interaction:

Parents of asthmatic children are regularly confronted with potentially difficult interactions with their child during medication administration [190]. The administering of medication may at times be fraught with child upset, crying and conflict [176]. Under such circumstances parents may, due to low levels of self confidence [176], retreat and give in to their child's wishes in the hope of avoiding conflict and upset [190]. By giving in to the child's wishes the parents may inadvertently give their child positive feedback for inappropriate behaviour, thereby exacerbating negative cycles of parent-child interaction [191].

1.8.4 Interventional strategies to improve adherence to inhalation therapy in preschool children

Research suggests that team-based management strategies and cohesive family climate promote adherence to prescribed medication [192]. Medication routines are related to medical adherence [177].

Complex dosing regimens have been shown to reduce patients' adherence [193]. Simplified dosing regimens (e.g., once-daily administration) would therefore be expected to improve asthma adherence [194]. However, asthma preventer dosing generally does not exceed twice a day in dosing frequency. In a study investigating dosing regimens and adherence in preschool children with asthma [154], no relation was found between frequency of prescribed regimen and good adherence. This study was an observational study limited by low patient numbers (n = 35) and the results should therefore be interpreted with caution.

Frequent reinforcement of the educational message to the parent/ caregiver will often improve adherence [169]. In the present technological age, computerized resources and programmes are being used in an attempt to improve adherence with promising results [172, 195]. These interventions are, however, expensive, resource intensive and require technical expertise.

Improved adherence	No impact on adherence
-Team-based management strategies	-Simplified dosing regimens
-Cohesive family climate	-Knowing the importance of inhaler (children)
-Medication routines	
-Frequent reinforcement of the educational message to the parent	
-Computerized resources and programmes	

Table 3. Summary from literature of factors associated with adherence to prescribed medication

Table 3 summarises factors and interventions from the literature associated with adherence to prescribed treatment in preschool children. As mentioned by Sherman et al (2001), improved outcomes are generally only seen with resource intensive intervention, and not with less aggressive measures [170].

1.8.5 Potential use of an incentive device –the Funhaler®- for improving adherence to prescribed aerosol treatment in preschool children.

As discussed above, adherence to asthma preventer therapy is important for asthma control in adults and older children. There is some evidence suggesting a dose dependent effect of inhaled steroids on preschool asthma [37]. Therefore, as improvement in adherence increases the cumulative drug dose delivered over time, improved adherence may well lead to an improved clinical outcome in preschool children.

Overall, adherence to asthma preventer therapy in children is poor. The few strategies that have been shown to have some beneficial effect on patients' adherence to prescribed treatment require considerable resources but have only modest effect. Improved outcomes are only seen with the most aggressive measures [170]. However, strategies to improve adherence to asthma therapy in children have up to now mostly focused on the parents,

with little attention being paid to the patient. Although medication is administered by the parent in this age group, the importance of parent-child interaction in influencing parental behaviour should not be under-estimated.

As oppositional behaviour of preschool children during aerosol drug administration is known to adversely affect adherence to prescribed medication, strategies to improve child behaviour around the drug delivery process may potentially improve parental adherence to their child's prescribed medication.

As mentioned in the section about spacer technique, the Funhaler® is a small volume valved spacer with a spinning disk and whistle on the expiratory arm [152, 153]. The function of the spinning disk and whistle combination is to act as an incentive for young children to cooperate when their inhaled asthma preventer medication is being administered. In a pilot study [153], parents reported subjectively improved co-operation from their children during drug administration when compared with co-operation using their previous spacer. Parents randomised to the Funhaler-group also displayed a more positive attitude towards medicating their children. The pilot study was, however, small (n = 30) and only spanned a two week period. A more recent study [160] investigated adherence to prescribed asthma treatment, over a three month period, in children aged 18 months to seven years. Subjects were randomised to using either the Funhaler®, or a conventional spacer, the Aerochamber Plus®, for administering their asthma medication. Although adherence was higher in the Funhaler-group, the difference in adherence between the Funhaler-group and the Aerochamber-group was not statistically significant. Again, this study was small (n = 47) and had may have been underpowered.

The dual concepts of focusing on the child instead of the parent, and using an incentive device to improve adherence to prescribed asthma treatment in preschool children, therefore merit further investigation.

1.8.6 Important questions regarding adherence to prescribed medication in preschool children

Following the above, questions that arise are:

- Does adherence to therapy correlate with improved asthma control in preschool children, as it does in older children and adults?
- Can adherence to prescribed treatment in preschool children with asthma be influenced by interventional strategies that focus on the child?

….and more specifically…..

- Would an easy to use incentive device that focuses on the patient and not the parent have a beneficial effect on adherence to prescribed treatment in preschool children with asthma?

1.8.7 Assessment of adherence to prescribed treatment in asthma

Various techniques for the measurement of patients' adherence to prescribed treatment have been used. Methods for measuring adherence described in the literature include: patient self report, clinical judgement by the health care provider, monitoring of remaining medication, pharmacy records, electronic monitoring of the medication device and biochemical measures [83, 157, 196]. These techniques vary substantially in accuracy. Direct measures of patient behaviour, such as electronic monitoring, are more accurate than indirect measures such as patient diaries, self-report, or clinician's judgement [157, 163, 196-198].

The literature reports the use of different devices for the monitoring of inhalation medication by pMDI: The Smartmist®, the MDI Chronolog®, the MDILog® which evolved from the MDI Chronolog®, the Doser CT® and the Smartinhaler® [160, 175, 197, 199-202]. The Smartmist® is a bulky device that encases the pMDI [202]. The Doser CT® is a pressure activated device that connects to the top of a pMDI canister [203]. The Doser CT® only records the number of daily uses over a period of 45 days [203]. The MDI Chronolog® is a microprocessor device built into the sleeve of a pMDI; when it is activated by pMDI actuation, it records the date and time of the actuation [163, 199]. A limitation of these electronic monitoring devices in research is that the researcher is unable to distinguish whether the patient actually received the dose or whether the device was fired into the air (dumping) [83]. The MDILog®, currently the most widely used monitoring device for inhaled asthma medication, addresses this problem by not only monitoring actuation but also components of spacer technique (shaking of the canister, inhaling medication, inhalation timing) [175]. The Smartinhaler® is a relatively new device that

replaces the pMDI actuator/sleeve [161]. The Smartinhaler® contains a microchip that records the time and the date of each actuation.

A limitation of using electronic adherence monitoring devices is common to measuring devices in general: use of a measuring device potentially interferes with the patient's medication habits.

1.9   Assessment of asthma control in preschool children

When investigating the influence of an intervention on asthma control, the perfect outcome variable would be an accurate representation of asthma control. The outcome variable should preferably have no relation to diseases that may mimic asthma. Furthermore, the outcome variable should be reproducible and reliable.

1.9.1   Asthma symptoms

Asthma symptoms can be measured by self-report or by diary card. Researchers have used symptom scores in clinical trials as a measure of both frequency and intensity of respiratory symptoms [204, 205]. Recording the number of days without symptoms may be a more robust measure of asthma control, as recording the number of days without symptoms may lend itself to less subjectivity than the recording of symptom intensity. Asthma symptoms often reported include wheeze, cough and shortness-of-breath [206-208]. To avoid using three different outcome variables some studies make use of the variable "symptom free days" to report the number of days over a period of time without any of the above symptoms [207, 208]. As wheezing is the most common asthma symptom, the use of "days without wheeze" may have advantages over using "symptom free days", as the term "symptom free days" is less specific than the term "days without wheeze" and could more easily be misinterpreted by patients and parents. An alternative method of quantifying asthma symptoms is to keep track of the frequency of a patient's asthma reliever use (bronchodilator use/ rescue medication) [209].

A major disadvantage of using self report or diary cards to measure asthma control is that both rely on the patient's interpretation of symptoms and on the patient's diligence in keeping a record of symptoms.

1.9.2　　　　　　　　Asthma exacerbations and systemic corticosteroid use

Asthma exacerbations can be defined as a worsening of a patient's asthma symptoms that requires either a change in medication (other than bronchodilator use) and/or requires visits to a general practitioner [37], or hospital emergency department. The frequency of asthma exacerbations may be measured as a marker of asthma control. Asthma exacerbations can be measured by self-report, or hospital records if the exacerbations were severe enough to lead to hospital admissions or Emergency Department visits. Asthma exacerbations are treated with systemic steroids and therefore the number of days or the number of times that the patient was prescribed systemic steroids could be used as a marker of asthma control.

1.9.3　　　　　　　　Lung function measurements

The measurement of lung function has been used for many years as an objective indicator of the severity of pulmonary disease. Most lung function studies performed in adults require patient cooperation. As preschool children have limited coordination skills and limited concentration spans, various techniques for measuring lung function have had to be adapted for use in preschool children. The most common lung function tests used in adults for monitoring asthma control are spirometry and peak expiratory flow.

1.9.3.1　　　　　　　Peak expiratory flow

Peak expiratory flow (PEF) is used in adults as a marker of airway obstruction, however PEF is of little value in preschool children [210, 211]. Regular monitoring of PEF does not provide additional benefit to daily recording of asthma symptoms and bronchodilator use [212]. Data recorded by patients and parents on PEF diaries are unreliable [210]. In children, changes in PEF correlate poorly with more accurate measures of lung function [213].

1.9.3.2　　　　　　　Forced expiratory flow

The use of spirometry in preschool children is at this stage limited to specialised research centres. In order to make spirometry feasible in preschool children, specially adapted quality control criteria are required [214, 215], and outcome variables different from the

outcome variables used in adults need to be used [216, 217]; for example, $FEV_{0.5}$ and $FEV_{0.75}$ are used instead of FEV_1. The use of spirometry in preschool children requires highly skilled technicians and the help of incentive devices. In spite of the spirometry on preschool children being performed at highly specialised research laboratories, fewer than 80% of three to five year olds are able to perform acceptable spirometry [218]. Spirometric techniques that require sedation e.g. the tidal rapid compression technique [219, 220] and the raised volume rapid thoraco-abdominal compression technique [221] are useful in infants, but not practical to perform on preschool children.

1.9.3.3   Plethysmography

Plethysmographic measurements of airway resistance are being used in preschool children to measure baseline lung function and bronchial responsiveness [222-224]. Specific resistance, a function of airway resistance and lung volumes, can be calculated by measuring changes in air flow relative to changes in plethysmographic volume during spontaneous breathing (i.e. breathing against a closed shutter not required). Data collection and quality control for plethysmographic measurements of airway resistance have not yet been standardised for use in preschool children.

1.9.3.4   The interrupter technique

The interrupter technique is another method that can be used for measuring airway resistance in preschool children. The interrupter technique is based on the assumption that pressures equalise rapidly throughout the airways during periods of no airflow. When the airway is occluded briefly, pressure at a patient's mouth will therefore reflect alveolar pressure. Interrupter resistance (Rint) is calculated by dividing the change in mouth pressure after occlusion of the airway, by airflow immediately prior to the occlusion. The interrupter technique requires minimal cooperation and is suitable for use in preschool children [225, 226]. Reversible airway obstruction in wheezy preschool children has been measured successfully using the interrupter technique [227, 228]. In spite of several problems with regard to the assumption on which the interrupter technique is based [229], the use of Rint shows promise as a method of measuring lung function in preschool children. However, methods for performing the measurement and for reporting the technique need to be standardised [225, 229].

1.9.3.5 Exhaled nitric Oxide

Nitric oxide (NO) is produced by the airway epithelium when L-arginine is converted to L-citrulline by the enzyme NO synthase [230]. Activity of the calcium independent form of nitric oxide synthetase is inducible by certain inflammatory markers. When detected in exhaled air, NO is a marker of airway inflammation [231]. Exhaled nitric oxide (eNO) can be measured by an in-line method, where the exhaled gas is analysed in real time, or by an off-line method, where the exhaled gas is collected and analysed later. Guidelines and standards for measuring eNO have been published [232]. For preschool children a tidal breathing technique has been developed that can be used for both the in-line and the off-line method [233, 234].

Exhaled NO is raised in asthmatics and in wheezy infants but also in various other respiratory conditions [233-239]. Cystic fibrosis is associated with reduced eNO levels and primary ciliary dyskinesia is associated with an almost complete absence of eNO [240, 241]. Exhaled NO levels drop in asthmatics and in wheezy infants when inhaled steroids are used [242].

In spite of extensive research done on eNO over many years, evidence that eNO can be used as a marker for asthma control is as yet inconclusive and unconvincing [243]. Hence, it is unlikely that eNO has a useful role in the regular monitoring of asthma control.

1.9.3.6 Forced oscillation testing

The forced oscillation technique (FOT) for measuring lung function requires only passive cooperation and no coordination, and is therefore suitable to perform on preschool children [222, 244, 245]. The FOT that is most commonly used in the preschool age group is performed as follows: Single or multiple frequency oscillations are applied at a patient's mouth using a speaker. The resulting air flow is measured at the patient's mouth. Respiratory system impedance (Zrs) is calculated using pressure and the resulting flow variables. Respiratory system resistance (Rrs) and reactance (Xrs) can be obtained as a function of frequency. Rrs comprises the pressure-flow relationship of the portion of the pressure oscillation that is 'in phase' with airflow. Xrs is related to the portion of pressure oscillation that is 'out of phase' with air flow. Xrs is related to the elastic forces of the respiratory system, and to inertial forces arising from the acceleration of tissue and gas in

the respiratory system [246]. Both baseline lung function and bronchodilator response are measured.

Diagnostic value of FOT:

Studies investigating the capacity of FOT to discriminate between healthy and asthmatic preschool aged children have had conflicting results [247-250]. Reasons for the conflicting results in these studies may be related to differences in the study populations, differences in methodology or differences in the interpretation of results (Table 4). For example, in studies where subjects where classified as asthmatic or healthy by questionnaires [248, 249], or by doctors in the community [250], the FOT did not discriminate between the healthy and the asthmatic subjects. In the only study where asthma was diagnosed in a specialist clinic [247], the baseline and change after bronchodilator in Rrs5 was significantly larger, and the Xrs5 significantly smaller, in the asthmatic group when compared with the healthy controls.

FOT as a measure of asthma control:

Nielsen et al (2000) showed that young asthmatic children's baseline Rrs5 (Rrs at 5 Hz) and Xrs5 (Xrs at 5 Hz) improved with inhaled steroids [224]. The use of inhaled steroids also reduced the bronchodilator response at Rrs5 and Xrs5 in young children [224].

Study	Subjects	Asthma diagnosis	Significant bronchodilator response	Difference between healthy and asthmatic	Comments
Hellinckx et al 1998 [248]	3 - 6.5 year old Belgian kindergarten children	Asthma diagnosed by questionnaire	30% decrease in Rrs10 40% decrease in Rrs5	No difference in baseline values or BDR between healthy and asthmatic	200μg salbutamol by spacer 20 min interval
Nielsen et al 2000 [224]	2.3 - 5.9 year old children	Asthma patients from teaching hospital's outpatient clinic	29% decrease in Rrs5	Baseline Rrs5 and Xrs significantly different between healthy and asthmatic children. BDR for Rrs5 but not Xrs5 significantly different between asthmatic versus healthy children.	500μg salbutamol via metal spacer 20min interval Also significant response to placebo → ? need for blinding
Marotta et al 2003 [249]	4 year old children at risk of asthma	Asthma diagnosed by questionnaire	15-20% decrease in Rrs10 20-25% decrease in Rrs5 To distinguish most asthmatics from non-asthmatics (in atopic subjects)	No difference in baseline BUT significant difference in BDR for Rrs5 and Rrs10	2.5mg albuterol nebulised 15 min interval
Thamrin et al 2007 [250]	2 - 6 year old	Diagnosed by general practitioners in the community	40% decrease in Rrs 65% increase in Xrs Rrs8 and Xrs8 most reliable	No difference in baseline values or BDR between healthy and asthmatic	600μg salbutamol via spacer 15min interval

Table 4. Previous studies comparing forced oscillation lung function in asthmatics versus healthy preschoolers. Rrs5 = resistance at five hertz; BDR = bronchodilator response; Xrs10 = reactance at ten hertz.

A recent study demonstrated that bronchodilator response measured by FOT is strongly influenced by baseline lung function. A 40% fall in Rrs or a 65% increase in Xrs appears to be indicative of a significant bronchodilator response (based on limits of agreement, taken from 95th percentiles in healthy children). The clinical significance of bronchodilator response measured by FOT has yet to be established.

Reference values for FOT in preschool children have been well documented [251]. Current best evidence suggests that, in preschool children, the most reliable indicators of lung function measured by FOT are resistance and reactance at eight hertz (Rrs8 and Xrs8) [251].

1.9.4   Quality of life measurements

Clinical indices only weakly correlate with how a chronically ill child functions in everyday activities [252]. The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease" [253]. In an attempt to address social and mental wellbeing as part of the burden of disease, the concept of Health Related Quality of Life (HRQoL) was developed. Quality of life is a distinct component of asthma health status [254].

Several generic measures of QoL have been developed for use in preschool children [255-258]. The PedsQL, developed by Dr James Varni [259, 260], has been validated as a reliable and responsive measure of health related quality of life in children. Advantages of the PedsQL include brevity, availability of age appropriate versions and parallel forms for child and parent [261]. A disease specific version of the PedsQL has been validated for asthma [259]. The PedsQL3.0 Asthma Module® was designed to measure paediatric asthma-specific health related quality of life. The PedsQL has specific questionnaires for 2-4 year old children and for 5-7 year old children.

A weakness in using QoL questionnaires in children includes low reliability of responses to the questionnaires [262]. Most preschool children will not be able to answer a QoL questionnaire and a proxy is therefore needed. Parents, who usually act as proxy for their preschool children, may not accurately perceive their child's quality of life [263, 264]. However, there is agreement between parents' and children's perception of QoL. Parent and child perceptions of QoL agree more for observable functioning (e.g. physical HRQoL) than for non-observable functioning (e.g. emotional and social HRQoL) [265]. Proxy and self-report correlation is higher for children with health problems than for healthy children [261].

1.9.5   Conclusions

All currently available measures of asthma control have unique strengths and weaknesses.

Diary cards measure asthma symptoms. Wheezing is the most common asthma symptom, and the use in diary cards of "days without wheeze" may have advantages over using other measures of asthma symptoms. Diary cards may potentially influence a study participants' behaviour or adherence to prescribed medication. The use of self report or diary cards to measure asthma control could be subjective, and diary card accuracy also depends on a patient or caregiver's diligence. However, diary cards are widely used in clinical trials as the filling in of diary cards depends less on parental recall than history taking at study visits would.

Asthma exacerbations are an important negative outcome measure of asthma control. However, when the frequency or duration of an asthma exacerbation is used as a measure of asthma control, the definition of an asthma exacerbation has to be accurately and well defined. Systemic corticosteroid use is at best an indirect marker of asthma exacerbations.

Lung function testing in preschool children could be used as an objective, albeit indirect marker of asthma control. In preschool children, many different lung function tests are available, but the precise role of each technique has not yet been determined. The FOT for measuring lung function requires only passive cooperation and no coordination, and is therefore suitable to perform on preschool children [222, 244, 245]. Reference values for FOT in preschool children have been well documented [251]. Current best evidence suggests that, in preschool children, the most reliable indicators of lung function measured by FOT are resistance and reactance at eight hertz (Rrs8 and Xrs8). A disadvantage of FOT is that it can only be performed in the laboratory.

QoL evaluation has the potential for measuring the effect of asthma on a patient's general wellbeing, but in the preschool child the accuracy of measurement may be compromised by the need for a proxy to fill out the questionnaires on behalf of the child. The PedsQL has been validated as a reliable and responsive measure of health related quality of life in children. A disease specific version of the PedsQL has been validated for asthma. A major advantage of the PedsQL, when used in a clinical trial, is its brevity.

As all current measures of asthma control have unique strengths and weaknesses, the use of multiple different measures (if resources allow) would improve the sensitivity and specificity in a clinical trial assessing the level of asthma control as an outcome measure in a given study population. Care should also be given to selecting asthma control assessments that match the objectives of the planned study.

2 CHAPTER TWO: Designing and validating a novel method for effectively recording and simulating breathing in patients using pMDI-spacers

2.1 Background

This chapter describes using a flow chamber for accurately recording patients' breathing while they inhale from a pMDI-spacer.

There are a number of studies where breath traces recorded *ex vivo* are utilized for the simulated estimation of drug delivery [108, 117, 267]. However, recording of *ex vivo* breathing traces for simulation generally involve an alteration to the patient-device interface. This chapter describes a method of assessing the influence of breathing on drug delivery by pMDI-spacers, which allows for the recording of breathing patterns while subjects are using the inhalation device tested, without addition of a measuring device, adaptor or filter to the patient-delivery device interface. In previous breathing simulation studies where recorded human breathing patterns were simulated, breathing patterns were either recorded separately (i.e. while subjects were not inhaling through the device being tested [108, 117], or pneumotachometers and/or filters were inserted between the subjects and the delivery device when breathing was recorded [267]. The methodology described in this chapter was designed to accurately record and simulate breathing of patients when they inhale medication/placebo from spacers. The methodology served two purposes: (1) we were able to record both inspiration and expiration using a single pneumotachometer, and (2) we eliminated the increase in dead space and resistance that would have inevitably occurred if both a filter and a pneumotachograph were placed between the spacer and the subject. Hence, the methodology allowed for breathing recording without changing the physical interface between the spacer and the subject.

The rationale for developing the above methodology was that subjects' breathing could potentially be significantly influenced by the medication delivery process, and metered (or

bolus) drug delivery via pMDI-spacer could potentially be very sensitive to small changes in breathing pattern (in contrast to continuous drug delivery via nebuliser).

The methodology validated in this chapter was used in the following chapter to determine the number of tidal breaths required to effectively inhale medication from different types of spacer devices, and to determine the efficacy of a single maximal inhalation for drug delivery in preschool children.

2.2   Methods

Study design

Materials and Methods:

Initially, tidal breathing traces were recorded from healthy adult subjects through a range of pMDI-spacers placed within a sealed flow chamber. *Ex vivo* drug delivery was measured simultaneously by placing an inspiratory filter between the spacer mouthpiece and the patient's mouth.

In vitro drug delivery measurements using salbutamol (Ventolin, GlaxoSmithKline, Melbourne, Australia) were then carried out using a flow-volume simulator (Series 1120, Hans Rudolph, Kansa, USA) to replicate the *ex vivo* traces. A paired comparison of *ex vivo/ in vitro* drug delivery was then performed in order to compare the accuracy of the drug delivery measurements obtained from the flow volume simulator.

Three configurations were used (described below, p.67) for the *ex vivo* recording and *in vitro* simulation, in order to validate different aspects of the flow chamber recording/simulation method for drug delivery estimation.

<u>Recording of *ex vivo* breathing traces</u>

Tidal breathing traces (configuration 1: n=43; configuration 2: n=14; configuration 3: n=12) through different spacers were recorded from two healthy, non-smoking adult male subjects, aged 25 and 28 years. Subjects were "coached" in order to obtain a series of traces over a wide range of inspiratory flows and volumes (Tables 5 and 6). Subjects were

asked to take five slow breaths through the spacer after each actuation of the pMDI. After each filter study, subjects were asked to increase or decrease their inhalation volumes, until a large range of filter doses (see below) were obtained. As the aim of this study was to test the accuracy of the flow volume simulator in estimating *ex vivo* drug delivery over a wide range of breathing patterns, "coaching" the subjects was necessary in order to obtain a large range of breathing patterns. Ethics approval was obtained from the ethics committee of Princess Margaret Hospital for Children, and the Telethon Institute for Child Health Research (1026/EP), and from the ethics committee of the University of the Free State (ETOVS 67/07).

Spacer	Mean inhalation volume in ml (SD)	Mean peak inspiratory flow in LPM (SD)	Spacer	Mean inhalation volume in ml (SD)	Mean peak inspiratory flow in LPM (SD)
Aerochamber Plus	47 (14)	7 (2)	Volumatic	48 (26)	6 (3)
	65 (29)	10 (4)		56 (32)	7 (4)
	68 (11)	9 (4)		82 (24)	10 (2)
	70 (42)	8 (4)		98 (9)	9 (1)
	159 (37)	19 (4)		126 (20)	10 (2)
	159 (49)	15 (6)		217 (37)	15 (2)
	162 (62)	24 (8)		276 (44)	24 (2)
	235 (64)	22 (5)		322 (66)	20 (3)
Funhaler	24 (5)	3 (1)		423 (68)	33 (5)
	61 (29)	7 (3)		438 (59)	25 (2)
	78 (30)	8 (2)		499 (38)	32 (9)
	97 (25)	9 (2)		572 (87)	30 (19)
	374 (112)	22 (4)		593 (96)	34 (5)
	410 (127)	22 (5)		673 (155)	40 (6)
	535 (118)	28 (7)		758 (83)	39 (5)
	548 (104)	33 (5)		952 (147)	43 (6)
Modified soft drink bottle	40 (13)	6 (2)		985 (163)	55 (3)
	48 (20)	6 (2)			
	56 (30)	7 (3)			
	137 (29)	11 (2)			
	254 (114)	22 (8)			
	404 (87)	28 (5)			
	428 (47)	30 (4)			
	512 (173)	31 (9)			
	587 (70)	34 (3)			
	762 (105)	48 (4)			

Table 5. Average inhalation volumes and average peak inspiratory flows for each set of five breathing patterns recorded and simulated in Configuration One.

Recording Nr	Mean inhalation volume in ml (SD)	Mean peak inspiratory flow in LPM (SD)
1	24 (16)	7 (3)
2	38 (18)	16 (7)
3	39 (15)	12 (5)
4	91 (48)	18 (8)
5	93 (35)	20 (8)
6	121 (38)	13 (5)
7	222 (39)	34 (5)
8	241 (77)	39 (10)
9	243 (96)	20 (6)
10	337 (160)	27 (12)
*11	751 (150)	47 (11)
12	857 (174)	52 (8)
13	880 (320)	34 (11)
*14	1237 (287)	69 (18)

Table 6. Average inhalation volumes and average peak inspiratory flows for each set of five breathing patterns recorded and simulated in Configuration Two and Three. *recordings 11 and 14 only simulated in Configuration Two.

In order to record the *ex vivo* breathing traces, the spacers were placed in transparent Perspex flow chambers, custom-built to hold each respective spacer with an attached pMDI (Figure 2). Each flow chamber was constructed to completely enclose the spacer, apart from the mouthpiece, within a minimum volume (Table 7).
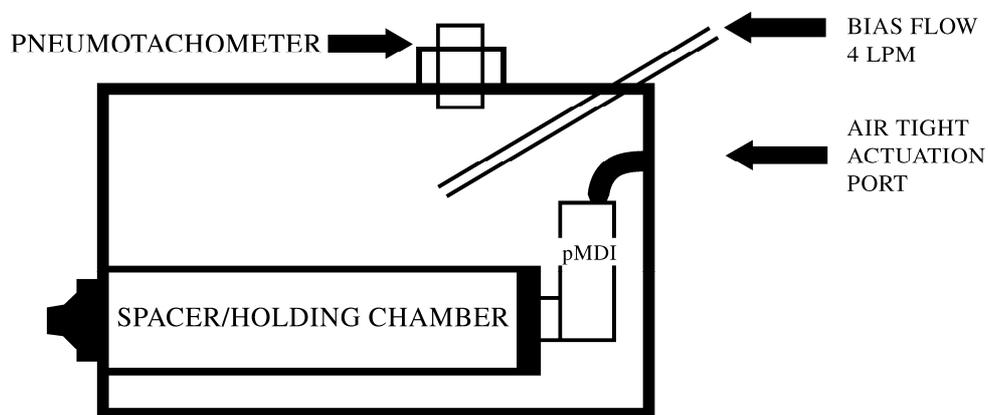
Figure 2. Flow chamber used to record breathing.

	Aerochamber Plus	Funhaler	Volumatic	Modified soft drink bottle
Length (cm)	19	23.5	28	25.5
Height (cm)	15	18	17	14.5
Width (cm)	7	8	12	8.5

Table 7. Dimensions of flow chambers used to record breathing using different spacer devices.

Five sides of the flow chamber were constructed to form an airtight seal. The sixth side could be removed in order to place a clean pMDI and spacer inside but was sealed in place while each experiment was conducted. A special fitting on the floor of the chamber held the back of the spacer and the pMDI sleeve in position. The mouthpiece of the spacer protruded through an opening in the front of the flow chamber, while the exhalation valve(s) were contained within the chamber. The interface between the front part of the spacer and the flow chamber was sealed with high viscosity putty. A rubber washer served to maintain the seal when certain spacers were used.

After inserting the spacer and pMDI, the 'door' (or back wall) of the flow chamber was secured with four elastic clips that were mounted on the back of the door. The elastic clips were secured over four corresponding mounts on the lateral walls of the flow chamber.

The pMDI was actuated by hand via an air tight rubber actuation port at the back of the air tight flow chamber. The flow chamber was air tight except for an opening in the roof (2.5cm in diameter) and an opening on the side (0.5cm in diameter). The opening in the side of the flow chamber was connected to tubing to allow a bias flow of medical air. The bias flow was introduced in order to prevent carbon dioxide build-up from exhaled air in the flow chamber. As the bias flow of medical air was constant, all the air inhaled and exhaled through the spacer passed through the pneumotachometer which was positioned at the top of the flow chamber (Figure 2).

Airflow was recorded with a 0-100 LPM pneumotachometer (Model RRS 100-HR, Hans Rudolph, Kansas, USA) which records flow at 50Hz. Inhalation volumes for each breath of the recorded breathing patterns (RSS files) were calculated by integration of the digital flow signal (i.e. calculating the area under the curve of the flow-time trace).

Configuration of the pneumotachometer and/ or flow chamber

Three different configurations were used. For each configuration, drug "inhaled" from a specific spacer was captured on a filter (Uni-filter Junior, GE Healthcare, Waukesha, USA) with a dead space of 20ml that was interposed between the spacer and either the human subject (*ex vivo*), or the flow volume simulator (in vitro). The configurations differed in the positioning of the pneumotachometer and filter, or whether the flow chamber was used when breathing was recorded or simulated. Filters were used for validation purposes only.

Configuration One:

This configuration was used to validate the accuracy of the breathing simulator, by comparing *ex vivo* to *in vitro* drug dose delivered to filter (Figure 3). Breathing was recorded by a pneumotachometer that was placed directly between a human subject and a pMDI-spacer combination. An additional filter was placed between the human subject and the pneumotachometer for infection control purposes. Breathing was simulated in an identical set-up, where the human subject was substituted by a breathing simulator. Filter studies were carried out with four different spacers: the 149ml Aerochamber Plus® (Trudell, London, Canada) (valved), the 225ml Funhaler® (Visiomed, Perth, Australia) (valved), the 750ml Volumatic® (GlaxoSmithKline, Melbourne, Australia) (valved) and a modified 500ml plastic soft-drink bottle (unvalved). The characteristics of the breathing patterns recorded and simulated in this configuration are described in table 5. Inhalation

volumes tested ranged from 26 to 1030ml. The peak inspiratory flow of the breathing patterns ranged from 2.9 to 57.1 LPM.
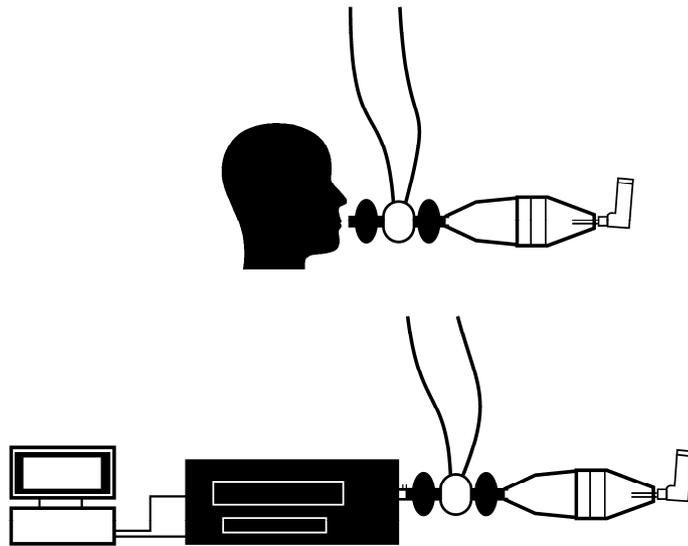
Figure 3. Configuration 1.

HUMAN SUBJECT

FILTER

PNEUMOTACHOMETER

SPACER / VALVED HOLDING CHAMBER &pMDI

FLOW-VOLUME SIMULATOR
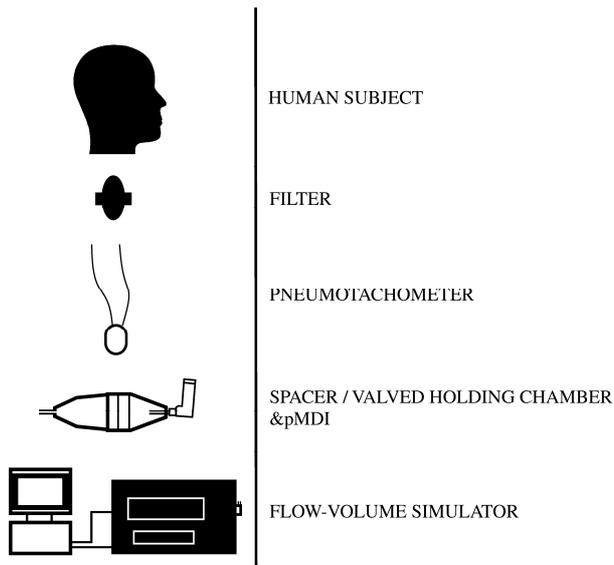
Legend. Figures 3 to 5.

<u>*Configuration Two:*</u>

This specific equipment configuration (Figure 4) was used to focus on the accuracy of the flow-chamber as a measuring instrument by comparing *ex vivo* to *in vitro* drug dose delivered to filter.   The flow-chamber was used to record breathing where the human subject was breathing through the spacer (Aerochamber Plus®).   An identical set-up was used when the breathing simulator was used to replace the human subject.   The characteristics of the recorded *ex vivo* breathing patterns are presented in Table 6.
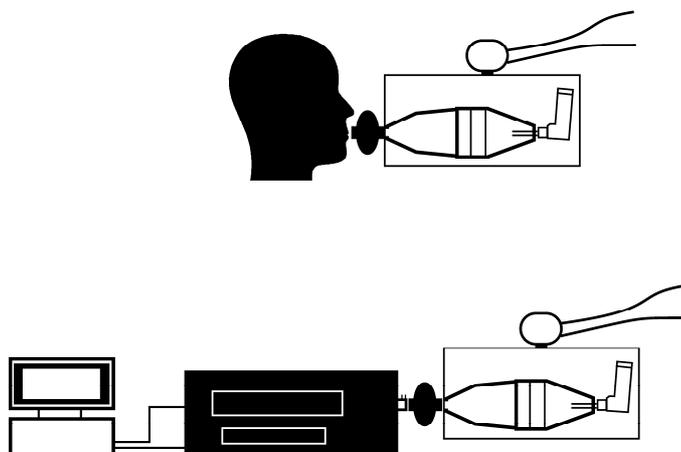
Figure 4. Configuration 2.

This configuration (Figure 5) was used in order to validate the equipment set-up for use in Chapter Three. As for the previous configurations *ex vivo* drug dose was compared to *in vitro* drug dose delivered to filter. A flow chamber was used to record breathing in the human subject, but was not used during simulation. The Aerochamber Plus® was used in this configuration. The characteristics of the recorded *ex vivo* breathing patterns are presented in Table 6.
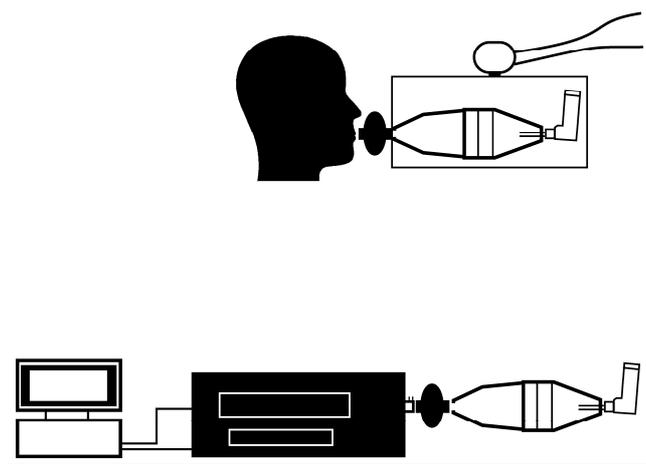
Figure 5. Configuration 3.

In vitro replication of breathing traces

The recorded breathing patterns were stored in RSS file format. The RSS-files were transferred to a flow-volume simulator by custom Hans Rudolph (Hans Rudolph, Kansas, USA) waveform converter software. The waveform converter software was used to digitally remove the bias flow that was introduced during the recording process before the breathing patterns were transferred to the breathing simulator in binary file format. An example of a recorded breathing trace is illustrated in Figure 6.
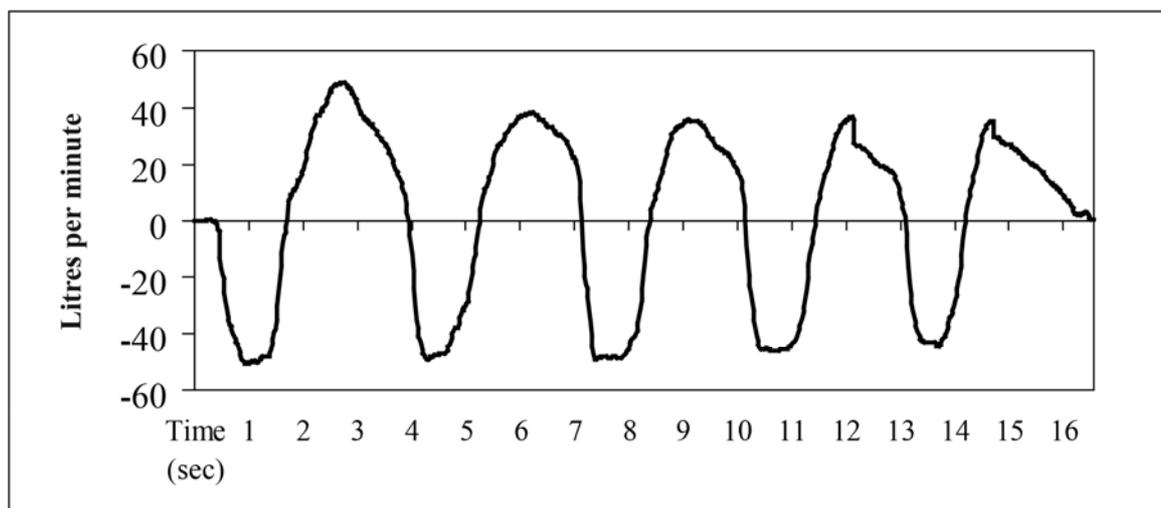
Figure 6. Example of a breathing pattern recorded and simulated. Flow (LPM) on the Y-axis is plotted against time (s) on the X-axis.

Ex vivo **and** *in vitro* **drug delivery measurements**

Drug delivery measurements using low resistance inspiratory filters (Uni-filter Junior, GE Healthcare, Waukesha, USA) with a dead space of 20ml were used to ensure that the equipment and technique, as described above, could be used to accurately record and simulate breathing.

Spacers were prewashed in a mild detergent and left to drip-dry before use in order to eliminate electrostatic build-up. pMDIs were shaken and waste-actuated 10 times before each experiment.

A pMDI was shaken and actuated once into the spacer. Subjects then took five tidal breaths through the spacer, commencing immediately after actuation. This entire procedure was repeated five times per filter to ensure that a quantifiable drug dose was collected, while the subjects' breathing was recorded simultaneously. Salbutamol deposited on the actuator, spacer and inspiratory filter, was then measured as described below.

For the *in vitro* drug delivery measurements, the five breathing traces recorded previously for each *ex vivo* filter study were simulated individually, with one pMDI actuation per five

tidal breath trace. The *in vitro* set-up and procedure was identical to that used for the *ex vivo* filters, except that the human subject was replaced by the breathing simulator.

Drug analysis

Filters, spacers and pMDI-actuators were disassembled. Salbutamol deposited on each part was eluted individually, using a methanol/water solution (90% HPLC-grade methanol/ 10% double deionised water) containing 0.01M NaOH. The absorbance of each sample was measured at a wavelength of 246 nm, in duplicate, using an ultraviolet spectrophotometer (UV-1601; Shimadzu Scientific Corporation, Kyoto, Japan). The absorbance of a series of reference standards (Salbutamol hemisulphate, Sigma-Aldrich, Sydney, Australia) over the concentration range 0.2-20 µg/ml were tested with each batch of samples, and found to be linear ($r^2 > 0.998$).

The recovery of a known amount of salbutamol from inspiratory filters using this method, has previously been tested and found to be 98.2% (SD 4.9; n=6)[266].

Data analysis

Drug delivery to inspiratory filters is presented as a proportion of the dose recovered from the pMDI actuator, spacer and filter. Comparison between drug dose on filter as "inhaled" by subjects compared to drug dose "inhaled" by breathing simulator was done using regression analysis and Bland-Altman plots.

In the scatter plots, *in vitro* filter dose on the Y-axis was plotted against *ex vivo* dose on the X-axis. In the Bland-Altman curves the difference between *in vitro* filter dose and *ex vivo* filter dose on the Y-axis was plotted against the mean difference (*ex vivo* filter dose + *in vitro* filter dose)/2 on the X-axis. Filter dose recovered was analysed as percentage of total dose recovered.

2.3   Results

In each of the three different configurations and with each spacer, the matching *ex vivo* and in vitro inspiratory filter doses were comparable.

Configuration One

Filter dose recovered was comparable between the *ex vivo* and the *in vitro* techniques (Figure 7). *Ex vivo* filter dose recovered ranged from 3.5 to 59.5% of total dose recovered. *In vitro* filter dose recovered ranged from 8.9 to 60.7% of total dose recovered. The median difference between *ex vivo* and *in vitro* filter doses recovered (for all spacers) was 0.4% (range -12.2% to 6.9%). With the Aerochamber Plus, there was a tendency for *in vitro* dose delivery to overestimate drug delivery but the overestimation did not exceed 6.9% of total dose recovered. With the Volumatic there was a tendency for *in vitro* filter dose to be slightly lower (median difference -3.9%) than *ex vivo* filter dose for doses smaller than 30% of total dose recovered. Conversely, with the Volumatic in vitro filter doses were slightly higher (median difference 2.6%) than *ex vivo* filter doses for doses larger than 40% of total dose recovered.
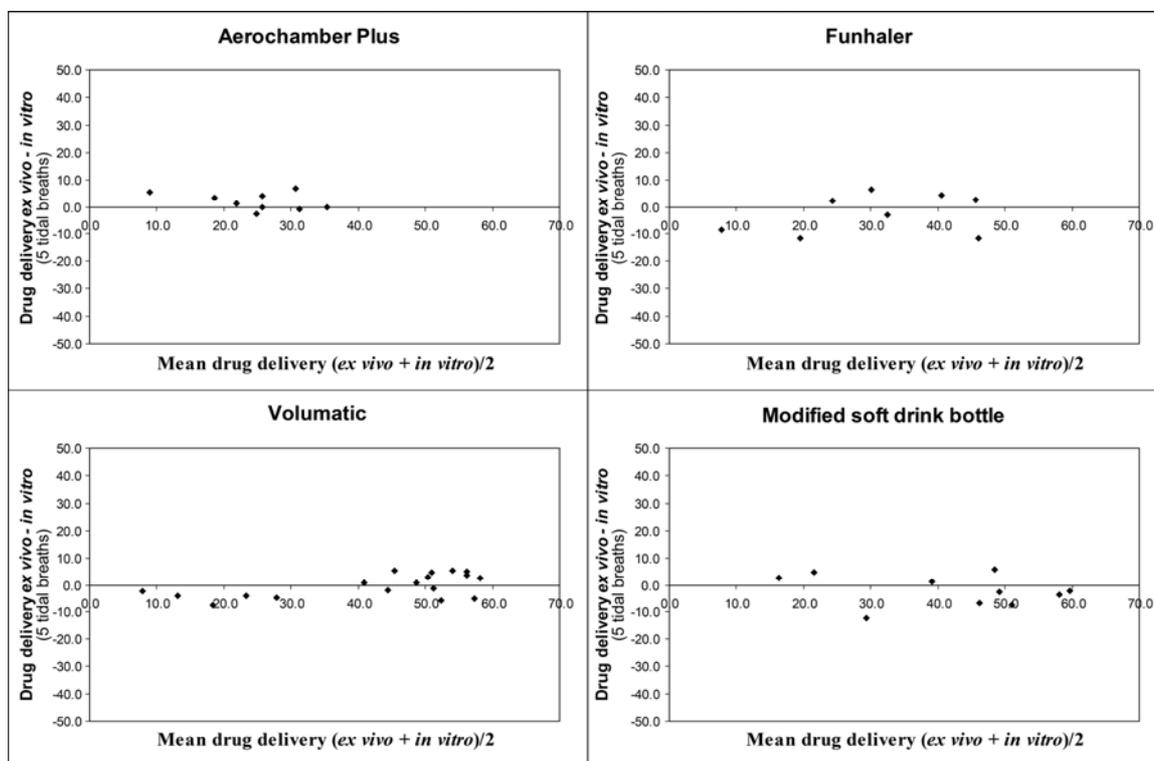
Figure 7. Configuration 1: Bland-Altman plot demonstrating difference between ex vivo and in vitro drug delivery for 5 tidal breaths plotted against mean drug delivery. Drug delivery represented as percentage of total dose recovered from filter, actuator and spacer.

There was a strong correlation between *ex vivo* and in vitro filter doses, for all spacers tested, $R^2 = 0.75$, $p = 0.01$; $R^2 = 0.76$, $p = 0.05$; $R^2 = 0.95$, $p < 0.01$; and $R^2 = 0.87$, $p < 0.01$ for the Aerochamber Plus®, Funhaler®, Volumatic® and modified soft drink bottle, respectively (Figure 8).

Mean inhalation volumes of subjects inhaling through the different spacers ranged between 47-235ml for the Aerochamber Plus®, 24-548ml for the Funhaler®, 48-985ml for the Volumatic®, and 40-762ml for the modified soft drink bottle. Mean peak inspiratory flows ranged between 6.6-21.7 LPM for the Aerochamber Plus®, 3.2-32.5 LPM for the Funhaler®, 5.6-55.3 LPM for the Volumatic®, and 5.6-47.7 LPM for the modified soft drink bottle. For all spacers, for all breathing patterns tested *in vitro* drug delivery corresponded with *ex vivo* drug delivery (Figures 7 and 8).
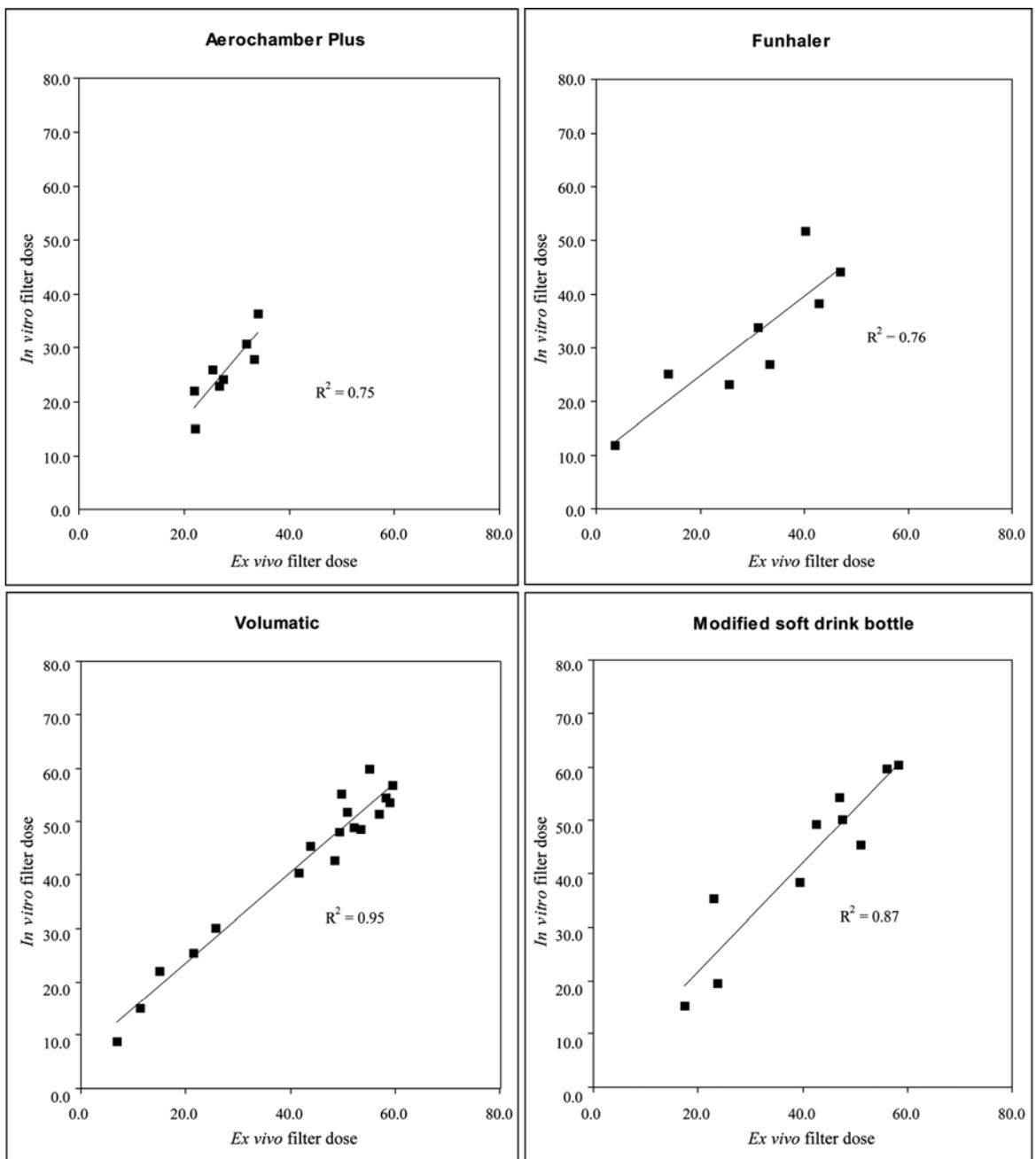
Figure 8. Configuration 1. Correlation between ex vivo filter dose and in vitro filter dose. Drug delivery represented as percentage of total dose recovered from filter, actuator and spacer.

Configuration Two

Filter dose recovered was comparable between the *ex vivo* and the *in vitro* techniques (Figure 9). *Ex vivo* filter dose recovered ranged from 19.2 to 49.3% of total dose recovered. *In vitro* filter dose recovered ranged from 22.3 to 50.7% of total dose recovered. *Ex vivo* filter doses correlated well with i*n vitro* filter doses ($R^2 = 0.87$, $p < 0.01$)). The median difference between *ex vivo* and *in vitro* filter doses recovered was -2.3% (range -9.0% to 5.0%).
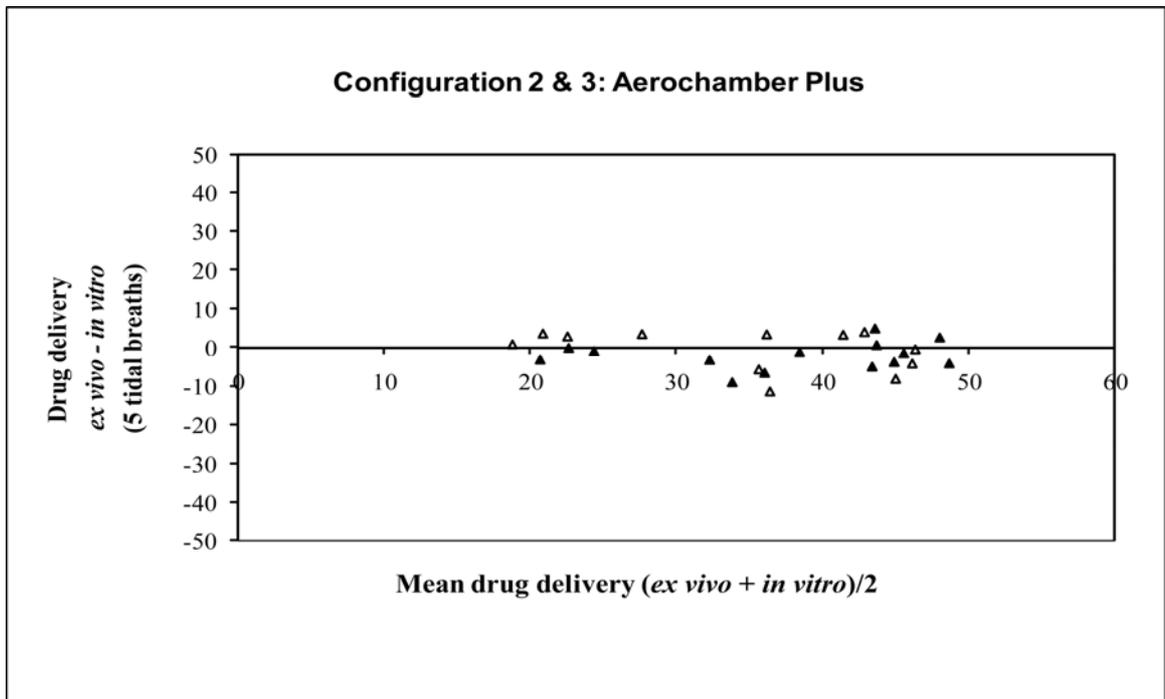
Figure 9. Configuration 2 & 3: Bland-Altman plot demonstrating difference between ex vivo and in vitro drug delivery for 5 tidal breaths plotted against mean drug delivery. Drug delivery represented as percentage of total dose recovered. Configuration 2 – closed triangles; Configuration 3 – open triangles. Spacer = Aerochamber Plus®

Configuration Three

Filter dose recovered was comparable between the *ex vivo* and the *in vitro* techniques (Figure 9). *Ex vivo* filter dose recovered ranged from 19.2 to 46.1% of total dose recovered. *In vitro* filter dose recovered ranged from 18.5 to 49.1% of total dose recovered. *Ex vivo* filter doses correlated well with i*n vitro* filter doses ($R^2 = 0.79$, $p < 0.01$)). The median difference between *ex vivo* and *in vitro* filter doses recovered was 1.7% (range - 11.5% to 3.9%).

Correlation between inhalation volume and inspiratory flow

Subjects inhaled faster as they took larger breaths, and *vice versa*. For each set of breathing patterns, mean peak inspiratory flow increased as mean inhalation volume increased. For all spacers, the increase in peak inspiratory flow was directly proportional to the increase in inhalation volume, with $R^2 = 0.82$, $p < 0.01$; $R^2 = 0.98$, $p < 0.01$; $R^2 = 0.94$; $p < 0.01$ and $R^2 = 0.98$, $p < 0.01$, respectively for the Aerochamber Plus®, Funhaler®, Volumatic® and modified soft drink bottle in Configuration 1, and $R^2 = 0.80$, $p < 0.01$ for the Aerochamber Plus® used in Configuration 2 and 3 (Figures 10 and 11).
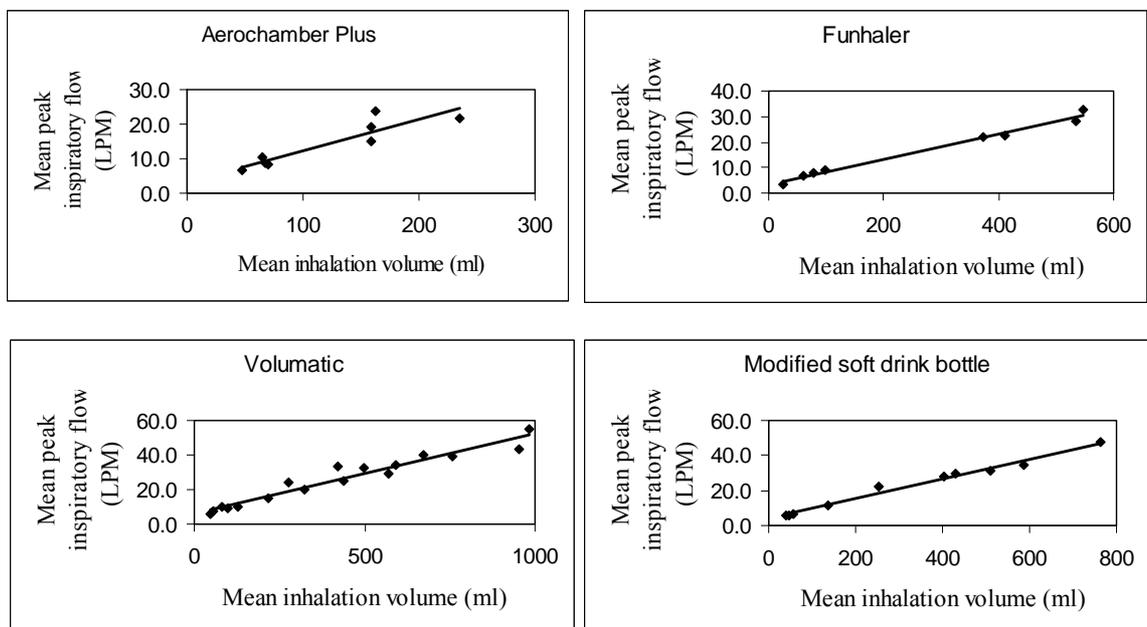
Figure 10. Configuration 1. Correlation between tidal volume and peak inspiratory flow in breathing patterns recorded and simulated. Mean peak inspiratory flow plotted against the mean inhalation volume for each set five of breathing patterns.
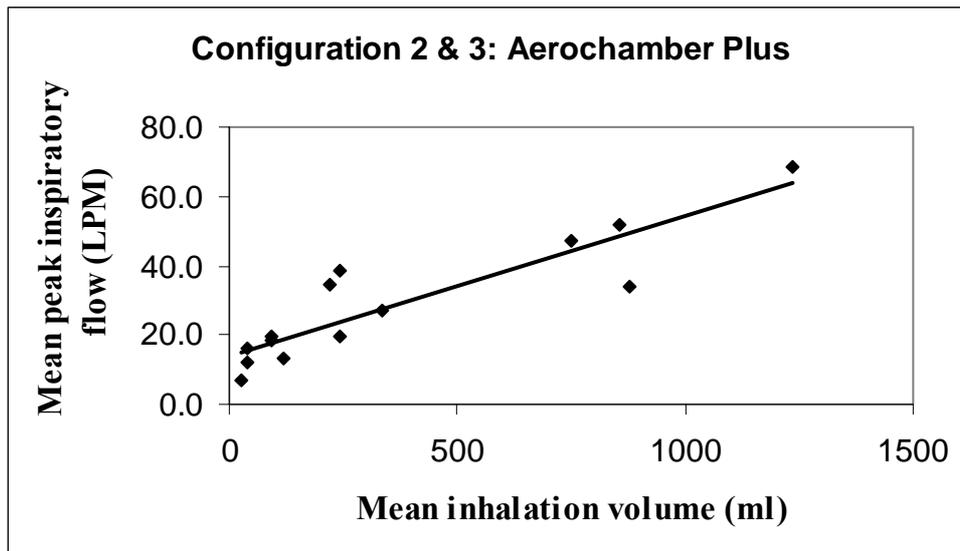
Figure 11.   Configuration 2 & 3.   Correlation between tidal volume and peak inspiratory flow in breathing patterns recorded and simulated.   Mean peak inspiratory flow plotted against the mean inhalation volume for each set five of breathing patterns.   Spacer = Aerochamber Plus®.

Influence of tidal volume and inspiratory flow on drug delivery

With all three configurations, drug delivery was related to inhalation volume and flow. Due to the strong correlation between mean inhalation volume and mean peak inspiratory flow, the precise influence of each individual parameter could not be ascertained.

Drug delivery increased with an increase in inhalation volume and flow, to reach a plateau at inhalation volumes of approximately 250ml with the Aerochamber Plus®, between 100 and 400ml with the Funhaler®, approximately 400ml with the Volumatic®, and between 400ml and 500ml with the modified soft drink bottle (Figure 12 and 13). The plateau in drug delivery occurred at approximately 30LPM with all spacers, with less of a plateau seen with the modified soft drink bottle (Figures 14 and 15).
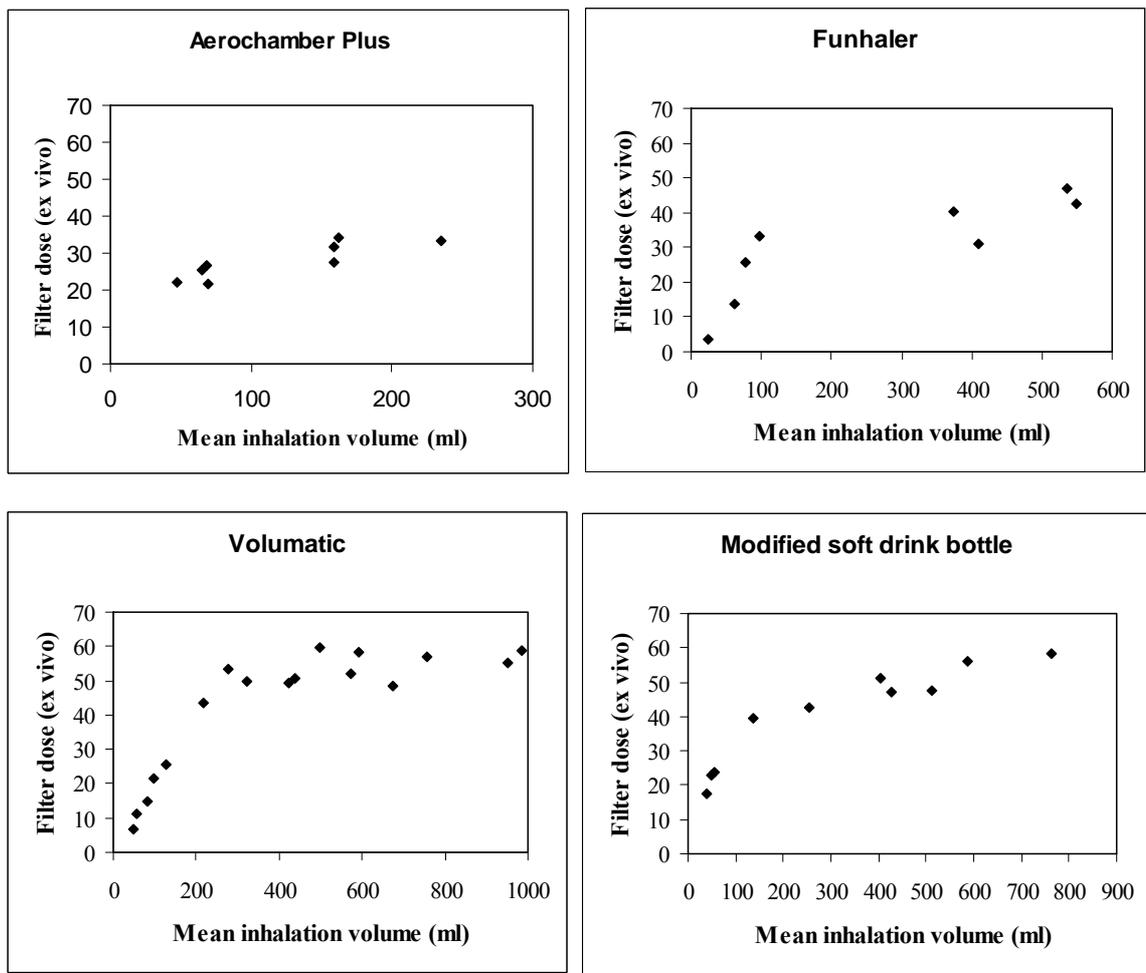
Figure 12. Configuration 1. Drug delivery (ex vivo filter dose as percentage of total drug dose recovered) plotted against mean inhalation volume for different spacers.
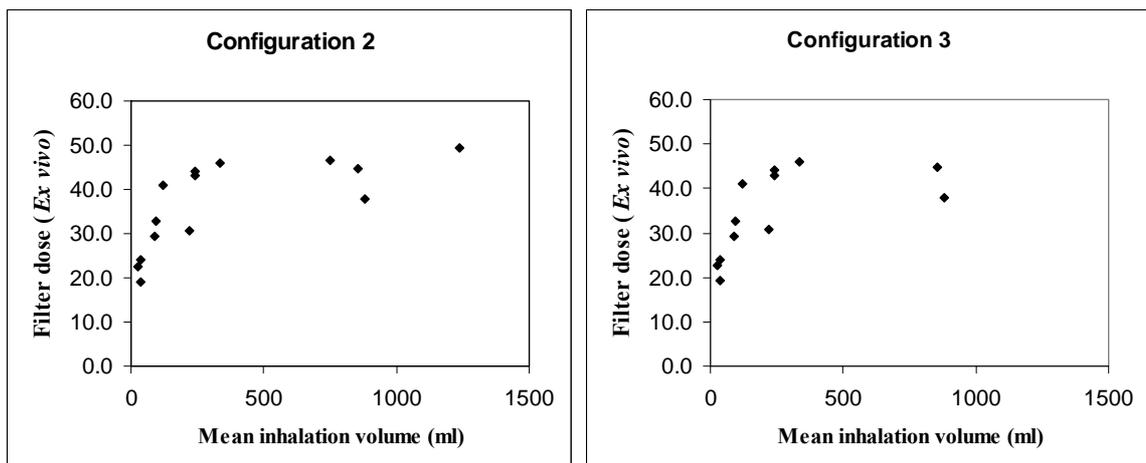
Figure 13. Configuration 2 & 3. Drug delivery (ex vivo filter dose as percentage of total drug dose recovered) plotted against mean inhalation volume for different spacers. Spacer = Aerochamber Plus®.
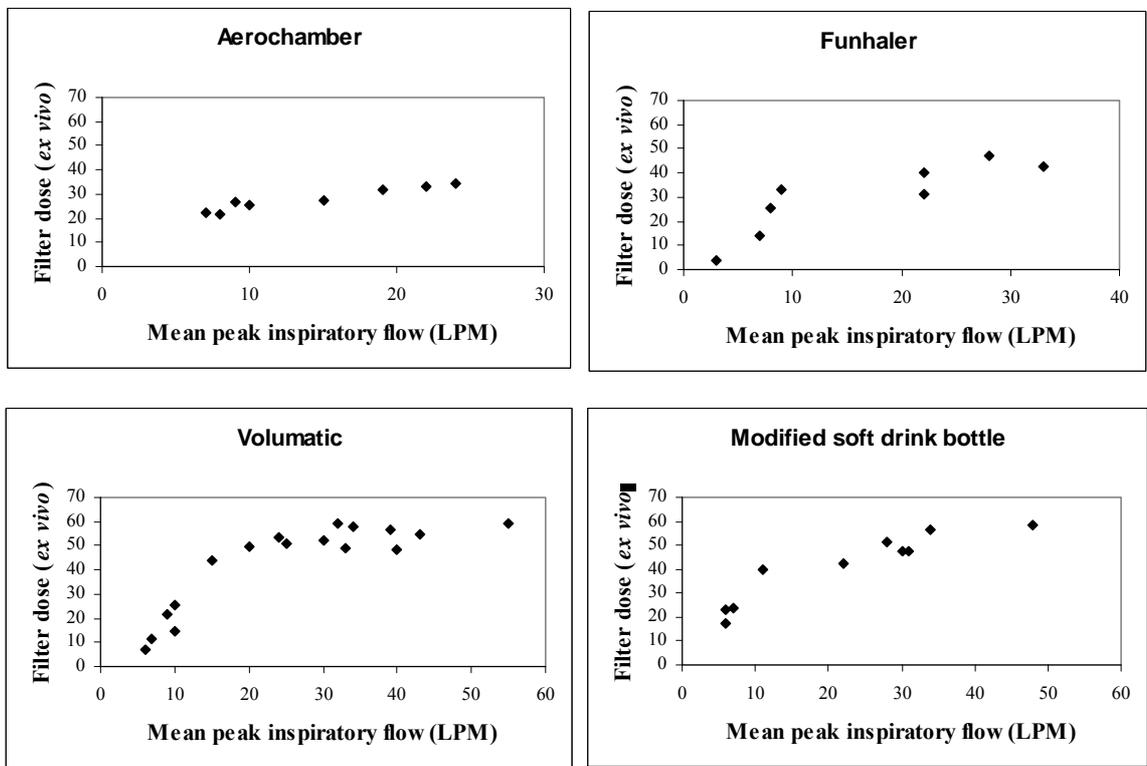
Figure 14. Configuration 1. Drug delivery (Ex vivo filter dose as percentage of total drug dose recovered) plotted against mean peak inspiratory flow of each corresponding set of breathing patterns.
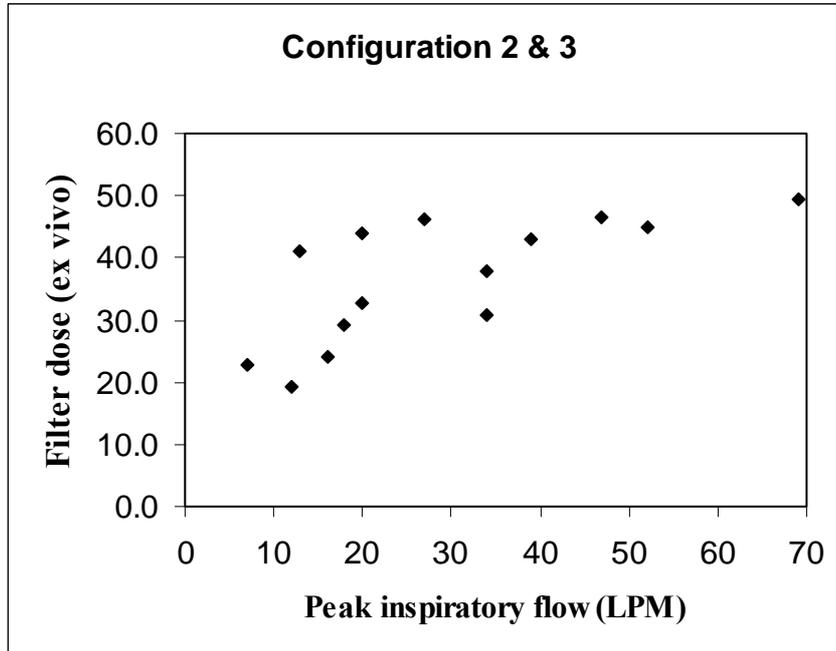
Figure 15. Configuration 2 & 3. Drug delivery (Ex vivo filter dose as percentage of total drug dose recovered) plotted against mean peak inspiratory flow of each corresponding set of breathing patterns. Spacer = Aerochamber Plus®.

2.4   Discussion

Data from Configuration One provided evidence that the simulated breathing patterns were satisfactorily in approximation to those of the subjects.

The flow-chamber was validated as a sufficiently precise method for recording breathing in *configuration two*:   The recorded (and then simulated) breathing patterns had a similar effect on drug delivery as the human subjects' breathing.

Breathing simulation without using a flow chamber during breathing simulation was validated in *configuration three*:   Drug delivery with a subject inhaling from a spacer placed in a flow-chamber corresponded to drug delivery with a breathing simulator without the use of a flow chamber.   The correlation between *ex vivo* and *in vitro* filter doses in configuration 3 ($R^2 = 0.79$) was comparable to the correlation between *ex vivo* and *in vitro* filter doses in configuration 1 (Aerochamber Plus®) and configuration 2 ($R^2 = 0.75$ and 0.87, respectively).

Although spacers are mostly prescribed for use in children and patients with coordination problems, in this thesis we made use of two healthy adult male subjects for breathing recording and drug delivery studies. As the aim of this study was to test the accuracy of our flow-chambers in recording breathing, and the accuracy of flow volume simulator in estimating *ex vivo* drug delivery over a wide range of breathing patterns, "coaching" the subjects was necessary in order to obtain a large range of breathing patterns.   Similar "coaching" would not have been possible in young children or in subjects with coordination problems. As output through pMDI-spacer is known to be sensitive to changes in breathing pattern, and slow inhalation is preferable to fast inhalation [114, 137], subjects were directed to inhale slowly during all recordings, and subjects were encouraged to vary their inhalation volume between different sets of recordings.   Although subjects were directed to breathe slowly at all times, and only vary their inhalation volume, both subjects appeared to have unconsciously increased their rate of inhalation as they increased their inhalation volumes (and *vice versa*). The nature of the study (validation of methodology with subjects

voluntarily changing their breathing patterns), prevented a systematic and exhaustive study of the influence of all inhalation parameters on drug delivery. These data should therefore not be used to definitively compare the efficacy of the spacers used.

Our data demonstrated that drug delivery through spacer was related to inhalation volume and flow. Drug delivery reached a plateau at lower inhalation volumes with the lowest volume spacer (Aerochamber Plus®). Previous studies also described inhalation volume dependence of drug delivery through spacers [69, 74, 115]. In a study by Barry and O'Callaghan (1999) where sinusoidal breathing patterns were used to determine budesonide delivery through a 145ml Aerochamber (earlier version of Aerochamber Plus) at various tidal volumes [115], drug delivery continued to increase at inhalation volumes exceeding 200ml. The inspiratory flows used by Barry and O'Callaghan were lower that the mean peak inspiratory flows where drug delivery started to plateau in this thesis.

With all three valved spacers used, increased drug delivery was found with increased inspiratory flows up to 30LPM. As a plateau in drug delivery was seen with peak inspiratory flows above 30LPM, a limiting effect of higher flows on drug delivery could not be excluded by the data. In a previous study Wildhaber et al (1996) did not demonstrate decreased drug delivery at higher flows through two valved spacers, when salbutamol delivery was studied at constant flows of 10, 30, and 60LPM [58]. Similarly, Dalby et al (1998) demonstrated an increase in drug delivery through valved spacers as constant inspiratory flow was increased from 28LPM to 55LPM [268]. The constant inspiratory flow used by both Wildhaber et al and Dalby et al is a possible reason for the seemingly disconsonant findings between their findings and the findings reported in this chapter. In a study using simulated breathing, Janssens et al (2004) demonstrated an increase in upper airway deposition and a decrease in "lung dose" as respiratory rates increased, but total spacer output did not decrease as respiratory rates increased [69]. However, the inspiratory flows in Janssens el al's study were lower than 30LPM. As mentioned above, the strong correlation between peak inspiratory flows and inhalation volumes described in this chapter excluded an accurate distinction between the respective influences on drug delivery of inhalation volumes and inspiratory flows.

With the Volumatic®, drug delivery reaching a plateau when inhalation volume reached only approximately half of the spacer volume, may have been partly caused by a large part of the actuated dose being concentrated in the front part of the spacer, in the first fraction of

a second post actuation. Time could also have influenced drug delivery, i.e. drug starts to settle out within the spacer if it takes too long to achieve the required volume to clear the spacer [113].

Spacers can be used with or without facemasks. Facemask use with spacer devices is usually recommended for adults with coordination problems and children under the age of four years [269]. The 2008 British Thoracic Society asthma guidelines [270] acknowledges that "in young (0-5 years) children, little or no evidence is available on which to base recommendations". At our hospital children are often trained to use spacer mouthpieces from the age of two. This thesis was therefore confined to testing spacer use without facemasks. If a spacer with a facemask was to be tested, a face model would have to be incorporated in the set-up as has been done previously in breathing simulation studies [72, 108, 117, 271, 272].

The study described above was limited to measuring total dose delivery (to a patient's mouth, before being inhaled or deposited onto the oropharyngeal surface). If drug was to be inhaled *in vivo*, the percentage of drug that potentially would have impacted on the pharynx and upper airways would be expected to increase at higher inspiratory flows [114].

The methodology described above could potentially be used for the following:

- To measure and simulate breathing patterns in specific patient groups, using specific inhalation devices, particularly in patient groups where it would be difficult to perform *in vivo* studies i.e. preschool children.
- To perform multiple comparisons of different inhaler devices. Once a database of breath recordings from different patient groups has been accumulated, the methodology described could be used to measure the influence of various external- or device related factors on breathing patterns, and subsequent drug delivery.
- To screen a wide variety of different inhalers/ spacers for specific populations, to eliminate sub-optimal devices, in order to then proceed to *in vivo* testing with the most optimal devices.

Conclusion:

A method using breathing simulation for assessing the influence of breathing on drug delivery via spacer, where the simulated breathing can be recorded on subjects while they

are using spacers, with minimum increase in dead space or resistance, and no physical alteration in the patient-device interface, was validated.

The results also demonstrate that drug delivery via spacer is a function of inhalation volume and flow.

3 CHAPTER THREE: Determining the minimum number of breaths and type of breathing required for effective drug delivery through pMDI-spacers

3.1 Background

Wheezing disorders are more common in young children [273, 274] than in any other age. Medication for these children is most commonly inhaled from valved spacer devices. Yet, how best to inhale from spacers is unknown for this age group and international guidelines lack uniformity and are mostly based on personal opinion [142, 143, 275].

This chapter describes a study that was designed to determine the relationship between the number of tidal breaths (and single maximal breath) and drug output from various pMDI-spacer combinations, . Based on technical data on *in vitro* spacer performance [74] and knowledge of tidal flow patterns in young children [68] we hypothesised that a number of breaths limited in relation to the size of the spacer would be sufficient for efficient drug inhalation via spacer in preschool children.

3.2 Aims and hypothesis

Aims: To determine the number of tidal breaths required to effectively inhale medication from different types of spacer/valved holding chamber devices, and to determine the efficacy of a single maximal inhalation for drug delivery in young children.

Hypothesis: Based on technical data on *in vitro* spacer performance [74] and knowledge of tidal flow patterns in young children [68], a number of breaths limited in relation to the size of the spacer would be sufficient for drug inhalation via the spacer in preschool children.

3.3   Methods

Breathing was recorded in preschool children inhaling placebo from spacers.   The recorded breathing patterns were simulated to determine the minimum number of breaths and type of breathing required for effective drug delivery through pMDI-spacers.

<u>Study participants</u>

This study was performed as a sub-study from a 12 month clinical trial which compared two valved spacer devices, the Funhaler® and the Aerochamber Plus®, in two- to six-year old children. Inclusion criteria for the clinical trial were that asthma had been diagnosed by a doctor in the community and that subjects were receiving inhaled steroids for treatment of their asthma. Ethics approval was obtained from the ethics committee of Princess Margaret Hospital for Children, and the Telethon Institute for Child Health Research (933/EP, and 1026/EP), and from the ethics committee of the University of the Free State (ETOVS 67/07). Parents or guardians provided written informed consent. Children gave verbal assent to have their breathing recorded. Children were recruited between May 2005 and October 2006 using local advertisements, flyers and from the Emergency Department and clinics at Princess Margaret Hospital for Children.

Three separate groups where investigated. The first group was recruited at the beginning of the clinical trial where tidal breathing was recorded and simulated in 34 subjects, aged (median (range) 55 (25-84) months; 20 male and 14 female, using either an Aerochamber Plus® or a Funhaler®.   In this subgroup, drug delivery with two tidal breaths was compared with drug delivery with nine tidal breaths. Subjects used the spacers allocated to them in the clinical trial in which they were participating. All 34 children were able to provide records of tidal breathing, but not all could perform the single maximal breath manoeuvre.

The second group was investigated at the end of the year long clinical trial when 84 children (age range 34 - 109 months) where screened for their ability to perform a single maximal inhalation.

The third group was selected to compare tidal with single maximal breaths; it was a subgroup of subjects from the above two groups (seen at the end of the main clinical trial)

and included the first two subjects from each year of age who could perform a single maximal breath. Both tidal breathing and single maximal breathing patterns were recorded from these children (n= 10, aged median (range) 59 (41 - 73) months) and simulated using 4 different spacers in a pseudo-randomised order. As tidal breathing with small volume spacers had already been investigated in subgroup one, single maximal breath was compared with nine tidal breaths for small volume spacers in this subgroup. Two, three, five and nine tidal breaths and single maximal inhalation was investigated for the large volume Volumatic spacer in this subgroup whereas only two, five and nine tidal breaths and single maximal inhalation was investigated for the smaller, unvalved, modified soft drink bottle. The recorded breathing patterns in this group were digitally analysed to calculate, for each subject and for every different spacer used, the mean inhalation volume of nine tidal breaths and the volume of each single maximal inhalation.

All subjects were weighed before breathing was recorded in order to estimate predicted tidal volume based on a predicted tidal volume of weight (kg) x 7ml [149].

Subjects recruited from clinical trial			**Spacers**	**Breathing patterns recorded**
Beginning of clinical trial Subjects aged two to six years old	First 34 subjects (out of possible 132) on whom adequate breathing traces were recorded		Aerochamber Plus® and Funhaler®	2 and 9 tidal breaths
One year later: last visit of clinical trial	Ability to perform SMI evaluated and breathing recorded on 84 subjects	First two subjects from each year group on whom both SMI and tidal breathing was recorded (n = 10)	Aerochamber Plus® and Funhaler®	SMI and 9 tidal breaths
			Volumatic®	SMI and 2, 3, 5, and 9 tidal breaths
			Modified soft drink bottle	SMI and 2, 5, and 9 tidal breaths

Table 8. Basic outline of protocol.

A custom built device was needed to accurately record breathing patterns in children inhaling from spacers. The device was designed to allow breathing to be recorded without changing dead space, resistance, or mouthpiece if the pMDI-spacers. The technique used for recording and simulating breathing is described in detail above.

Breathing was recorded in children while they were inhaling placebo (GlaxoSmithKline, Australia) from different spacers. The recorded tidal breathing patterns were digitally analysed to isolate different numbers of breaths. All breathing patterns were then individually transferred to a breathing simulator (Hans Rudolph, Kansas, USA). A filter was interposed between the breathing simulator and a spacer device that was connected to a salbutamol (Ventolin; GlaxoSmithKline, Australia) pMDI. Immediately after actuation of the pMDI simulation of the recorded breathing patterns commenced. Simulated drug delivery was measured using the same spacer type that was used during the *ex vivo* recording of breathing patterns. Simulated breathing patterns matched those recorded with the relevant spacer.

Spacers and breathing patterns

Four different spacers were investigated; two small volume spacers (the 149ml Aerochamber Plus®, Trudell, Canada and the 225ml Funhaler®, Visiomed, Australia) and two large volume spacers (the 750ml Volumatic®; and a modified 500ml plastic soft drink bottle. This range of spacer devices was selected to represent types commonly used in children: The Aerochamber Plus is a commonly used small volume spacer. The Volumatic® is a commonly used large volume spacer. The Funhaler® is an example of an incentive spacer which may have potential to facilitate a child's breathing and therefore drug delivery. The modified soft drink bottle is an example of an unvalved spacer device and was tested because modified soft drink bottles are being used as spacer devices in some developing countries.

Statistical analysis

Comparisons were made between filter doses recovered for different breathing patterns using SPSS version 15.0. Paired samples were compared using the Wilcoxon Signed

Ranks Test. Unpaired samples were compared using the Mann-Whitney U test. Where the data were normally distributed, unpaired samples were compared using the Students t-test. Linear regression was used to correlate data. Bland-Altmann plots were used to compare different measurement techniques.

3.4   Results

The minimum number of tidal breaths required to effectively inhale salbutamol from a spacer depended on the type of spacer used (Figure 16). With the small volume spacers (Funhaler® and Aerochamber Plus®) there was no significant difference in drug delivery between two tidal breaths and nine tidal breaths. Drug delivery via the Funhaler® mean (95CI) was 39% (34-43) and 38% (35-42) for two and nine tidal breaths respectively. Drug delivery via the Aerochamber Plus® mean (95CI) was 40% (34-46) and 41% (36-47) for two and nine tidal breaths respectively. With the Volumatic, drug delivery after two tidal breaths was significantly less than after nine tidal breaths; mean (95CI) 37% (33-41) and 43% (40-46), respectively (p=0.02; Wilcoxon Signed Ranks). There was no statistically significant difference in drug delivery after three tidal breaths mean (95CI) (40% (36-44%) and nine tidal breaths 43% (40-46) for the Volumatic®. With the (unvalved) modified soft drink bottle, there was no significant difference in drug delivery between two, five or nine tidal breaths.
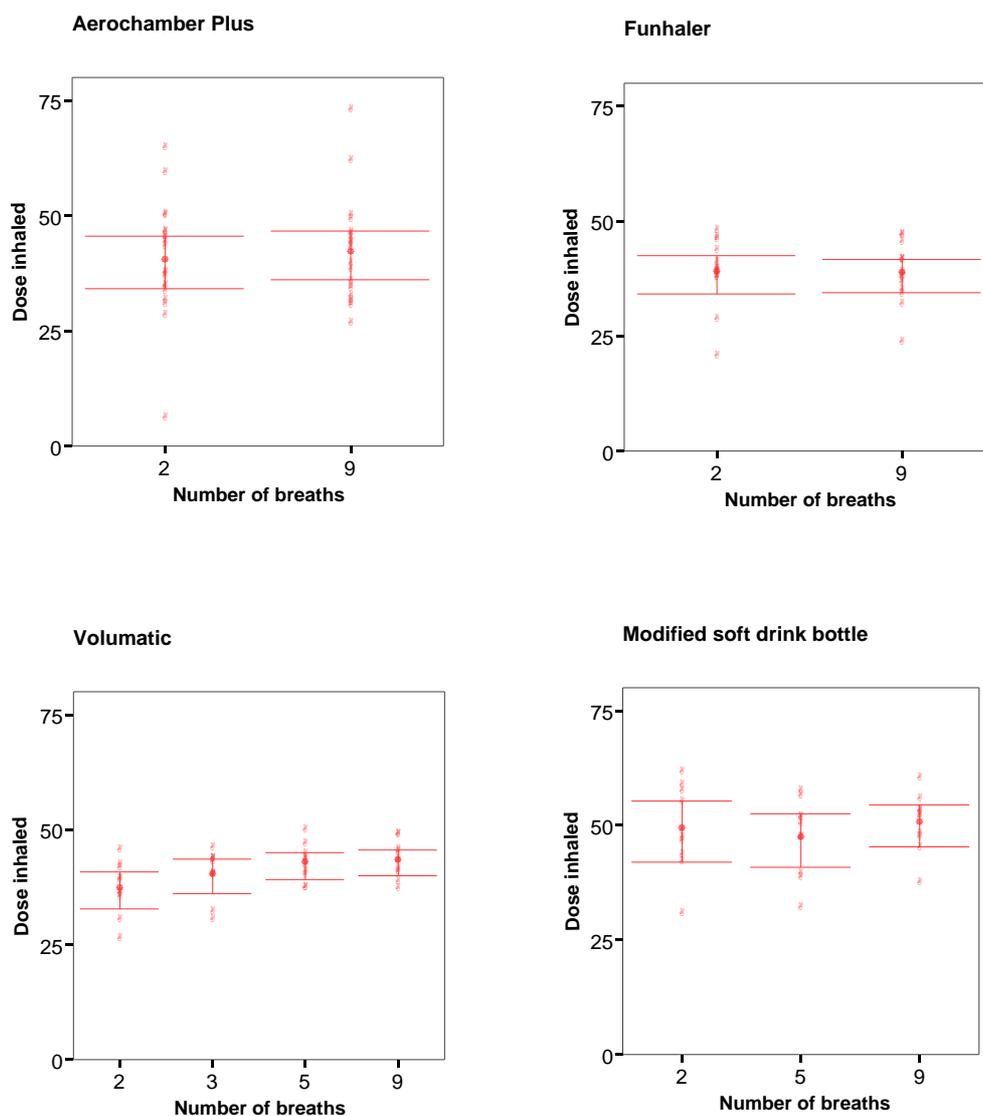
Figure 16. Salbutamol doses recovered from filters are reported as percentage of total dose recovered from filter, spacer and pMDI sleeve. Error bars show 95% CI of mean.

Inhalation volumes were almost double the expected tidal volumes. The inhalation volume mean (SD) of subjects using the Aerochamber Plus®, the Funhaler®, the Volumatic® and the modified soft drink bottle was respectively 393ml (247), 432ml (225), 384ml (185), 445ml (167) during tidal breathing and 515ml (164), 550ml (239), 503ml (213), 448ml (259) for the single maximal breath manoeuvre (Figure 17). The mean (SD) weight of these subjects was 19.8kg (4.44). If tidal volume was predicted using the formula wt (kg) x 7ml, the mean tidal volume for these subjects would have been 138.6ml.
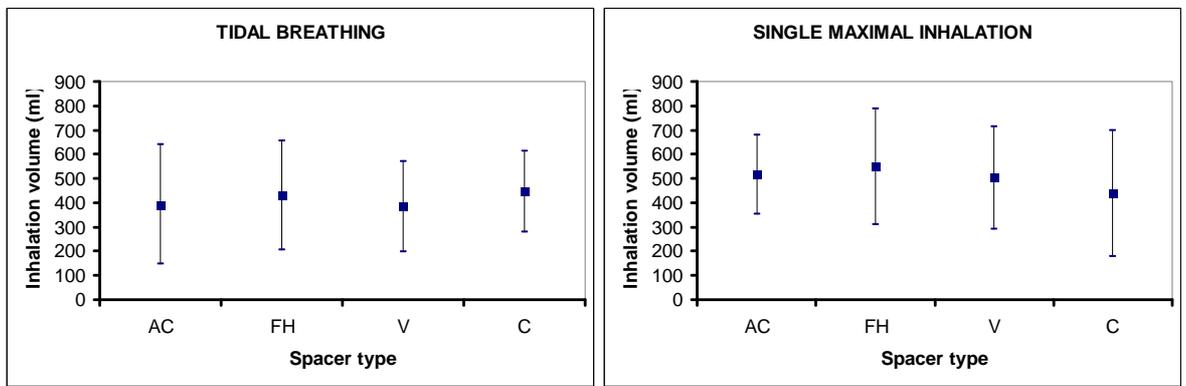
Figure 17. Mean (SD) inhalation volumes of subjects inhaling from different spacers. FH = Funhaler®; AC = Aerochamber Plus®; V = Volumatic®; C = Modified soft drink bottle.

With tidal breathing, mean peak inspiratory flows (SD) of subjects using the Aerochamber Plus®, the Funhaler®, the Volumatic® and the modified soft drink bottle was respectively 49 (21), 50 (24), 46 (17), and 52 (19) LPM. Inspiratory flows with the single maximal inhalation technique was only marginally higher at 61 (15), 66 (24), 61 (26), and 62 (25) LPM with the Aerochamber Plus®, the Funhaler®, the Volumatic® and the modified soft drink bottle respectively (Figure 18).
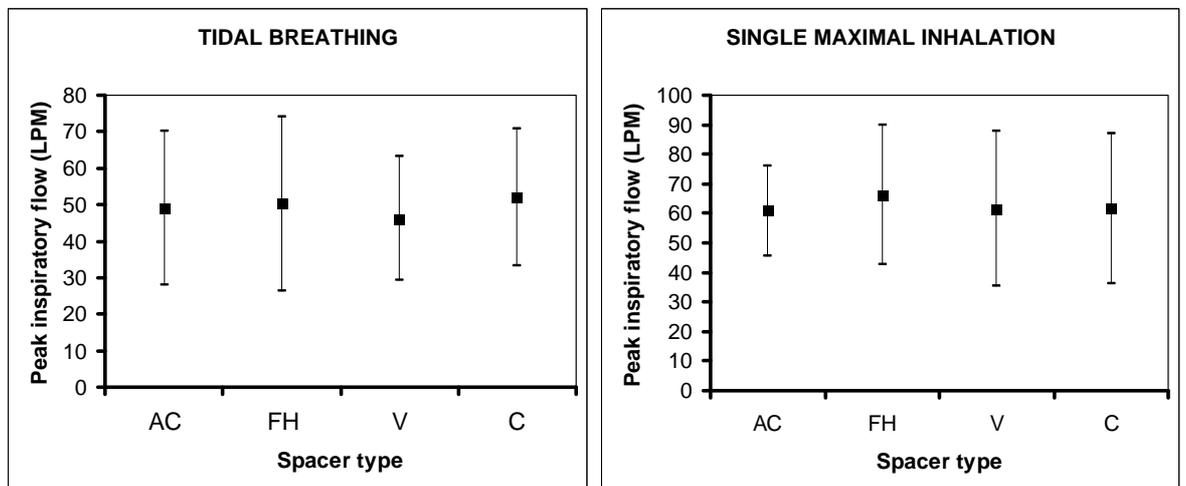
Figure 18. Mean (SD) peak inspiratory flow of subjects inhaling from different spacers. FH = Funhaler®; AC = Aerochamber Plus®; V = Volumatic®; C = Modified soft drink bottle.

100% of seven year old children, 84% of six year olds, 76% of five year olds, 38% of four year olds and 20% of three year olds could perform a single maximal breath manoeuvre (Figure 19). There was an age dependant gender difference and females were able to

perform a single maximal breath manoeuvre earlier than their male counterparts (100% by six years of age). During this manoeuvre, two of the children screened, were noted to be inhaling through their noses. This observation was made possible because their breathing was being recorded, and would not have come to light by clinical observation only.
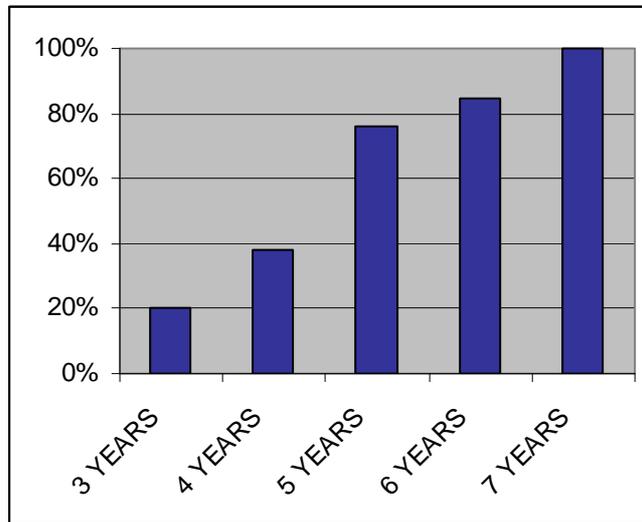
Figure 19. Percentage of children able to perform single maximal inhalation (Breath holding not tested).

Nine tidal breaths resulted in significantly greater drug delivery to filter than single maximal inhalation for both the Funhaler® ($p=0.04$) and the Volumatic® ($p=0.01$) (Figure 20). There was no significant difference in drug delivery to filter between single maximal inhalation and nine tidal breaths with both the Aerochamber Plus® and the modified soft drink bottle. With the methodology not allowing for asynchrony between pMDI acuation and inhalation, the highest total drug delivery was seen with the (valveless) modified soft drink bottle.

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Aerochamber Plus

Funhaler

Volumatic

Modified soft drink bottle

Figures: scatter plots with error bars showing DRUG DELIVERY (y-axis, 0–75) versus BREATHING PATTERN (x-axis: 9 TIDAL BREATHS, SINGLE MAXIMAL BREATH) for each device.
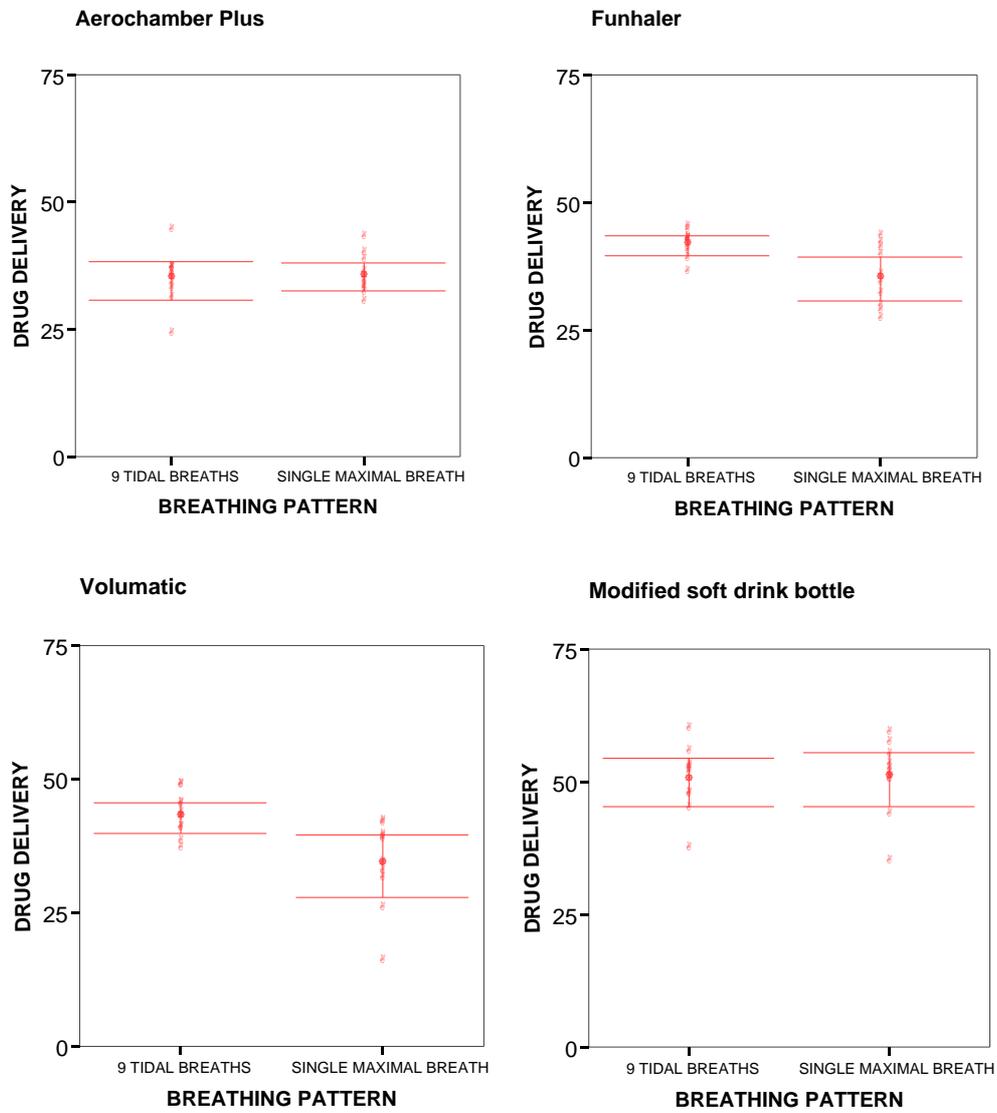
Figure 20. Salbutamol doses recovered from filters, reported as percentage of total dose recovered from the filter, spacers and pMDI sleeve. Error bars represent 95% confidence intervals.

3.5   Discussion

This study has lead to two major new findings that for the first time define the information needed to instruct young children for optimal use of spacers. Firstly, young children, breathing tidally through spacers take much larger breaths than during normal tidal breathing. Secondly, we were able to define the number of tidal breaths needed for efficient use of different sized spacer devices: Two for an unvalved spacer, two for the small volume valved spacers, and up to three for the large volume valved spacer.

The finding that inhalation volume of young children breathing tidally through spacers differs from normal tidal breathing was not unexpected, as it has previously been demonstrated that instrumentation influences breathing pattern [119]. The recorded breath volumes were, however, higher than anticipated. The peak inspiratory flows recorded on children breathing tidally through spacers were also significantly higher than flows used in previous spacer related paediatric breathing simulation studies [63, 65, 69, 72, 74, 108, 113, 115, 117].

Our study demonstrates that a single maximal inhalation does not result in improved drug delivery over tidal breathing in young children. As the mean volume of the single maximal breaths was smaller than the volume of the Volumatic spacer, increased drug delivery with a number of tidal breaths could be expected. The reason for increased drug delivery with tidal breathing over a single maximal breath with the Funhaler® is not clear from these data.

This study was not designed to determine drug dose delivered to a patient's lungs. The filter dose captured during breathing simulation represents the total drug dose that would reach a patient's mouth and not the lung dose. However, one would not anticipate that the lung dose would be increased by taking further breaths through a spacer once the maximum total dose delivery has been reached.

Due to the nature of the study, breath holding was not examined. Although breath holding appears to be beneficial for lung deposition in adults [137], breath holding is difficult and unlikely to significantly improve lung deposition in children [150].

The relatively high drug doses delivered with the modified soft drink bottle highlights the role that valves in spacers play in filtering out drug particles that otherwise may have been inhaled; however, dose delivered would be expected to decrease significantly in an unvalved device if pMDI actuation is followed by exhalation by a patient instead on inhalation. Breathing simulation was performed with the start of inhalation in synchrony with actuation of the pMDI, simulating a best case scenario for drug delivery.

The ten patients selected for testing in the latter part of the study were not randomly selected, but due to their ability to perform both tidal breathing and a single maximal breath. Hence, the selected group may have produced better results than those who were unable to perform a single maximal breath, but these would be the ones in whom this technique may be considered.

Different bronchodilators are available for use in acute asthma and a range of different inhaled steroids are available for asthma preventive therapy in preschool children. Salbutamol was used for *in vitro* testing in our study as salbutamol is a commonly used bronchodilator and the need for knowing the minimum number of breaths needed to effectively inhale medication from a spacer is perhaps greatest in busy hospital emergency departments, where multiple doses of bronchodilators are administered to acute asthmatics as frequently as every 20 minutes during severe acute asthma attacks.

When using pMDI-spacers in young children and infants, cooperation during administration is the most important determinant for efficient drug delivery [84]. Preschool children, who are known to have short attention spans, may be more likely to cooperate with spacer use if they are required to take fewer, rather than more breaths through spacer devices.

CONCLUSION

This study demonstrated that inhalation volumes and flows of young children using spacers are larger than expected, and therefore only a few tidal breaths are required for drug delivery. These results potentially could be applied in clinical practice by all clinicians treating young children who require inhaled medication.

4   CHAPTER FOUR: Clinical trial

4.1   Background

The efficacy of inhaled corticosteroids as asthma preventer medication in preschool children is recognised [276]. In many parts of the world, inhaled corticosteroids are almost exclusively administered to preschool children via pMDI-spacers. Effective delivery of medication to a patient is a basic requirement if drug efficacy is to be expected. For inhaled corticosteroids, spacer technique and adherence to prescribed medication are both important determinants of drug delivery. Spacer technique is often suboptimal in preschool children, and inhalation is a critically important part of spacer technique. Adherence to prescribed medication is also often suboptimal in preschool children. This study aims to examine the association between both spacer technique and adherence to prescribed inhaled corticosteroid therapy, and asthma control in preschool asthmatic children. The study also aims to examine whether an incentive spacer device, the Funhaler®, improves drug delivery, by improving spacer technique and/or adherence to prescribed medication.

The Funhaler's potential capacity to influence both spacer technique and adherence to prescribed medication in preschool children lies in the visual and auditory feedback provided by the spinning disk and whistle, located on the expiratory arm of the Funhaler®. As the incentive component of the Funhaler® is located on the expiratory arm, an effect on the user's expiration could be expected. A change in expiration could be considered to be associated with a change in the subsequent inhalation, thereby influencing drug delivery. As the nature of an incentive is to stimulate, the likelihood that the incentive on the expiratory arm of the Funhaler® would increase exhalation volume, followed by an increase in inhalation volume, and subsequent drug delivery, was thought to be a worthwhile hypothesis.

The audio-visual feedback provided by the Funhaler® could potentially also make the drug delivery process more agreeable to preschoolers. Improved agreeability of the drug delivery process could lead to reduced parent-child conflict during the drug delivery process. A reduction in parent-child conflict during the drug delivery process could

improve adherence to prescribed inhaled corticosteroids in preschool children. Therefore, the likelihood that use of the Funhaler® would improve adherence to prescribed inhaled treatment in preschool children, by positively influencing parent-child interaction during the drug delivery process, was also investigated.

The Funhaler® was chosen as an intervention because of its novel incentive properties, ease of implementation as an intervention, and potential to positively influence both spacer technique and adherence to medication. The Funhaler® currently is the only spacer device purposely designed for use in preschool children. No intervention with the aim of improving adherence to prescribed inhalation treatment has ever been specifically aimed at the preschool child. Interventions aimed at improving adherence to medication in preschool children are usually aimed at the children's parents, who are responsible for their children's medication administration.

The methods section below will describe a clinical trial where the Funhaler® was compared with the Aerochamber Plus®. The Aerochamber Plus® was chosen as a control because of its known acceptable drug delivery properties, widespread use; and most importantly, its *in vitro* equivalence to the Funhaler® in *in vitro* drug delivery. Differences in outcome could therefore be expected to relate to *in vivo* performance.

The study population used was preschool children in the community with 'doctor diagnosed asthma', who were being prescribed inhaled corticosteroids.. In the literature, the definition of asthma in the preschool age group has always been a contentious subject, with terms like wheezy bronchitis used interchangeably with asthma[277]. More recently, and after completion of the clinical trial described below, the European Respiratory Task Force on Preschool Wheeze has suggested that wheeze-syndromes in preschool aged children should be classified into episodic (viral) wheeze and multiple trigger wheeze[278]. However, the characterisation and classification of preschool wheeze syndromes and different asthma phenotypes in preschool children is still a contentious issue[279]. In Australia, preschool children with wheeze are usually labelled with "asthma" and treated with inhaled corticosteroids, when symptoms recur frequently and have appeared to respond to bronchodilators. The decision to study preschool children with 'doctor diagnosed asthma' who were being prescribed inhaled corticosteroids in the community, therefore, ensured that the study population was representative of a population in which spacer technique, and adherence to prescribed inhaled medication, was likely to be

important. Information was collected about atopy, as well as family history of atopy and asthma, and skin prick allergy testing was done, in order to better define the asthma "phenotypes" of the subjects studied.

Other factors being equal, proficiency in spacer technique would determine eventual inhaled mass, from a specific pMDI-spacer combination, to a subject. Total drug delivery to filter was used to quantify proficiency in spacer technique. Filter dose is not an accurate measure of drug delivery to a subject's airways, but is a more objective measure of spacer technique than previously-used measures of spacer technique i.e scoring by an observer the different steps of pMDI-spacer use by the subject [125, 126].

Adherence to prescribed inhaled corticosteroids was measured by electronic monitors that document the time and date that the pMDI was actuated. Subjects were not blinded to the fact that their adherence was being monitored. Analysis of the electronic adherence monitor data could not differentiate between medication administration and the contrived "dumping" of medication. However, electronic monitoring of adherence is accepted as the current "gold standard" for adherence monitoring.

Various measures of clinical outcome were used in the clinical trial. As discussed in chapter one, all clinical outcome measures have individual strengths and weaknesses, and a combination of different outcome measures would complement each other. In the clinical trial diary cards were used to measure asthma symptoms and reliever (bronchodilator) use. In addition to asthma symptoms, oral corticosteroids use as prescribed by doctors in the community, was also documented on diary cards and used as an indirect marker of asthma exacerbations. In order to include patient outcome measures that extend beyond traditional clinical measures, QoL measurements were made using the PedsQL version 3.0 asthma module. The PedsQL was used because it has been validated specifically for use in preschool children with asthma, and because of its brevity (beneficial when multiple parameters are being assessed at a single study visit). The PedsQL version 3.0 has been shown to demonstrate reliability, validity, and responsiveness in paediatric asthma [260].

Lung function testing was used as a secondary outcome measure. FOT was used in the clinical trial to measure lung function. FOT is suitable to perform on preschool children as only passive cooperation and no coordination is required. The proven capacity of FOT to

detect change when inhaled corticosteroids are used in young asthmatic children [224] made it particularly suitable for use in a study where potential changes to the delivery of inhaled corticosteroids was being studied.

4.2   Aims and Hypothesis

Aims:

- To investigate the effect of proficiency in spacer technique, as measured by drug inhaled onto a filter, on clinical outcome in preschool asthmatic children.

- To investigate the effect of adherence to prescribed inhaled asthma medication on clinical outcome in preschool asthmatic children.

- To investigate the influence of an incentive spacer device on proficiency in spacer technique, adherence to prescribed treatment, and clinical outcome in preschool asthmatic children.

Hypothesis:

- Proficiency in spacer technique correlates positively with improved clinical outcome in preschool children with asthma.

- Good adherence to prescribed medication regimens correlates positively with improved clinical outcome in preschool children with asthma.

- Use of an incentive spacer, the Funhaler®, improves proficiency in spacer technique and/or adherence to prescribed medication, and thereby improves clinical outcome in preschool children with asthma.

4.3　　　　　Methods

A randomised, controlled, prospective clinical trial was performed. The Funhaler® is a small volume spacer with a spinning disk and whistle on the expiratory arm [152, 153]. The function of the spinning disk and whistle combination is to act as an incentive for young children to cooperate when their inhaled asthma preventer medication is being administered. The Aerochamber Plus® is a standard small volume spacer. Subjects in the study group were given Funhalers® for delivery of daily asthma preventer medication. Subjects in the control group were given Aerochamber Plus® spacers for delivery of daily asthma preventer medication. The Funhaler® and the Aerochamber Plus® have similar *in vitro* drug delivery characteristics [280]. The rationale for the incentive assessment part of this study was therefore: Taking in to account any confounding variables, any difference in terms of drug delivery and adherence to prescribed medication could be ascribed to the incentive component of the Funhaler®.

4.3.1　　　　　Study participants

Preschool children in the community (two to six-years old) in whom asthma had been diagnosed by a doctor, and who were being prescribed inhaled steroids for treatment of their asthma, were eligible for inclusion in the study. Exclusion criteria were known or suspected immunodeficiency; other chronic lung diseases (such as bronchopulmonary dysplasia or cystic fibrosis); known allergy to study medication; and having been administered systemic steroids in the three months prior to enrolment. Ethics approval was obtained from the ethics committee of Princess Margaret Hospital for Children and the Telethon Institute for Child Health Research (933/EP), and from the ethics committee of the University of the Free State (ETOVS 67/07). Parents or guardians provided written informed consent. Children were recruited between May 2005 and October 2006 using local advertising, flyers and direct recruitment from the Emergency Department and clinics at Princess Margaret Hospital for Children.

Study power calculation:

To demonstrate a 20% difference between the study group and the control group, at 80% power, and a significance of 0.05, 160 subjects would be required.

4.3.2   Protocol

Subjects were seen at a screening visit, at a baseline visit and then followed up for a year. The study protocol is outlined in Table 9.

Screening visit: After subjects were checked for eligibility, eligible subjects who were on inhaled steroids other than fluticasone were changed over to equivalent doses of fluticasone. Subjects who were on combination medication (inhaled steroid and long acting beta stimulant) other than fluticasone-salmeterol were changed over to equivalent doses of a fluticasone-salmeterol combination. Subjects who were using spacers with face masks were instructed to use the mouthpiece of the spacer instead of using a facemask. Spacer technique was checked, and corrected if necessary. Background information was obtained by standardized questionnaire about symptoms of wheezing and coughing, personal and family history of atopy and asthma and smoking in the house.

Instruction on using spacers: At the screening visit, as well as every subsequent visit, each subject and their parents were shown an instruction video, demonstrating the correct procedure for using a spacer. The video included the following steps:

- Shake the pMDI and take off the cap.

- Insert pMDI correctly into spacer.

- Place mouthpiece of spacer into subject's mouth.

- Actuate pMDI.

- Let subject take five tidal breaths.

- Repeat the process if needed.

- Wash spacer in a mild dishwashing detergent every two weeks, do not rinse and leave spacer to drip-dry.

Run-in period: After the screening visit there was a month long run-in period. The run-in period was used to ensure that all subjects' asthma were stable after receiving instructions on technique, changing face mask to mouthpiece where needed, and after changing other inhaled steroids to fluticasone (Flixotide®, GlaxoSmithKline) where needed.   Stable

asthma was defined as having daytime symptoms less than twice a week, having night time symptoms once a month or less, and a history of not requiring oral steroids for the past three months. If a subject's asthma was unstable, the run-in period was extended and the medication dose adjusted if considered appropriate by the study doctor.

Randomisation: After the screening period, subjects were randomized into two groups: In the study group, the subjects' parents were given an incentive spacer (Funhaler®) to administer their children's asthma preventers. In the control group, the subject's parents were given an Aerochamber Plus®, to administer their children's asthma preventers. Randomisation was done independently by the pharmacy. Randomisation was done by block randomisation using blocks of ten.

Follow-up: After randomisation, patients were followed up at three monthly intervals for a year. At each visit inhalation technique was checked and corrected if necessary. At each visit, the dose of inhaled asthma preventer medication was reduced if the subject's asthma was controlled and the parents agreed to it. Asthma control was defined as having daytime asthma symptoms less than twice a week and night time awakenings less than once a month. At each visit, if the subject's asthma was not controlled, the dose of the study medication was increased, if appropriate. Doctors in the community were allowed to change the dose of preventer medication but study participants were instructed to notify the study coordinator if any change in medication dose was made. Study medication (fluticasone +/- salmeterol) was prescribed by the study doctor at each visit, dispensed to the study nurse by the pharmacy at Princess Margaret Hospital for Children, and handed out to the subjects' parents after the study visit.

Allergy testing: At the final study visit, skin prick testing was performed on all willing participants. Allergens tested were house dust mite, rye grass pollen, cat dander, and egg white. Skin prick testing was deemed positive if the wheal caused by the allergen was larger than the positive control, and larger than 3mm in diameter. A small number of parents refused skin prick testing on their child, on the grounds that their child had had skin prick allergy testing performed on them within the previous six months. These parents were asked whether the skin prick tests that had been performed were positive, and their answers were documented.

4.3.3   Outcome measures

<u>Asthma symptoms</u>

The primary outcome measure for the study was "event free days" as documented on a diary card, filled out by subjects' parents during the week before each follow-up visit. Symptoms were divided into night time symptoms, and daytime symptoms. Specific rows on the diary cards provided space to document "wheeze", "cough" and "other symptoms". Bronchodilator use was also recorded each day for a week before each study visit. Event free days were defined as days where no asthma symptoms were reported, and no rescue bronchodilator use was reported. The header on the diary cards read "Asthma symptoms 7 days prior to appointment".

A second diary card was used to record asthma exacerbations and days of systemic steroid use in the three month interval between follow-up visits. Used diary cards were collected and new diary cards were handed out at each study visit.

<u>Proficiency in spacer technique</u>

Filter studies are explained in detail in Part One of the methodology section. In brief, when using a pMDI-spacer, there are many patient-related factors that determine drug dose inhaled. A filter interposed between the patient and the spacer can be used to determine the total drug dose delivered to a subject, and is therefore an indirect measure of proficiency in spacer technique. The rationale for using filter dose as a measure of proficiency in spacer use, was that, controlling for other factors a subject's breathing pattern would be the major factor determining drug delivery from the pMDI- spacer. It was thought that, if the incentive device on the Funhaler® could influence breathing pattern, it could potentially influence drug delivery, and eventually clinical outcome. Thus, for this study proficiency in spacer technique was defined as the quantity of salbutamol inhaled onto a filter when using a pMDI-spacer.

Study subjects were asked to participate in a filter study at the baseline visit and at the three-, six-, and nine month follow-up visits. With each filter study parents were asked to

administer five separate puffs of salbutamol (Ventolin®, GlaxoSmithKline, Australia) to their child. Five 100μg puffs were required to ensure that sufficient drug for measurement would be deposited on each filter. Filter studies were performed before reviewing pMDI-spacer technique.

Adherence monitoring

Smartinhaler® (Nexux6, Auckland, New Zealand) [281] electronic monitoring devices were used to monitor adherence to prescribed medication. Smartinhaler® devices were handed out to all participants at the baseline visit. Smartinhaler® devices replace the original sleeve/ actuator of a pMDI. During the study the first canister of inhaled asthma preventer medication (that was dispensed at each visit) was fitted in a Smartinhaler® device. Study participants where instructed, when the pMDI canister needed replacement, to fit each new pMDI canister into the Smartinhaler® device. Adherence data from Smartinhaler® devices were uploaded at each follow-up visit. Subjects were not blinded to the fact that the Smartinhaler® was monitoring their adherence to prescribed medication.

Smartinhalers® record the date and time of every pMDI actuation. Specialized software, that accompanied the Smartinhalers® in order to upload information from Smartinhaler® devices, was used to input the number of medication doses prescribed. The software calculated the number of doses actuated as a fraction of doses prescribed for each period of the day before 12pm or after 12pm. Doses actuated before 12pm was considered to be morning doses. Doses actuated after 12pm was considered to be evening doses.

Subjects were only considered to be adherent for a specific dose if their pMDI was actuated the number of times that their fluticasone was prescribed e.g. if a subjects were prescribed two puffs twice a day, and only actuated their pMDI once in the morning, they were considered as non-adherent for their morning dose. Manually checking all the raw adherence data confirmed that, subjects very rarely actuated their pMDIs for only a fraction of the number of doses prescribed.

Subjects who actuated their pMDIs more than the prescribed number of times, in a morning or evening period, were considered to be adherent to the prescribed number of doses for that (morning or evening) dose. When more than eight doses were actuated within a few seconds from each other, the subjects were thought to be "dumping" doses. "Dumped"

doses were not considered as being administered in adherence to prescribed doses, and were excluded from all calculations.

In summary, adherence to each individual dose was determined by analysing Smartinhaler® data. Mean adherence between study visits was measured as the number of times that the whole prescribed dose was given expressed as a percentage of the total number of doses prescribed.

Quality of Life measurements

The PedsQL 3.0 Asthma Module® questionnaire for two to four year children was administered to subjects' parents, who served as proxy for their children. For five to seven year old children the PedsQL module had separate questionnaires for parents and children. While both parent and child questionnaires were administered, to remain as consistent as possible in obtaining QoL data between the two to four year old children and the five to seven year old children, only the parental questionnaires were analysed.

Lung function testing

At each study visit, lung function testing was performed on all participants who were willing. Although written consent for the study was obtained at the beginning of the study, verbal consent for FOT was obtained at each study visit from both parents and study subjects.

Lung function testing was performed by FOT. Rrs and Xrs were derived from the Zrs that was measured at different frequencies. Commercially available equipment (I2M, Chess Medical, Belgium) that was built on the specifications by Landser et al [282], in accordance with European Respiratory Society guidelines [283], was used. The forced oscillation signal was a pseudorandom signal consisting of frequency components between four and 48 Hz. The measurement period of the pseudorandom signal was eight seconds.

Measurements were made with the patient sitting in the upright position and his/her cheeks supported by an investigator. Nose clips were used during measurements. In the few cases where the patients refused to wear a nose clip, one of the patient's parents occluded the patient's nose with their fingers. Suregard® (Bird Healthcare, Australia) filters were

interposed between the patients and the measuring equipment for infection control purposes. Three or more measurements were performed until the standard deviation of Rrs8 was less than 10%. After the initial measurements, 600µg of salbutamol (Ventolin®, GlaxoSmithKline) was administered with the spacer to which each subject was randomised. Measurements were repeated 15 minutes after the initial measurements. Baseline (pre-bronchodilator) lung function was reported as Z-scores, calculated as per the formula derived by Hall et al [251]. Bronchodilator response was reported as percentage change, relative to baseline measurements. Subjects who had been administered a short acting β-stimulant within four hours before the measurements, and subjects who had been administered a long acting β-stimulant within twelve hours before the measurements, were excluded from this analysis.

Screening visit	Baseline visit*	Three month visit	Six month visit	Nine month visit	Twelve month visit#

-Exclusion criteria
 	
-Symptom questionnaire
 	
-Clinical examination
 	
-FOT
 	
-Inhaled steroid changed to fluticasone
 	
-All subjects instructed on use mouthpiece of spacer
	Diary cards
	    Asthma symptoms week before visit
	    Preventer medication use since previous visit
	    Systemic steroid use since previous visit
	Quality of life questionnaire
	Electronic adherence monitor (Smartinhaler) download
	Filter study on study participants (all visits except for the twelve month visit)
	FOT
	Breathing patterns while using pMDI-spacers recorded by flow-chamber, as per Part One of thesis (all visits except for the twelve month visit)
	    Asthma preventer medication provided				

	*Randomise				#Skin prick testing

Table 9. Outline of protocol for clinical trial

<u>Statistical analysis</u>

Statistical analysis was performed using SPSS version 15.0. Paired samples were compared using the Wilcoxon Signed Ranks Test. Unpaired samples were compared using the Mann-Whitney U test. Where the data were normally distributed, unpaired samples were compared using the Students t-test. Linear regression was used to correlate data.

Generalized estimating equations (GEEs) were used to analyse repeated measures, when basic statistics indicated that a more detailed analysis may be of benefit to clarify results.

4.4 Results

4.4.1 Demographics

Two hundred and twenty eight children were screened for eligibility. Ninety six children were excluded: 47 did not meet the inclusion criteria, and 49 either actively or passively refused to participate. One hundred and thirty two subjects were included in the study. Recruitment was discontinued at 132 subjects, when it became clear during an interim analysis, that there would be no significant difference in the main outcome marker, event free days (see Appendix for declaration by statistician). The male: female ratio of subjects included in the study was 8:5 (Table 10).

	Funhaler group	Aerochamber Plus group	Total
Male	42	40	82
Female	23	27	50
Total	65	67	132

Table 10. Number of subjects randomised.

Subjects in the Funhaler and Aerochamber Plus groups were comparable in terms of age characteristics and exposure to tobacco smoke, as per parental report (Table 11). Due to an oversight, one subject was randomized on his seventh birthday.

	Funhaler®	Aerochamber Plus®	p
Age in months Median (range)	51 (24-84)	51 (25-83)	0.94
Smokers living in home n (%)	11 (17)	15 (22)	0.29
Mother smokes N (%)	5 (8)	9 (13)	0.40

Table 11. Age and cigarette smoke exposure.

Comparable numbers of subjects were randomised per year group in the Funhaler and in the Aerochamber Plus groups. Overall, subjects were not evenly distributed by age, with the three- and four-year olds better represented than other year groups (Table 12).

Age in years	Frequency (%)		
	Funhaler	Aerochamber Plus	Both groups
2	10	10	20 (15)
3	18	19	37 (28)
4	16	16	32 (24)
5	10	10	20 (15)
6*	11	12	23 (17)
Total	65	67	132 (100)

* Single subject randomised on 7th birthday included in this group

Table 12. Distribution of subjects per year group.

4.4.2   Atopy

More subjects in the Funhaler group had a positive skin prick test compared with subjects in the Aerochamber Plus group, but the difference between the groups was not significant. Subjects in the Funhaler group, specifically male subjects, were more likely to have had eczema diagnosed by a doctor ($p = 0.01$, and $p = 0.02$ for all subjects, and for males, respectively) (Table 13).

		Total	Funhaler	Aerochamber Plus	p-value Chi sq (2-sided)
Skin prick test positive (or parental report of recent positive skin prick test)		31 (34%)	18 (43%)	13 (27%)	0.12
Skin prick test positive in study		23 (28%)	14 (37%)	9 (20%)	0.14
Doctor diagnosed eczema	All subjects	73 (55%)	43 (66%)	30 (45%)	0.01*
	Male	46 (56%)	28 (67%)	18 (45%)	0.02*
	Female	27 (54%)	15 (65%)	12 (44%)	0.39
1st degree relative with atopy		116 (88%)	60 (92%)	56 (84%)	0.06

Table 13. Comparison of groups in terms of atopy.

4.4.3 Study drop-outs

Over the one-year follow-up period, 21 subjects (16%) dropped out of the study: Six subjects were lost to follow-up, four moved away from the study centre, five cited time constraints, four lost interest, one cited parental illness and one cited not liking the spacer allocated for the study. One hundred and eleven patients (84%) completed the study. Table 14.

	Funhaler group	Aerochamber Plus group	Total
Lost to follow-up (or repeatedly did not attend scheduled visits)	5	1	6
Moved away from study area	1	3	4
Time constraints	5	0	5
Parental illness	1	0	1
Not liking holding chamber allocated	1	0	1
Lost interest	4	0	4

Table 14. Reasons for subjects not completing the study.

Subjects in the Funhaler group were more likely to drop out of the study (Figure 21). The majority of subjects who discontinued taking part in the study did so between the three month and the nine month visits. The difference between drop-out numbers between the Funhaler and the Aerochamber Plus groups became significant by the six month visit (p=0.04). By the final visit seventeen (26%) subjects randomised to the Funhaler group versus four (six percent) in the Aerochamber Plus group had dropped out of the study (p < 0.01). No specific reason was recorded for the higher drop-out rate in the Funhaler group, except for one subject, who cited not liking the Funhaler, as the reason for dropping out.
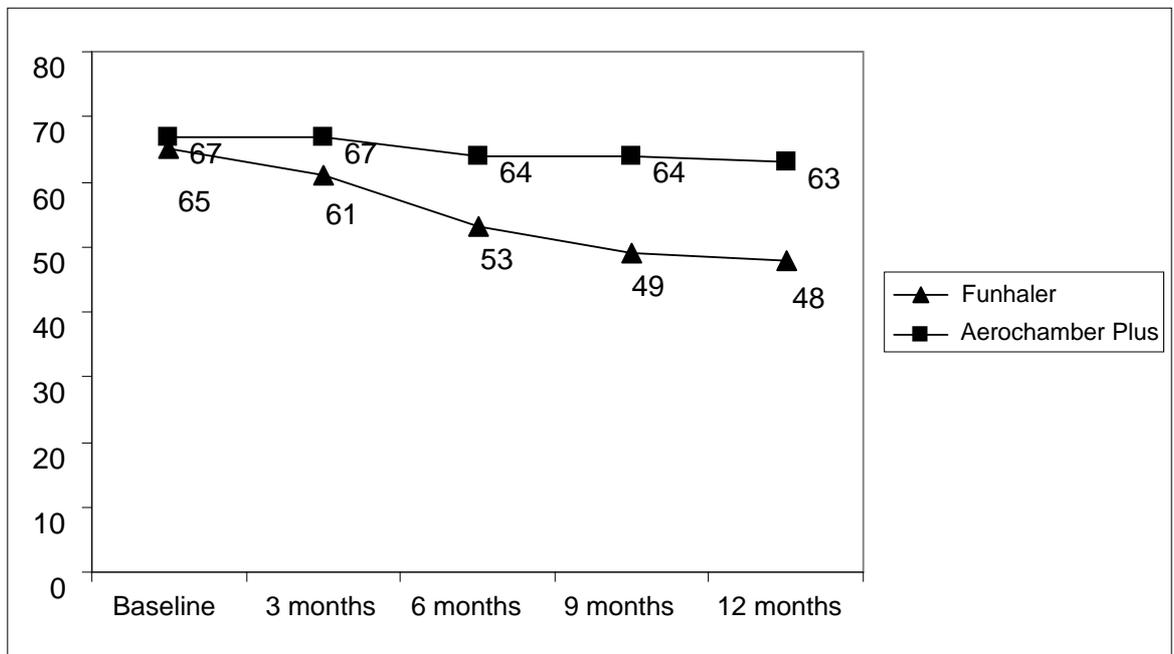
Figure 21. Number of subjects attending specific study visits.

4.4.4 Drug dose prescribed

A number of subjects were weaned off their inhaled steroids during the course of the study. There was no significant difference in fluticasone dose prescribed between the Funhaler group and the Aerochamber Plus group (Table 15).

	Funhaler	Aerochamber Plus	P (Chi square)
	N (%)	N (%)	
0-3 months	65 (100)	67 (100)	1
3 - 6 months	56 (92)	59 (88)	0.57
6 – 9 months	44 (83)	49 (77)	0.49
9 – 12 months	33 (67)	45 (70)	1

Table 15. Subjects being prescribed fluticasone during the clinical trial. Numbers in brackets indicate the percentage of subjects still taking part in the clinical trial, who were still being prescribed fluticasone.

The mean fluticasone dose prescribed gradually decreased during the course of the clinical trial (Figure 22).
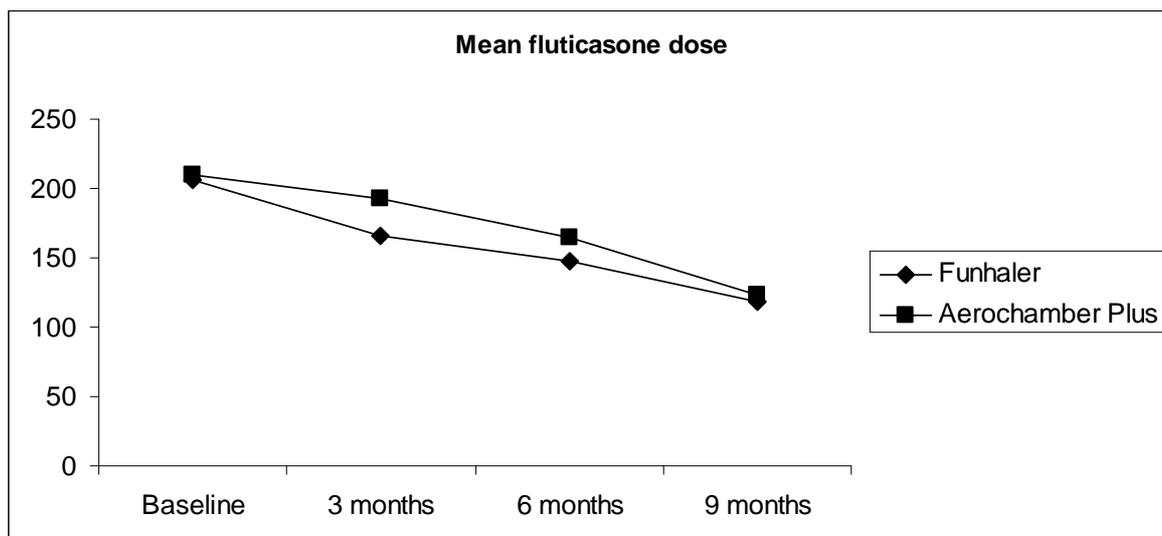
Figure 22. Mean daily fluticasone dose in microgram (y-axis) prescribed at each study visit (x-axis).

At no point in the clinical trial was there a significant difference between the Funhaler and the Aerochamber groups in terms of fluticasone dose prescribed. (Table 16).

	Funhaler Median (range)	Aerochamber Median (range)	p
Baseline	200 (50-500)	200 (50-500)	0.85
3 months	100 (0-500)	200 (0-500)	0.17
6 months	100 (0-500)	100 (0-500)	0.60
9 months	100 (0-500)	100 (0-500)	0.84

Table 16. Fluticasone dose (μg) prescribed at each study visit.

A large number of subjects were prescribed salmeterol during the study: Fifty (37.9%) at the baseline visit, decreasing to 44 (33.3%) at the final visit. There was no significant difference between the Funhaler group and the Aerochamber Plus group in terms of salmeterol dose prescribed. (Table 17).

Number (%) of subjects receiving salmeterol.			
	Funhaler (n=65)	Aerochamber Plus (n=67)	All subjects (n=132)	Chi sq (2-sided)
Baseline	24 (36.9)	27 (40.3)	51 (38.6)	0.69
3 months	21 (32.3)	23 (34.3)	44 (33.3)	0.99
6 months	23 (35.4)	25 (37.3)	48 (36.4)	0.64
9 months	18 (27.7)	25 (37.3)	43 (32.6)	0.80

Table 17. Number of subjects on salmeterol after study visits.

4.4.5   Outcomes

The baseline visit will be discussed first. Thereafter results will be discussed in the order that the hypotheses were presented. The relation between factors that influence aerosol drug delivery (i.e. proficiency in spacer technique and adherence to prescribed medication) and clinical outcome will be presented, followed by the influence of the Funhaler on the above factors. Finally the influence of the Funhaler on clinical outcome will be discussed.

4.4.6   Baseline visit

There were significant differences between the Funhaler group and the Aerochamber Plus group at the baseline visit. As the differences at baseline influenced the data analysis, the baseline visit will first be discussed separately.

4.4.6.1   Baseline visit: Proficiency in spacer technique as measured by drug delivered to filter

There was no significant difference between the Funhaler group and the Aerochamber groups in terms of proficiency in spacer technique, as determined by filter dose, at the baseline study visit.

4.4.6.2   Baseline visit: Adherence to medication

There was no significant difference in adherence between the Funhaler group and the Aerochamber Plus group at the baseline study visit.

4.4.6.3   Baseline visit: Symptom free days

The Funhaler group reported significantly less days without wheeze ($p = 0.02$), and significantly less bronchodilator free days ($p = 0.03$) than the Aerochamber Plus group in the seven days before the baseline visit. When stratified for gender, males in the Funhaler group continued to report significantly less days without wheeze ($p = 0.01$) than the Aerochamber Plus group. (Table 18).

		Baseline visit		
		Funhaler	**Aerochamber Plus**	**p**
		Mean (95%CI)	**Mean (95%CI)**	
Event free days		6.41 (6.07-6.76)	6.66 (6.41-6.90)	0.54
Wheeze free days	**All subjects**	5.92 (5.44-6.39)	6.49 (6.16-6.83)	0.02*
	Male	6.05 (5.51 – 6.59)	6.78 (6.55 – 7.00)	0.01*
	Female	5.70 (4.75 – 6.64)	6.07 (5.31 – 6.83)	0.49
Cough free days		4.98 (4.39-5.58)	5.43 (4.89-5.97)	0.15
Bronchodilator free days		5.63 (5.12 - 6.15)	6.28 (5.91 - 6.66)	0.03*

Table 18. Baseline visit only. Symptom free days as reported by diary card for the week before each study visit.

4.4.6.4   Baseline visit: Quality of life

Quality of life scores, as determined by PedsQL version 3 (asthma module), were significantly different at the baseline visit; with the Funhaler group scoring lower (lower score suggests lower QoL) than the Aerochamber group at the time of randomisation.   The respective quality of life scores (mean (95%CI)) at the baseline visit for the Funhaler group and the Aerochamber Plus groups were 2047 (1967-2126) and 2157 (2083-2231) (p=0.05) respectively. The lower QoL scores in the Funhaler group was consistent with the fewer wheeze free days, and fewer bronchodilator free days reported by the Funhaler group at the time.

4.4.6.5   Baseline visit: Lung function

There was no significant difference (p > 0.05, t-test) between the Funhaler group and the Aerochamber Plus group in terms of bronchodilator response, or baseline lung function, at Rrs8, or Xrs8.

4.4.7 **All visits: Overall proficiency in spacer technique as measured by drug delivered to filter**

Throughout the clinical trial, there was large inter-subject variation in proficiency in spacer technique, as measured by drug dose deposited on filter (Figure 23). Mean drug dose recovered from filters ranged from zero to 136μg (as the mean of five 100μg doses). Accepting ten percent variability in the nominal dose emitted from the pMDI, and a ten percent margin of error in measurements, could not explain the two measurements above 120μg. The two measurements above 120μg were therefore considered to be faulty measurements.
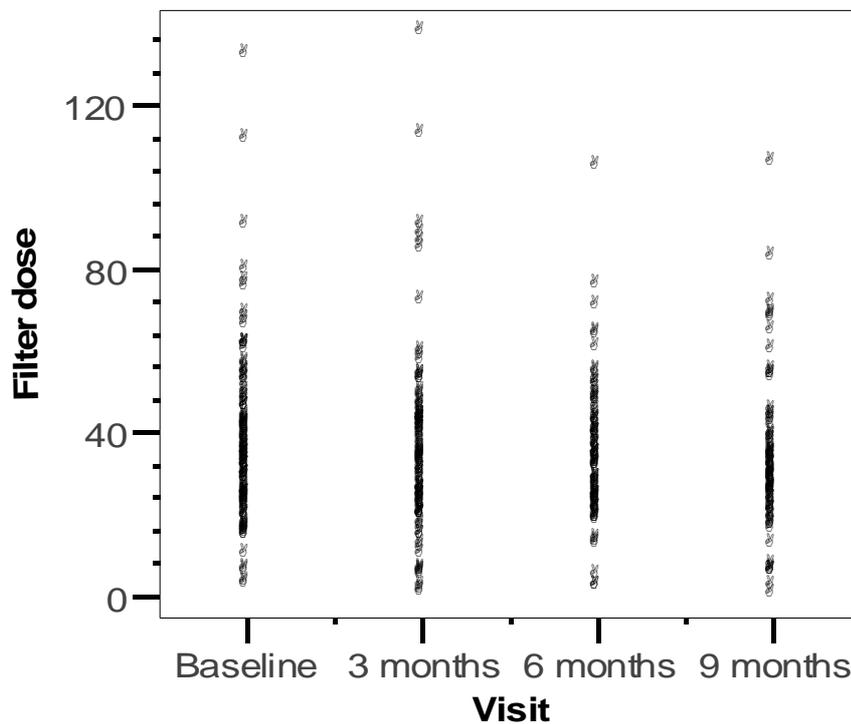
Figure 23. Scatter plot illustrating proficiency in spacer technique, as measured by drug dose deposited on a filter. Filter studies were performed on all willing subjects at the first four study visits. Filter dose is given as salbutamol collected on filter, in micrograms (average of five 100μg doses).

The mean filter dose (per five 100μg puffs, divided by five) recovered at each visit remained in the mid- to low 30's (Table 19). Overall, there was no significant change in mean filter dose ($p > 0.05$ (paired sample t-tests)) from one visit to the next, or between the

first study visit, and the last study visit. Intra-subject variation in filter dose from one visit to the next was large.

Visit	n	Mean (95CI) salbutamol dose recovered from filter
Baseline	125	36.6 (33.2 - 40.1)
3 months	110	35.3 (31.3 - 39.4)
6 months	90	34.2 (30.8 - 37.5)
9 months	85	32.4 (28.6 - 36.3)

Table 19. Salbutamol dose inhaled on filter by subject at study visits. Filter dose in microgram (mean of five 100μg doses).

4.4.8 Correlation between proficiency in using delivery device and QoL

Proficiency in using delivery device, as measured by drug dose deposited on a filter interposed between subject and spacer, correlated positively with quality at life at the three month study visit (correlation coefficient = 0.19, p = 0.05) (Table 20). There was no significant correlation between filter dose and quality of life at the other study visits. When stratifying by age (subjects < 4 years at randomisation), there was no significant correlation, at any of the study visits, between proficiency in using delivery device, and quality of life. When stratifying by gender, there was no significant correlation, at any of the study visits, between proficiency in using delivery device, and quality of life.

		Quality of life score (PedsQL version 3, asthma module)			
		Baseline	3 months	6 months	9 months
Proficiency in using delivery device (filter dose)	Correlation Coefficient	0.10	0.19	0.11	0.04
	Sig. (2-tailed)	0.25	0.05*	0.30	0.75
	N	121	109	88	84

Table 20. Correlation between proficiency in using delivery device, as measured by drug dose deposited on a filter interposed between subject and spacer, and quality of life at the corresponding visit.

With GEE analysis there was no correlation between proficiency in using the delivery device and QoL (p > 0.05), even after correcting for age, gender, adherence to prescribed medication, and QoL at the baseline visit.

4.4.9 Correlation between proficiency in using delivery device, and other measures of clinical outcome

There was no correlation between proficiency in using the delivery device (filter dose), and symptom control as determined by diary card, in the week running up to each study visit. (Table 21). There was no correlation between proficiency in using the delivery device (filter dose), and the number of days where oral steroids were used (prescribed in the community and documented by parents on diary cards) to control asthma symptoms.

After stratifying subjects by age (year groups) there was still no correlation between proficiency in spacer technique and asthma symptoms. When stratified by gender, there was no correlation between proficiency in using the delivery device (filter dose) and asthma symptoms, except at the six month visit, where, in female subjects filter dose correlated significantly with wheeze free days (correlation coefficient = 0.37, p = 0.02).

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		Proficiency in using the delivery device (filter dose)			
		Baseline	3 months	6 months	9 months
Number of days no wheeze	Correlation Coefficient	0.03	0.09	0.15	-0.06
	Sig. (2-tailed)	0.78	0.36	0.18	0.57
	N	121	105	87	81
Number of days no cough	Correlation Coefficient	< 0.01	-0.10	0.07	-0.09
	Sig. (2-tailed)	0.98	0.30	0.55	0.45
	N	121	105	86	81
Bronchodilator free days	Correlation Coefficient	0.03	0.02	-0.05	-0.04
	Sig. (2-tailed)	0.75	0.82	0.64	0.7
	N	123	108	90	84
Event free days	Correlation Coefficient	0.09	-0.01	0.06	-0.14
	Sig. (2-tailed)	0.33	0.96	0.59	0.2
	N	121	108	90	84

Table 21. Correlation between proficiency in spacer technique, as measured by drug dose deposited on a filter interposed between subject and spacer, and symptom free days in week before study visit, as determined by diary card.

GEE analysis confirmed that there was no significant correlation ($p > 0.05$) between proficiency in using the delivery device and markers of asthma control. Correcting for age, gender, and adherence to prescribed medication did not influence the results.

In order to examine whether very poor spacer technique resulted in poor clinical outcome, poor spacer technique was arbitrarily defined at a filter dose lower than 20µg. Only 20 subjects had filter doses lower than 20µg (out of a possible 100µg) at the baseline visit. As the low numbers prevented statistical comparison, subjects with filter doses lower than 25µg were analysed. There were 37 subjects who had filter doses lower than 25µg at the baseline visit. When subjects with filter doses ≤ 25µg, at the baseline visit were compared with the rest of the subjects, there was no significant difference ($p > 0.05$) between the groups in terms of any clinical outcome measure.

4.4.10   Role of incentive device in influencing proficiency in spacer technique

Using GEE analysis, after correcting for age and gender, the Funhaler group had significantly higher proficiency in spacer technique as determined by filter dose ($p = 0.05$). The improved proficiency in spacer technique in the Funhaler group was limited to subjects who were younger than 4 years of age at the baseline visit ($p < 0.01$). Subjects in the Funhaler group who were four years and older at the baseline visit did not show improved spacer technique over the Aerochamber Plus group ($p = 0.87$).

When analyzed visit-by-visit, drug delivery to filter in subjects who were younger than four years of age at randomization, was significantly higher in the Funhaler group, at the three month and the nine month visits ($p = 0.01$ and 0.01, respectively (t-test)) (Table 22 and Figure 24). For older children, drug delivery was not significantly higher in the Funhaler group.

	Funhaler		Aerochamber Plus		
	n	mean (95CI)	n	mean(95CI)	P (t-test)
Baseline	24	34 (29 - 39)	28	34 (25 - 43)	0.99
3 months	24	36 (29 - 43)	26	24 (19 - 30)	0.01*
6 months	17	32 (24 - 40)	19	29 (22 - 36)	0.57
9 months	16	42 (2 - 56)	21	24 (17 - 31)	0.01*

Table 22. Subjects younger than four years at baseline visit. Comparison between Funhaler and Aerochamber Plus, in terms of filter studies performed at separate study visits. Filter dose in microgram (mean of five doses).
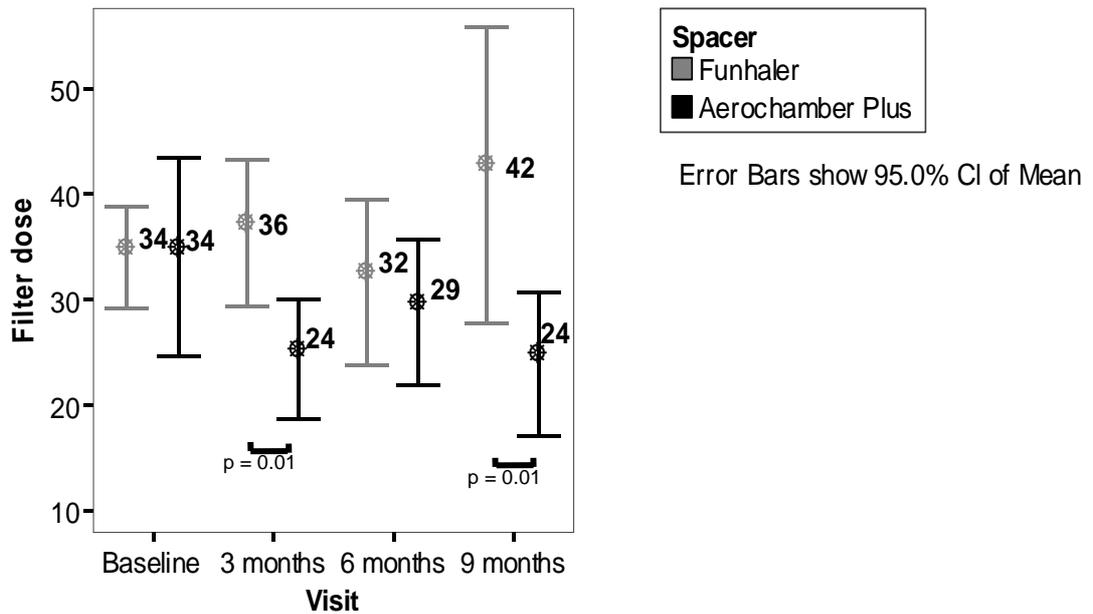
Figure 24. Subjects younger than four years at baseline visit. Error bars comparing Funhaler and Aerochamber Plus, in terms of filter dose collected at separate study visits. Mean filter doses indicated as values in figure.

As seen in figure 25, throughout the study, there were significantly more subjects in the Aerochamber Plus group who demonstrated poor spacer technique (filter doses lower than 20μg) at the baseline visit, and at the three month visit (p = 0.01; Chi-sq for both visits).
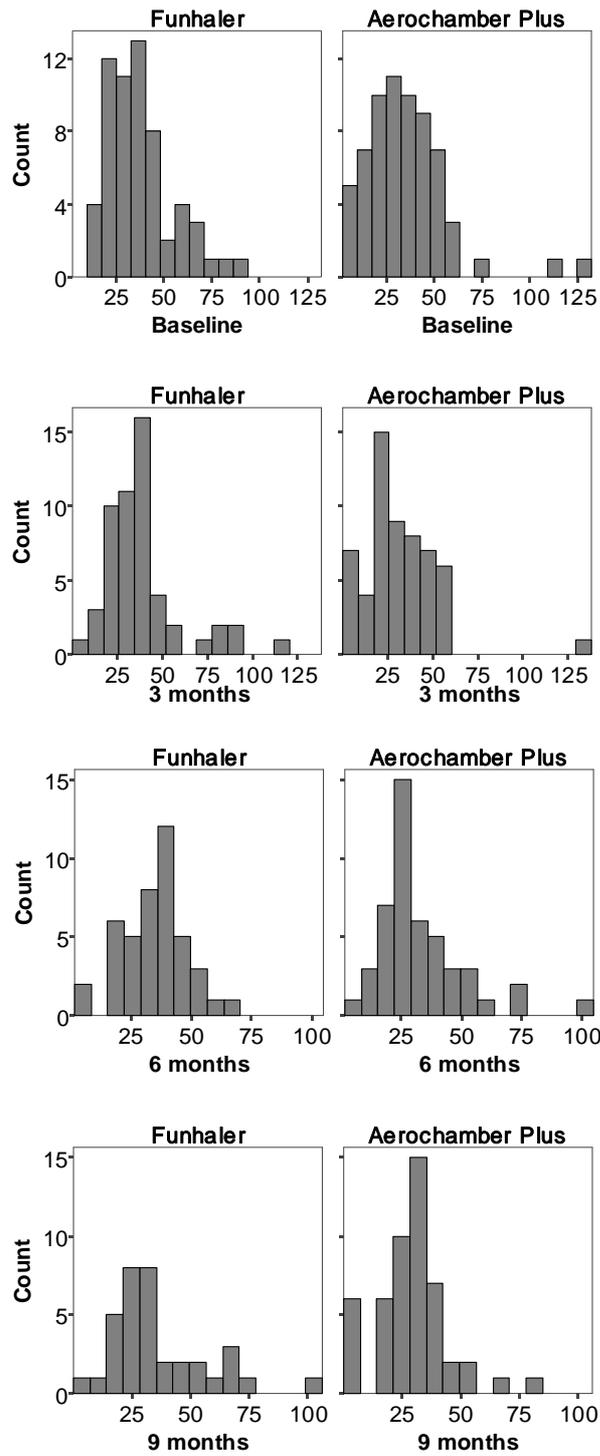
Figure 25. Histogram plotting the number of subjects (Y-axis) grouped by filter dose collected (X-axis) at various study visits. Funhaler group was compared with Aerochamber Plus group.

4.4.11 Adherence to prescribed medication

Electronic adherence data were recovered on 80% of subjects during the first three months of the study. Recovery of adherence data decreased to 65% for the final three months of the study. As seen in Table 23, data recovery was similar for the Funhaler and the Aerochamber Plus groups. Reasons cited by parents for not bringing back the electronic adherence monitoring devices (or bringing back damaged devices) were as follows: Lost device, forgot to bring device to study visit, did not know the device was not water proof, device was stolen. A small number of devices (+/- 10%) failed during the study period. A number of parents admitted that they at times failed to insert new pMDI canisters into the Smartinhaler® monitoring device, when the old pMDI canisters needed replacement.

	Funhaler	Aerochamber Plus	All subjects
	N (%)	N (%)	N (%)
0 – 3 months	47 (77)	56 (84)	103 (80)
3 – 6 months	44 (83)	52 (81)	96 (82)
6 – 9 months	34 (69)	42 (66)	76 (67)
9 – 12 months	31 (65)	41 (65)	72 (65)

Table 23. Electronic adherence data recovery.

Inter subject variability in adherence to prescribed medication was marked throughout the study. Adherence to prescribed medication ranged from 1% to 99% (Figure 26). The median adherence dropped significantly ($p < 0.01$; Kendalls W) over the course of the study. Median (range) adherence was 68.5% (14.0 – 99.0), 60.6% (1.0 – 99.0), 60.0% (0.5 – 99.5%) and 50.4% (0-100) for each respective three month period.
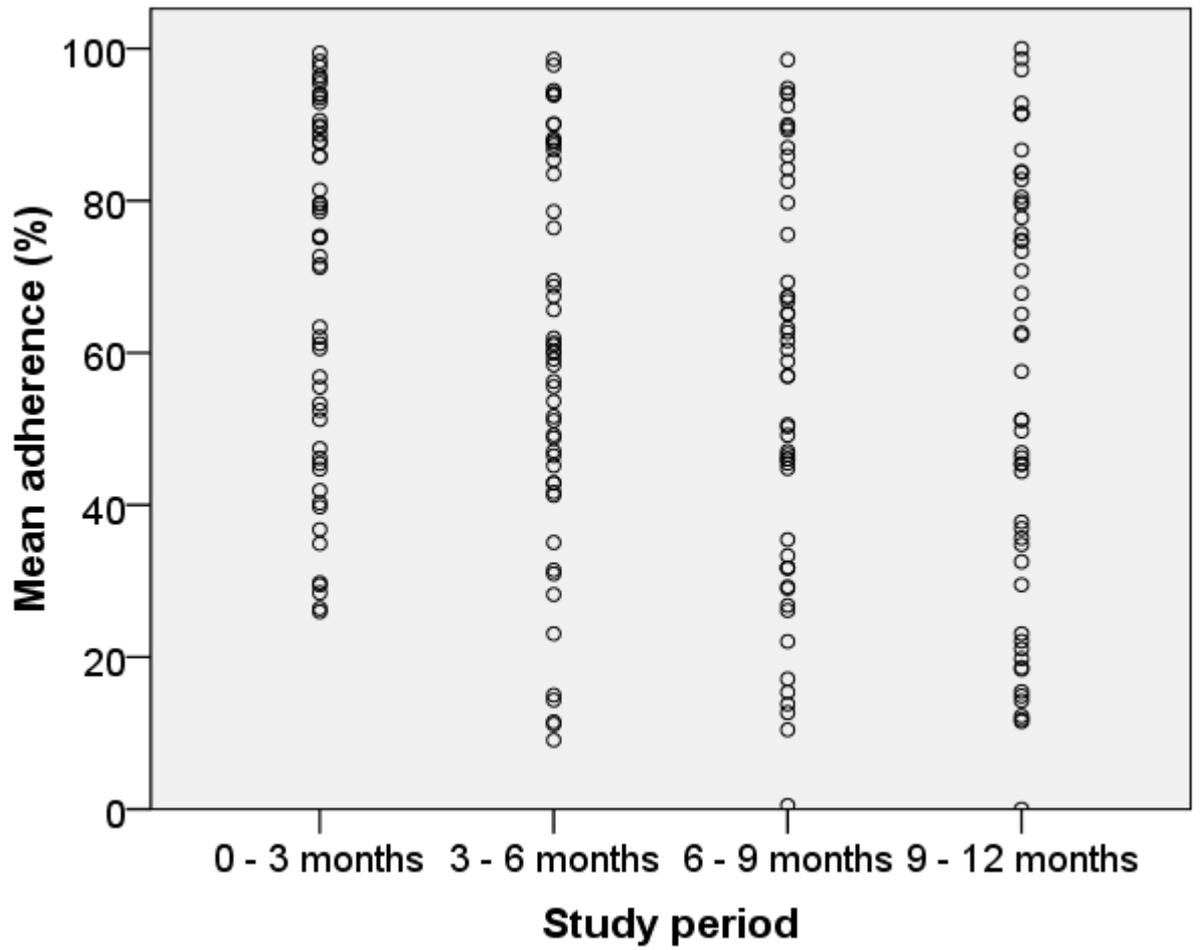
Figure 26. Scatter plot illustrating mean adherence to prescribed medication, for each subject, over the year long study period.

4.4.12   Correlation between adherence to prescribed treatment and QoL.

Using GEE analysis, after correcting for age and gender, adherence to prescribed medication throughout the study period correlated with QoL at the baseline visit (p = 0.03). Adherence did not correlate with QoL throughout the rest of the study (p = 0.32).

4.4.13   Correlation between adherence to prescribed treatment and other markers of clinical outcome.

GEE analysis revealed a significant correlation between adherence to prescribed medication and bronchodilator free days (r = 0.01; p = 0.02) throughout the study. After correcting for age, gender, proficiency in spacer technique, and bronchodilator free days at baseline, the significant correlation between adherence to prescribed medication and bronchodilator free days remained (r = 0.01; p = 0.01).

Furthermore, there was a significant correlation between adherence to prescribed medication and number of symptom free days (p < 0.05), at various points, and for different variables in the study: At the baseline visit, there was a significant correlation (r = 0.35; p < 0.01) between adherence and days without wheeze. There was no significant correlation between adherence and days without wheeze at any other point during the study (Table 24). With GEE, however, there was no significant correlation between adherence and days without wheeze throughout the study. Results were not influenced by correcting for age, gender, proficiency in spacer technique, or wheeze at the baseline visit.

At each individual study visit, there was no significant correlation between adherence to prescribed medication and the number of days without cough, bronchodilator free days and event free days in the week before each visit.

		Adherence to prescribed medication			
		0 - 3 months	3 - 6 months	6 - 9 months	9 - 12 months
Number of days no wheeze	Correlation Coefficient	0.35	0.05	0.08	0.16
	Sig. (2-tailed)	< 0.01*	0.62	0.50	0.19
	N	101	93	74	66
Number of days no cough	Correlation Coefficient	0.11	0.19	0.16	0.16
	Sig. (2-tailed)	0.11	0.06	0.18	0.21
	N	101	92	74	67
Number of bronchodilator free days	Correlation Coefficient	0.18	0.16	0.22	0.12
	Sig. (2-tailed)	0.07	0.13	0.06	0.30
	N	103	96	76	71
Event free days	Correlation Coefficient	0.19	0.10	0.14	0.01
	Sig. (2-tailed)	0.05	0.32	0.24	0.91
	N	103	96	76	71

Table 24. All subjects: Correlation between asthma symptoms (diary card for the week before each study visit) and electronically monitored adherence over the three month period in between study visits.

Day and night-time symptoms analysed separately:

When daytime and night time symptoms were examined separately, there was a significant positive correlation between the number of nights without wheeze and adherence to prescribed treatment in the first three months of the clinical trial (Table 25).   The correlation between nights without wheezing and adherence remained during the three to six month, and nine to twelve month parts of the study, but was not significant for the six to nine months part of the study period. With GEE analysis there was a significant correlation between adherence to prescribed medication and nights without wheeze, throughout the study period (r = 0.01; p = 0.01).   The correlation between adherence to prescribed medication and nights without wheeze remained after correcting for age, gender, proficiency in spacer technique, and the number of nights without wheeze at the baseline

visit (r = 0.01; p < 0.01). GEE analysis also revealed a significant correlation between adherence to prescribed treatment and (daytime) days without wheeze (r = 0.01; p = 0.01). The correlation ceased to be significant after correcting for age, gender, proficiency in spacer technique, and (daytime) days without wheeze at the time of the baseline visit.

		Adherence to prescribed medication			
		0 - 3 months	3 - 6 months	6 - 9 months	9 - 12 months
Number of days no wheeze	Correlation Coefficient	0.34	0.13	0.13	0.22
	Sig. (2-tailed)	< 0.01*	0.22	0.28	0.07
	N	103	96	76	71
Number of nights no wheeze	Correlation Coefficient	0.20	0.26	0.16	0.30
	Sig. (2-tailed)	0.04*	0.01*	0.18	0.01*
	N	103	96	76	71
Number of days no cough	Correlation Coefficient	0.14	0.142	0.092	0.03
	Sig. (2-tailed)	0.16	0.17	0.43	0.83
	N	103	96	76	71
Number of nights no cough	Correlation Coefficient	0.20	0.15	0.10	0.01
	Sig. (2-tailed)	0.05*	0.14	0.39	0.96
	N	103	96	76	71

Table 25. All subjects: Correlation between asthma symptoms (day time and night time symptoms separated) and electronically monitored adherence over the three month period in between study visits.

When stratified by age (subjects younger than four years at randomisation), the only significant correlation between adherence and asthma symptoms were found at the three month visit, where adherence correlated positively with wheeze free days (correlation coefficient = 0.44, p = 0.01). When stratified by gender, there was a significant correlation, in male subjects, between adherence and cough free nights at three months, as well as a significant correlation between adherence and wheeze free nights at six months (Table 26).

In females, there was a significant correlation between adherence and wheeze free days, wheeze free nights-, and cough free days at the three month visit (Table 27).

		Adherence to prescribed medication			
		0 - 3 months	3 - 6 months	6 - 9 months	9 - 12 months
Number of days no wheeze	Correlation Coefficient	0.20	0.08	0.07	0.20
	Sig. (2-tailed)	0.12	0.55	0.78	0.20
	N	60	60	18	44
Number of nights no wheeze	Correlation Coefficient	0.06	0.27	0.07	0.20
	Sig. (2-tailed)	0.63	0.04*	0.78	0.19
	N	60	60	18	44
Number of days no cough	Correlation Coefficient	0.19	0.09	0.05	-0.15
	Sig. (2-tailed)	0.14	0.50	0.83	0.33
	N	60	60	18	44
Number of nights no cough	Correlation Coefficient	0.27	0.09	-0.12	-0.17
	Sig. (2-tailed)	0.04*	0.50	0.63	0.28
	N	60	60	18	44

Table 26. Male subjects: Correlation between asthma symptoms (diary card for the week before each study visit) and electronically monitored adherence over the three month period in between study visits.

		Adherence to prescribed medication			
		0 - 3 months	3 - 6 months	6 - 9 months	9 - 12 months
Number of days no wheeze	Correlation Coefficient	0.50	0.26	-0.08	0.25
	Sig. (2-tailed)	< 0.01*	0.13	0.78	0.20
	N	43	36	14	27
Number of nights no wheeze	Correlation Coefficient	0.33	0.23	-0.11	0.43
	Sig. (2-tailed)	0.03*	0.18	0.70	0.03
	N	43	36	14	27
Number of days no cough	Correlation Coefficient	0.07*	0.25	0.19	0.33
	Sig. (2-tailed)	0.67	0.13	0.50	0.09
	N	43	36	14	27
Number of nights no cough	Correlation Coefficient	0.11	0.35	0.19	0.28
	Sig. (2-tailed)	0.50	0.04	0.52	0.16
	N	43	36	14	27

Table 27. Female subjects: Correlation between asthma symptoms (diary card for the week before each study visit) and electronically monitored adherence over the three month period in between study visits.

When the Funhaler and Aerochamber Plus groups were analysed separately, adherence correlated more markedly with symptom control in the Funhaler group, with a significant correlation extending to days without cough (Table 28). In the Aerochamber Plus group, adherence to prescribed treatment correlated only with wheeze free days in the first three months of the study (Table 29).

		Adherence to prescribed medication			
		0 - 3 months	**3 - 6 months**	**6 - 9 months**	**9 - 12 months**
Number of days no wheeze	Correlation Coefficient	0.38	0.29	0.25	0.30
	Sig. (2-tailed)	0.01*	0.06	0.16	0.11
	N	47	44	34	30
Number of nights no wheeze	Correlation Coefficient	0.30	0.36	0.14	0.40
	Sig. (2-tailed)	0.04*	0.02*	0.42	0.03*
	N	47	44	34	30
Number of days no cough	Correlation Coefficient	0.39	0.12	0.23	-0.02
	Sig. (2-tailed)	0.01*	0.43	0.20	0.92
	N	47	44	34	30
Number of nights no cough	Correlation Coefficient	0.35	0.17	0.07	0.03
	Sig. (2-tailed)	0.02*	0.27	0.70	0.90
	N	47	44	34	30

Table 28. Funhaler group: Correlation between asthma symptoms (diary card week before study visit) and electronically monitored adherence over the three month period in between study visits.

		Adherence to prescribed medication			
		0 - 3 months	3 - 6 months	6 - 9 months	9 - 12 months
Number of days no wheeze	Correlation Coefficient	0.33	-0.09	-0.01	0.14
	Sig. (2-tailed)	0.02*	0.55	0.94	0.38
	N	56	52	42	41
Number of nights no wheeze	Correlation Coefficient	0.13	0.07	0.15	0.21
	Sig. (2-tailed)	0.33	0.62	0.34	0.19
	N	56	52	42	41
Number of days no cough	Correlation Coefficient	-0.03	0.11	-0.01	0.04
	Sig. (2-tailed)	0.81	0.42	0.95	0.80
	N	56	52	42	41
Number of nights no cough	Correlation Coefficient	0.10	0.06	0.11	< 0.01
	Sig. (2-tailed)	0.49	0.67	0.48	1.00
	N	56	52	42	41

Table 29. Aerochamber Plus group: Correlation between asthma symptoms (diary card week before study visit) and electronically monitored adherence over the three month period in between study visits.

At no point in the study was there any significant correlation between adherence to medication and event free days, or days on systemic corticosteroids. Stratification in terms of age, gender, or spacer group did not influence the results.

4.4.14 Role of incentive device in influencing adherence to prescribed medication

There was no significant difference in adherence between the Funhaler group and the Aerochamber Plus group for any three month period during the clinical trial (Figure 27).
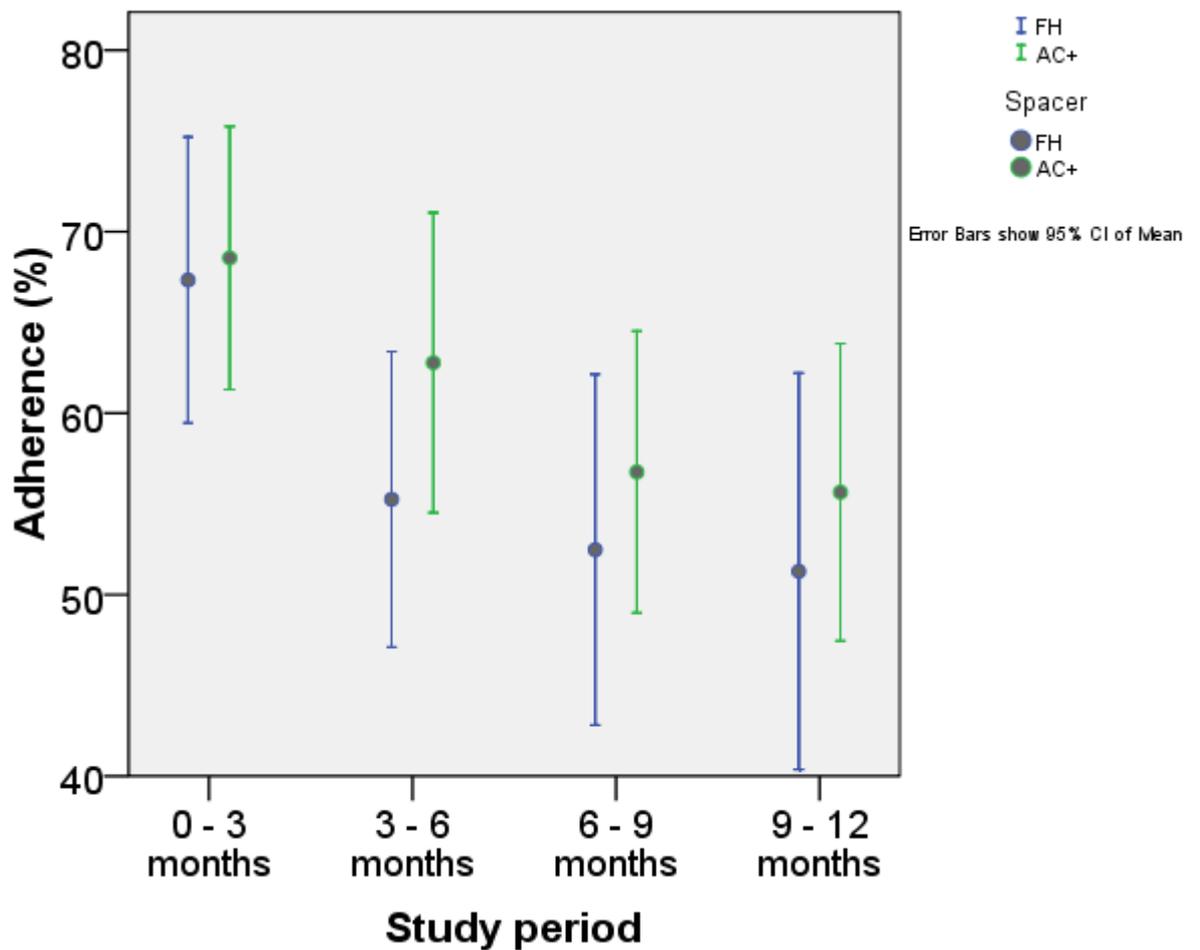
Figure 27.   Error bars comparing the mean (95CI) adherence between the Funhaler and the Aerochamber Plus groups.

Using GEE analysis, there was no significant difference in adherence to prescribed medication between the Funhaler group and the Aerochamber Plus group (p = 0.93). Correcting for age and gender did not influence the results.

When stratified for gender, females in the Aerochamber Plus group demonstrated higher adherence than females in the Funhaler group (Table 30).   However, with GEE analysis there was no significant difference in adherence in females between the Funhaler group and the Aerochamber Plus group.

Visit	Funhaler	Aerochamber Plus	p
	median (range)	median (range)	
3 months	67.3 (26.0 – 98.0)	63.8 (15 – 97)	0.77
6 months	53.8 (11.0 – 94.0)	68.8 (11.0 – 97.0)	0.04*
9 months	47.2 (0.5 – 94.2)	61.1 (15.4 – 94.8)	0.25
12 months	43.8 (0.0 – 91.4)	56.0 (11.5 – 92.8)	0.25

Table 30. Female subjects only: Mean adherence to prescribed dose of asthma preventers, during the three months leading up to study visits.

4.4.15   Role of incentive device in influencing clinical outcome.

As mentioned before, the Funhaler group and the Aerochamber Plus group were not equal at the time of randomisation (baseline visit) in terms of clinical outcome measures:

Asthma symptoms.

The Funhaler group reported significantly less days without wheeze ($p = 0.02$), and significantly less bronchodilator free days ($p = 0.03$) than the Aerochamber Plus group in the seven days before the baseline visit (Tables 31 and 33).

After the baseline visit, the only significant difference in symptoms between the Aerochamber group and the Funhaler group was at the six month study visit. At the six month visit, the Funhaler group reported significantly less cough free days ($p = 0.03$; Mann Whitney U) (Table 32).

	Wheeze free days		
	Funhaler	Aerochamber Plus	p
	Mean (95%CI)	Mean (95%CI)	
Baseline	5.92 (5.44-6.39)	6.49 (6.16-6.83)	0.02*
3 month visit	6.46 (6.05-6.86)	6.55 (6.22-6.89)	0.97
6 month visit	6.31 (5.91-6.72)	6.32 (5.89-6.75)	0.93
9 month visit	6.19 (5.68-6.69)	6.25 (5.78-6.72)	0.73
12 month visit	6.26 (5.76-6.76)	6.09 (5.54-6.64)	0.93

Table 31. Wheeze free days as reported by diary card for the week before each study visit.

	Cough free days		
	Funhaler	Aerochamber Plus	p
	Mean (95%CI)	Mean (95%CI)	
Baseline	4.89 (4.39-5.58)	5.43 (4.89-5.97)	0.15
3 month visit	5.44 (4.81-6.07)	5.85 (5.31-6.38)	0.32
6 month visit	4.79 (3.98-5.60)	6.07 (5.57-6.56)	0.03*
9 month visit	5.79 (5.18-6.41)	5.05 (4.37-5.73)	0.13
12 month visit	6.07 (5.50-6.63)	5.29 (4.63-5.94)	0.11

Table 32. Cough free days as reported by diary card for the week before each study visit.

	Bronchodilator free days		
	Funhaler	**Aerochamber Plus**	**p**
	Mean (95%CI)	**Mean (95%CI)**	
Baseline	5.63 (5.12 - 6.15)	6.28 (5.91 - 6.66)	0.03*
3 month visit	6.08 (5.59 - 6.57)	5.95 (5.44 - 6.47)	0.90
6 month visit	5.83 (5.26 - 6.40)	6.20 (5.73 - 6.68)	0.17
9 month visit	6.25 (5.79 - 6.71)	5.81 (5.24 - 6.38)	0.67
12 month visit	6.17 (5.69 - 6.65)	6.10 (5.65 - 6.54)	0.99

Table 33. Bronchodilator free days as reported by diary card for the week before each study visit.

GEE analysis did not reveal any significant difference between the Funhaler group and the Aerochamber Plus group in terms of wheeze, cough, or bronchodilator use (p > 0.05). Correcting for age, gender and symptoms at the baseline visit did not influence the results.

Number of days where oral steroids were used.

At no point in the study, was there a significant difference between the Funhaler group and the Aerochamber Plus group, in terms of the number of days where oral steroids were used, as documented by parents on a separate diary card. Stratifying by age and gender did not reveal any significant difference between groups.

Asthma exacerbations.

Parents were requested to document the number of days in between study visits, where subjects experienced asthma exacerbations. As the parents were never given a definition of asthma exacerbations, the documentation was found to be too subjective to analyse.

Quality of life.

Quality of life scores, as determined by PedsQL version 3 (asthma module), were significantly different at the baseline visit; with the Funhaler group scoring lower than the Aerochamber group at the time of randomisation (Table 34). Quality of life scores were therefore reported relative to the baseline visit scores (Table 35). There was no significant difference between the Funhaler group and the Aerochamber Pus group, at any stage of the clinical trial, in terms of in quality of life relative to baseline. Stratifying by age (subjects younger than four years, as well as year groups) and gender did not make any significant difference to the results.

	Quality of life scores				
	Funhaler		**Aerochamber Plus**		**p**
	n	**Mean (95%CI)**	**n**	**Mean (95%CI)**	
Baseline	61	2047 (1967-2126)	67	2157 (2083-2231)	0.05*
3 month visit	60	2190 (2105-2275)	67	2231 (2146-2316)	0.5
6 month visit	50	2268 (2167-2370)	64	2395 (2329-2461)	0.03*
9 month visit	48	2340 ((2253-2426)	62	2365 (2289-2440)	0.66
12 month visit	38	2372 (2280-2464)	51	2388 (2280-2464)	0.81

Table 34. Quality of life scores, as determined by PedsQL version 3 (asthma module), completed by parents at every study visit.

	Quality of life scores relative to baseline scores				
	Funhaler		Aerochamber Plus		p
	n	Mean (95%CI)	n	Mean (95%CI)	
3 month visit	58	138 (57 – 217)	67	74 (-9 – 157)	0.31
6 month visit	48	188 (78 – 297)	64	238 (160 – 315)	0.40
9 month visit	46	310 (209 – 410)	62	215 (133 – 296)	0.18
12 month visit	36	313 (187 – 439)	51	257 (166 – 348)	0.79

Table 35. Relative quality of life scores, as determined by PedsQL version 3 (asthma module), completed by parents at every study visit. Quality of life scores reported relative to scores at baseline.

Using GEE analysis, and correcting for age, gender, and quality of life at the baseline visit, there was still no significant difference in quality of life between the Funhaler group and the Aerochamber Plus group (p = 0.42).

4.4.16 Lung function

Lung function studies (forced oscillation technique) were attempted on all willing study subjects, at all study visits. Acceptable lung function data (Table 36) were obtained in the majority of older subjects. Success in obtaining acceptable lung function data in the younger subjects was limited by movement artefacts, and the subjects' willingness to co-operate for a sufficient period of time. At all study visits, a number of subjects had to be excluded due to administration of long acting β-agonists within twelve hours before the study visits.

		Baseline	3 months	6 months	9 months	12 months
Groups		N (%)	N (%)	N (%)	N (%)	N (%)
2 years		2 (10.0)	3 (15.0)	4 (20.0)	6 (30.0)	5 (25.0)
3 years		13 (35.1)	17 (45.9)	21 (56.8)	19 (51.4)	23 (62.2)
4 years		17 (53.1)	20 (62.5)	19 (59.4)	14 (43.8)	20 (62.5)
5 years		14 (70.0)	15 (75.0)	16 (80.0)	15 (75.0)	13 (65.0)
6 years		16 (72.7)	17 (77.3)	10 (45.5)	15 (68.2)	12 (54.5)
All age groups	**FH**	28 (43.1)	31 (47.7)	27 (41.5)	31 (47.7)	29 (44.6)
	AC+	34 (50.7)	42 (62.7)	44 (65.7)	39 (58.2)	45 (67.2)
	Total	62 (47.0)	73 (55.1)	71 (53.8)	70 (53.0)	74 (56.1)

Table 36. Number of subjects per age group, and per study- and control group, on whom lung function testing was successfully performed. Subjects who were administered long acting beta stimulants less than 12 hours before the study visit were not included. Only subjects with pre- and post bronchodilator measurements shown. FH = Funhaler, AC+ = Aerochamber Plus.

Subjects' baseline (pre-bronchodilator) resistance at eight Hertz were slightly higher than the population mean (mean z-scores per study visit ranging from 0.47 to 0.60). Subjects' baseline reactance at eight Hertz was slightly higher than the population mean (mean z-scores for Xrs8 ranging from 0.06 to 0.22). Lung function results for all visits are presented in tables 37 and 38.

	Baseline	3 months	6 months	9 months	12 months
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Rrs8	0.57 (0.30, 0.84)	0.53 (0.28, 0.78)	0.47 (0.18, 0.76)	0.56 (0.35, 0.76)	0.60 (0.40, 0.80)
Xrs8	0.14 (-0.13, -0.40)	0.22 (-0.01, 0.05)	0.22 (-0.04, 0.47)	0.06 (-0.18, 0.30)	0.09 (-0.15, 0.34)

Table 37. Z-scores of pre-bronchodilator (baseline) lung function of all subjects.

	Baseline	3 months	6 months	9 months	12 months
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Rrs8	-12.3 (-8.1, -16.4)	-13.5 (-10.1, -16.9)	-13.3 (-10.4, -16.1)	-12.5 (-9.5, -15.6)	-13.3 (-10.3, -16.3)
Xrs8	19.1 (9.6, 28.7)	20.9 (13.2, 28.6)	24.4 (17.7, 31.0)	28.5 (22.8, 34.3)	27.1 (19.5, 34.8)

Table 38. Bronchodilator response in all subjects, given as percentage change relative to baseline lung function.

4.4.16.1   Correlation between lung function and drug delivery/ proficiency in spacer technique.

Filter dose and bronchodilator response at the corresponding study visit.

As bronchodilator response was used as a marker of clinical outcome, and the magnitude of bronchodilator response could potentially have been influenced by the subjects' proficiency in inhaling the bronchodilator (and thus bronchodilator dose inhaled), the possibility of a

correlation between proficiency in inhaling salbutamol (filter dose, as used throughout the study) and bronchodilator response, was not investigated.

Baseline lung function and filter dose.

There was no significant correlation between filter dose (as described earlier) and baseline (pre-bronchodilator) lung function, at any of the study visits. With GEE analysis there was no significant correlation between filter dose and baseline (pre-bronchodilator) lung function ($p > 0.05$) throughout the study. Correcting for age, gender, adherence to prescribed medication, and lung function measured the beginning to the study, did not significantly influence the results.

4.4.16.2 Correlation between adherence to prescribed medication and lung function.

Using GEE analysis, there was no significant correlation between Rrs8, or Xrs8 and adherence to prescribed medication ($p = 0.09$ and $p = 0.08$, respectively). After correcting for age and gender, lung function at the baseline visit, and proficiency in spacer technique (filter dose), there was still no significant correlation between Rrs8 or Xrs8 and adherence to prescribed medication ($p = 0.08$ and $p = 0.14$, respectively).

4.4.17 Influence of the Funhaler on lung function

There was no significant difference ($p > 0.05$, t-test) between the Funhaler group and the Aerochamber Plus group in terms of bronchodilator response, or baseline lung function, at Rrs8, or Xrs8 (Tables 39 and 40). In subjects younger than four years of age at time of randomisation, there was no significant difference ($p > 0.05$) between the Funhaler group and the Aerochamber Plus group, in terms of baseline lung function or bronchodilator response. There were too few data to stratify subjects per year of age.

	Group	Baseline	3 months	6 months	9 months	12 months
		Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Rrs8	FH	-12.0 (-5.6, -18.4)	15.3 (9.7, 20.8)	14.0 (9.2, 18.7)	14.0 (8.7, 19.3)	12.4 (7.0, 17.0)
	AC+	-12.4 (-6.6, -18.4)	-12.1 (-7.7, -16.5)	-12.8 (-9.1, -16.6)	-11.4 (-7.7, -15.1)	-13.9 (-10.2,-17.7)
Xrs8	FH	20.9 (8.6, 33.2)	19.4 (8.3, 30.6)	26.5 (14.6, 38.3)	31.7 (22.8, 40.5)	21.8 (6.4, 37.3)
	AC+	17.6 (2.9, 32.3)	21.9 (11.0, 32.8)	23.1 (14.9, 31.3)	26.0 (18.2, 33.8)	30.5 (22.4, 38.6)

Table 39. Comparison of bronchodilator response in Funhaler (FH) versus Aerochamber Plus (AC+) groups. Bronchodilator response presented as percentage change relative to baseline lung function. No significant difference ($p > 0.05$) between groups at any study visit.

	Group	Baseline	3 months	6 months	9 months	12 months
		Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Rrs8	FH	0.85 (0.42, 1.27)	0.65 (0.24, 1.06)	0.53 (-0.11, 1.18)	0.79 (0.37, 1.22)	0.80 (0.40, 1.21)
	AC+	0.30 (-0.03, 0.63)	0.44 (0.12, 0.75)	0.43 (0.15, 0.71)	0.38 (0.20, 0.55)	0.48 (0.28, 0.68)
Xrs8	FH	0.013 (-0.41, 0.44)	0.26 (-0.11, 0.64)	0.15 (-0.32, 0.62)	-0.11 (-0.55, -0.32)	0.11 (-0.54, 0.56)
	AC+	0.26 (-0.08, 0.60)	0.19 (-0.12, 0.50)	0.26 (-0.06, 0.57)	0.19 (-0.08, 0.46)	0.14 (-0.10, 0.38)

Table 40. Comparison of pre-bronchodilator (baseline) lung function in Funhaler (FH) versus Aerochamber Plus (AC+) groups. Data presented as Z-scores.

Using GEE analysis, there was no significant difference in Rrs8 or Xrs8 between the Funhaler group and the Aerochamber Plus group (p = 0.09 and 0.46 respectively). After correcting for lung function at the baseline visit, as well as for age and gender, there was still no significant difference in Rrs8 or Xrs8 between the Funhaler group and the Aerochamber Plus group (p = 0.84 for both Rrs8 and Xrs8).

4.5   Discussion

4.5.1   Summary of main findings

4.5.1.1   Proficiency in spacer technique

<u>Proficiency in spacer technique versus clinical outcome</u>

The clinical trial results suggested that proficiency in spacer technique did not translate to improved clinical outcomes. Results were likely to have been influenced by various factors, including large variations in prescribed medication dose, carry over effect of being involved in a study and limitations in the study design (discussed below, under "Limitations of study").

<u>Role of incentive device in influencing proficiency in spacer technique</u>

Subjects younger than four years of age in the Funhaler group demonstrated a higher proficiency in spacer technique, than subjects younger than four years of age in the Aerochamber Plus group. The improved spacer technique, in children younger than four years of age who were using the Funhaler®, was not unexpected. It is intuitive that very young children would be more likely to be influenced by the simple incentive utilized by the Funhaler (spinning disk and whistle).

There were a greater number of subjects with poor spacer technique in the Aerochamber Plus group. Use of the Funhaler® therefore appeared to specifically improve drug delivery in those subjects who, with a conventional spacer, would have inhaled very low doses of medication. However, cross-over study would be more suited to prove the above.

The hypothesis that the Funhaler may improve spacer technique in preschool children was therefore shown to be partially correct: The Funhaler had a positive influence on spacer technique in children younger than four years of age, and on a group of children who would have had very poor spacer technique had they used a conventional spacer. The Funhaler®, therefore, should be considered for use in children younger than four years of age, and in older children where poor spacer technique is suspected.

As mentioned above, incentive devices are widely used to influence breathing during lung function measurements, but to the author's knowledge this is the first study to demonstrate a positive influence of an incentive device on spacer technique.

<u>Overall proficiency in spacer technique</u>

There was large intra-subject variation in proficiency in spacer technique, as measured by filter dose. The large variation in proficiency in spacer technique which results in a large variation in inhalation drug delivery to preschool children highlights the importance of pursuing ways to improve inhalation drug delivery to preschool children, in order to reduce the variability in prescribed medication that eventually reaches patients.

4.5.1.2   **Adherence to prescribed medication**

<u>Correlation between adherence and clinical outcome.</u>
Throughout the clinical trial, there were significant positive correlations between adherence to prescribed treatment and measures of asthma control (notably bronchodilator free days, and nights without wheeze) in some analyses. The hypothesis that adherence to prescribed medication regimens correlates positively with improved clinical outcome in preschool children with asthma, was therefore proved correct. The correlation between adherence and clinical outcome was not unexpected, as a similar correlation was demonstrated in older children [162, 163].

Decreasing numbers in diary cards returned (130 at baseline decreased to 109 at the final visit), and decreasing adherence data (103 at three months decreased to 72 at twelve months) may have influenced the results towards the end of the study, causing a reduction in the number of outcome measures that correlated with adherence as the study progressed.

An unexpected finding was that adherence to prescribed medication is influenced by QoL: Adherence to prescribed medication throughout the study period correlated with QoL at the baseline visit. Adherence did not correlate with QoL throughout the rest of the study. One could therefore conclude that adherence was influenced by baseline QoL, and not *vice-versa*. Bearing in mind that in young children, adherence to prescribed treatment is caregiver dependant; if QoL in young children is associated with improved adherence to prescribed treatment, then it follows that either the child's behaviour influences the

caregiver's adherence, or that overall higher QoL in the family unit is related to improved adherence.

Barlett et al (2004) demonstrated that maternal depression is linked to poor adherence [284]. Our results indirectly support the concept mentioned by Barlett that identifying and addressing poor psychological adjustment in mothers/families may facilitate medication adherence in paediatric asthmatic patients. Further research into the link between QoL and adherence to prescribed medication may be warranted.

Role of incentive device in influencing adherence to prescribed medication

There was no significant difference in adherence between the Funhaler group and the Aerochamber Plus group throughout the clinical trial. The hypothesis, that the Funhaler would improve adherence to prescribed inhaled medication in preschool children, could not be supported.

Overall adherence during clinical trial

There was a very large range in mean adherence to prescribed medication (1% to 99%). The results were in keeping with previous studies where adherence was monitored in preschool children [154, 159-161]. This study was larger, over a longer period of time and with more objective measurements than previous studies investigating adherence to inhaled medication in preschool aged children. Until now, the longest that adherence to inhaled medication was monitored electronically in preschool children was 50 days [159]. The year long time frame of our clinical trial, allowed for the "study effect" to wear off. Hence, mean adherence therefore gradually dropped during the course of the study. Mean adherence was 66% for the first three months, and decreased to 52% for the final three months of the study. The decrease in adherence could be ascribed to regression to the mean, or to a natural decrease adherence rates as a factor of time.

In spite of parents of subjects being motivated enough to attend five study visits over a thirteen month period, and being aware that their adherence was being monitored, the mean adherence of subjects was low, in keeping with previous studies of adherence to inhaled medication in preschool children [154, 159-161], outlined in Table 2, section 1.8.1.

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4.5.1.3   Role of incentive device in influencing clinical outcome.

The study group and the control group were not equal at the time of randomisation (baseline visit) in terms of clinical outcome measures. At the baseline visit the Funhaler group reported significantly fewer days without wheeze, significantly fewer bronchodilator free days, and scored lower on QoL than the Aerochamber Plus group. Statistical analysis therefore had to correct for differences between the Funhaler group and the Aerochamber Plus groups in terms of baseline symptoms. Correction of differences at the baseline visit in terms of the more pronounced symptoms and lower QoL in the Funaler group at the baseline visit could potentially have masked significant improvements in the Funhaler group later on in the study. Different methods were used for QoL and for other markers of clinical outcome, to correct for the inequality at the beginning of the study, between the study group and the control group. After correction for the difference at baseline, there was no significant difference between the Funhaler group and the Aerochamber group in any of the clinical outcome measures.

The hypothesis, that use of an incentive spacer, the Funhaler, improves clinical outcome in preschool children with asthma, could therefore not be supported.

4.5.1.4   Influence of the Funhaler on lung function

There was no significant difference between the Funhaler group and the Aerochamber Plus group in terms of bronchodilator response, or baseline lung function. Stratifying for age, and analysing only the atopic subjects, did not influence the results. The FOT data could therefore not demonstrate a difference between groups in any aspect of the study.

4.5.2   Limitations of study

4.5.2.1   Asthma diagnosis

Subjects were diagnosed with asthma by doctors in the community. The diagnosis of asthma was therefore not standardised. Asthma severity in the study population varied, ranging from subjects who required inhaled steroids throughout the study, to subjects who were successfully weaned off all asthma medication after three months. The large number of subjects who were successfully weaned off their asthma preventer medications suggests

that a significant number of subjects may not have had asthma at all, or may have been overtreated at the commencement of the study.

It is well recognised that asthma can be difficult to diagnose in young children. The latest trend is to not diagnose asthma in preschool children, but to classify preschool wheeze into episodic viral wheeze and multiple trigger wheeze[278]. However, the better part of our study population had frequent wheezing episodes and a predisposition towards atopy, and therefore represent a relatively homogenous population of atopic preschool wheezers consistent with asthma.

4.5.2.2 Differences between study group and control group.

In spite of randomisation, the Funhaler group differed significantly from the Aerochamber group in terms of the following:

- Increased asthma symptoms at the time of randomisation
- Lower quality of life at the time of randomisation
- Higher drop-out rate.
- Higher atopy /doctor diagnosed eczema

As clinical outcome was an important aspect of the study, the difference in symptomatology at the start of the study made the comparison of the two groups difficult. In the analysis, corrections were made for atopy, and the differences in clinical outcome measures at the start of the study, but it is not possible to know to what extent the abovementioned differences may have still influenced the results.

4.5.2.3 Filter dose as a measure of proficiency in spacer technique

Total drug delivery to filter was used as a marker of spacer technique. Rapid inhalation, which is associated with increased drug deposition in the upper airway, and decreased drug delivery to the lower airways, could potentially have resulted in improved drug delivery to filter. Total drug delivery to filter is therefore an imperfect measure of proficiency in spacer technique. However, the strength of using total drug delivery to filter as a measure of proficiency in spacer technique lies in its ability to quantify the result of a complex set of patient-device interactions. Other measures of proficiency in spacer technique, like

documenting a subject's expertise in performing a set of steps of spacer use, relies on subjective observation, and the cumulative effect that various degrees of missteps would have on drug delivery would be virtually impossible to quantify.

In the clinical trial, where filter dose was used as a measure of proficiency in spacer technique, the rationale was that, if a subject inhaled his/her asthma preventer effectively in the months before the study visit, the subject may have improved asthma control.

As filter dose only represents total drug delivery to the mouth, and not respirable dose, it is a relatively blunt instrument in determining drug delivery to the airways. Breathing pattern is an important component of spacer technique. Differences in breathing pattern may have influenced the respirable fraction of drug delivery. Differences in respirable fraction would not have been picked up by filter studies. It is possible that a stronger correlation between spacer technique and measures of asthma control could have been demonstrated if a more precise measure of drug delivery to the airways was used.

4.5.2.4   Variation in prescribed dose of asthma preventers

Subjects were not prescribed a homogenous fluticasone dose at the start of the study, but were prescribed the fluticasone dose that they were being prescribed in the community (or equivalent fluticasone dose, if they were being prescribed different corticosteroid formulations in the community). During the course of the clinical trial, the fluticasone dose prescribed was increased and decreased according to asthma symptoms. If parents were not comfortable with their child's medication being decreased, a subject's medication would remain the same. Doctors in the community also could make changes to their patients' fluticasone dose, as long as the study co-ordinator was notified. Subjects with poor spacer technique were not necessarily prescribed higher doses of inhaled fluticasone.

The variation in dose of prescribed fluticasone from subject to subject, and from visit to visit, made data interpretation challenging. The large inter-subject variation in drug delivery and adherence to medication may have had a mitigating effect on the difference in prescribed medication, thereby weakening most the outcome measures of the study.

Control of symptoms in run-in period

A weakness in the study design was the requirement for subjects to have "stable" asthma at the baseline study visit. Subjects who were experiencing regular asthma symptoms were not randomised, but had their run-in period extended. As a result of the above requirement, subjects had little room for improvement in symptoms after being randomised. Subjects who were experiencing more frequent asthma symptoms may have been more "responsive" to any intervention. Reducing the fluticasone dose during the run-in period until symptoms occurred, before randomising subjects, could theoretically have improved the study design, but would have been extremely time consuming and laborious without guaranteed benefit.

4.5.2.5   Subjects on long acting β-stimulants

A significant number of subjects were prescribed salmeterol during the study. Salmeterol has been shown to improve asthma control in adults and children older than 4 years of age [285], but published literature about salmeterol use in two to six year old asthmatic children is scarce. It is possible that salmeterol use during the study may have influenced results i.e. suppression of asthma symptoms may have influenced the correlations between asthma symptoms and various parameters. Salmeterol use was unlikely to have biased comparisons between the Funhaler and the Aerochamber Plus group, as salmeterol use was similar between groups.

4.5.2.6   Inadequate measures of clinical outcome

Asthma symptoms were reported by parents, on diary cards, for the week before every study visit. The short duration of symptom recording before every visit limited the sensitivity of the outcome measures. It is therefore possible that differences in clinical outcome, between the study group and the control group, could have been missed. The only measures that parents were asked to constantly report throughout the clinical trial, were "days with asthma exacerbations", and "days of oral steroid use". During the course of the study, it was realised that "days with asthma exacerbations" would have limited use, as the concept was never defined, and never explained to the subjects' parents. Although "days of oral steroid use" was recorded, as an indirect marker of asthma exacerbations, there was never any correlation between "days of oral steroid use" and other relevant variables during the study. Also, there was at no point during the study any significant difference in "days of oral steroid use" between the study group and the control group.

4.5.2.7   Study effect

The possibility that proficiency in spacer technique, and/or adherence to prescribed treatment, may have improved in all subjects as a direct result of participating in a clinical trial, cannot be excluded. Subjects were motivated enough to attend several study visits over a course of a year. Subjects were not blinded to the fact that their adherence was being monitored, and subjects were given regular feedback with regards to spacer use. Results may have been confounded by the "study effect".

4.5.3   Strengths of study

4.5.3.1   Novel concept

A major strength of this study was that the concept of improving inhalation technique and adherence to prescribed medication, by the use of a specifically designed incentive delivery device, is a novel concept. Incentive devices are used to influence children's breathing during lung function testing, but the influence of an incentive spacer on children's breathing has never been studied before.

As mentioned above, previous attempts to improve adherence in preschool children focused on the children's parents. This is the first study aimed at improving adherence to inhaled medication in preschool children, which targeted the intervention primarily at the children, and not their parents.

4.5.3.2   Filter dose as a measure of proficiency in spacer technique

This is the first clinical trial where proficiency in spacer technique was objectively quantified by using filter studies. The objective quantification of spacer technique made it possible to investigate the influence of spacer technique on various other variables.

4.5.3.3   Electronic monitoring of adherence

Electronic monitoring is currently the gold standard for the monitoring of adherence to prescribed medication. This study is the largest and longest study to date where adherence to inhaled treatment was monitored electronically in preschool children. The year long

duration of the clinical trial allowed for the "study effect", which may have falsely elevated adherence in the first months of the study, to wear off, thereby allowing for a more accurate assessment of adherence.

4.5.4   Application of results

The improved spacer technique in children under four years of age, and the decreased numbers of subjects with very poor spacer technique (filter doses <= 20μg) in the Funhaler group indicates that prescription of the Funhaler in the clinical setting may be considered in young patients who are suspected to have poor spacer technique.

The large variation in proficiency in spacer technique, which results in a large variation in inhalation drug delivery to preschool children, should be acknowledged when analysing research studies in which inhaled medication is used as an intervention. The variation in drug delivery should also be kept in mind when clinicians treat patients with inhaled medication. Research that focuses on the improvement of the accuracy in aerosol drug delivery for preschool children should continue.

The mean adherence to prescribed medication was low, and varied greatly. Although this is not a novel finding, the results underscores the importance for health care providers to take the variation in adherence into account when managing preschool children with asthma.

The positive correlation between adherence to prescribed treatment, and measures of asthma control reinforce the need to include a focus on adherence to medication, when treating asthmatic preschool children. The lack of any continuing positive influence of the Funhaler® on adherence to prescribed medication suggest that more development of incentive devices aimed at preschool children would be required if incentive inhalation devices are to be effective in improving adherence in this age group. Alternatively, the role of incentive spacers like the Funaler® may be limited to helping very young children in developing good inhalation technique.

5 CHAPTER FIVE: Conclusion and future directions

PMDI-spacers are currently the most commonly used and efficient method for delivering inhaled asthma medication to preschool children. Correct spacer technique is essential for optimal drug delivery though pMDI-spacers. Preschool children are instructed to breathe normally (tidally) through spacer devices. Until now, there was little evidence on the number of breaths required for optimal drug delivery, and whether the single maximal breath technique should be taught to preschool children was unclear.

In this thesis a method for accurately recording and simulating breathing was validated. The method allowed breathing to be recorded while subjects were inhaling medication or placebo through spacers, with minimal interference between the subject and the spacer. The validated methodology was then used to determine that the inhalation volumes of young children using spacers were larger than expected, and that only a few (e.g. two) tidal breaths are required for efficient drug delivery. The results also suggested that all female children are able to perform a single maximal breath at six years of age, and all male children are able to perform a single maximal breath from seven years of age. However, the results suggested that in young children, single maximal inhalation does not result in improved drug delivery over tidal breathing.

These results potentially could be applied in clinical practice. In busy hospital emergency departments, where preschool asthmatics may require multiple repeated doses of bronchodilators, with each dose requiring multiple pMDI actuations, requirement for fewer breaths after each pMDI actuation could contribute to improved patient cooperation and expedite the delivery of effective treatment. In the home setting, asthma preventers are administered regularly over the medium to long term. The obviation of the requirement to take multiple inhalations through a spacer each time that medication is administered, may potentially expedite the drug delivery process, making it more acceptable to the preschool child, and reduce parent child conflict, which is known to often be associated with the drug delivery process. Also, health care providers can feel more confident about the instructions that they give to parents of preschool children about spacer use.

After the question, about how preschool children should breathe through spacers, was answered, two important determinants of inhaled drug delivery (proficiency in spacer technique and adherence to prescribed medication) both known to often be sub-optimal in preschool asthmatic children, were examined in a clinical trial. In the randomised controlled clinical trial, the effect of an incentive device, the Funhaler®, on spacer technique, and adherence to prescribed inhalation corticosteroids in preschool children, was studied. Results suggested that the Funhaler® had a positive influence on <u>spacer technique</u> in children between two and four years of age, but the effect did not carry through to four to six-year old children, and was not large enough to improve clinical outcome. Use of the Funhaler® therefore appeared to specifically improve drug delivery in those subjects who, with a conventional spacer, would have inhaled very low doses of medication. The Funhaler® was therefore partially successful as an incentive device, as its use positively influenced drug delivery in a specific sub-group of preschool children.

The clinical trial results suggested that proficiency in spacer technique did not translate to improved long term clinical outcomes. Regular use of inhaled corticosteroids has been shown to reduce asthma symptoms in preschool children. The lack of association between proficiency in spacer technique and clinical outcome was disappointing, as improved spacer technique (measured by improved drug delivery) should improve asthma symptoms if the drug administered via the spacer is effective in decreasing asthma symptoms. However, as a recent meta-analysis highlighted [276], the benefit of inhaled corticosteroids when used in clinical trials for the treatment of preschool asthma, appears to be modest. Therefore, the relationship between dose and response is often difficult to observe, even in tightly controlled dose-response studies. Also, there is large inter-subject variability in response to treatment, which can also make any true changes hard to detect. Thus, the lack of association between proficiency in spacer technique and long term clinical outcome, in this thesis, was not especially surprising.

In addition to the above, there are inevitable inherent limitations in design in a clinical study, such as the one described in this thesis, which may have further reduced the chances of detecting a correlation between proficiency in spacer technique and clinical outcome. Most notably would be the large variation in prescribed fluticasone dose between subjects and even between study visits. Therefore, based on the results of this study only, one would not exclude the possibility that improved spacer technique could still have an important impact on clinical outcome in preschool asthmatic children. As the Funhaler®

had a positive influence on spacer technique in children between two and four years of age, and specifically appeared to improve drug delivery in those subjects who would have inhaled very low doses of asthma preventers with conventional spacers, the potential of the Funhaler® to improve clinical outcome in two to four year old children who are at risk of inhaling sub-optimal doses of asthma preventers, could not be ruled out. Clinicians should consider the option of prescribing the Funaler® for very young children to help improve spacer technique.

Based in the Funhaler's performance, the concept of using an incentive device to improve spacer technique in preschool children has shown potential. However, if the incentive component of an incentive spacer remains a spinning disk and whistle only, its usefulness may also remain limited to a sub-group of very young children for a limited time. As very young children are possibly the sub-group who are at highest risk of poor inhalation technique, a device more compact and robust than the Funhaler® may potentially be applied more effectively in this subgroup. Also, as interest of a young child in the single mode of feedback offered by the Funhaler® may decay with time, a device that provides a range of feedback ideas directed at holding the interest of a young child for much longer would be worth exploring. Furthermore, an incentive that is attached to the inspiratory arm of the spacer may be more effective, as the quality of feedback on the inspiratory arm could be linked to characteristics of the patient's inhalation i.e. more pleasurable feedback for slow, deep inhalation, thereby improving drug delivery to the lungs.

Results of the clinical trial suggest that <u>adherence</u> to prescribed medication regimens correlate positively with improved clinical outcome in preschool children with asthma. Use of the Funhaler® did not improve adherence to prescribed medication in preschool children with asthma. Funhaler® therefore failed as an incentive device to improve adherence in preschool asthmatic children. Once again, this does not prove that all incentive devices will fail to improve adherence, but it does indicate that any future design for an incentive device will need to consider providing feedback that is more interesting to the child.

The results of this study also suggest that future attempts to improve adherence to prescribed medication in preschool children would be most successful if they are aimed at addressing issues related to the parents of the children. A cohesive family climate, medication routines, and the frequent reinforcement of the educational message to parents have been shown to be related to improved adherence to prescribed inhaled medication in

preschool children. In the clinical situation, ways of facilitating the establishment of good medication routines should therefore be pursued, and the importance of adhering to prescribed regimens should be emphasised frequently. The importance of a healthy, cohesive family environment can never be underestimated, and health care providers should continually be alert to opportunities where they can contribute to the functioning of their patient's family unit, as a healthy family environment's positive influence on a child's health will not be limited to adherence to prescribed medication.

The future of incentive aerosol delivery devices in preschool children is not clear. As noted above, improved incentive devices that provide more pleasurable, or more varied, feedback may potentially be more effective. More pleasurable and more varied feedback could potentially be provided by computerised electronic incentive devices (different game each time used).

The findings of this study have <u>further important implications for future</u> studies and clinical work. Firstly, the demonstrated wide variation in both proficiency in spacer technique, and adherence to prescribed medication in young children, should be taken into account during the development and analysis of clinical trials. As the large variation, during clinical trials, in proficiency in spacer technique, and adherence to prescribed medication, is likely to influence results, an awareness of the variation in spacer technique and drug delivery may contribute towards the accurate interpretation of results. When inhaled drugs are used in clinical trials, regular supervision by the research team, uniformity of delivery devices used, and the use of devices that are known to deliver a more consistent, and narrower dose range, could contribute to a reduction in variation in drug delivery. Accurate adherence monitoring during clinical trials could be used to statistically correct for inter-subject variability in adherence. While researchers should continue to be aware of the well known "study effect", implementation of the abovementioned suggestions may improve the accuracy and statistical power of clinical trials.

Finally, the wide variation in both proficiency in spacer technique, and adherence to prescribed medication, both factors that determine drug delivery to patients, highlight the importance of pursuing ways to improve inhalation drug delivery to preschool children in order to eliminate the variability in prescribed medication that eventually reaches patients. The delivery to the lungs of a constant, reliably repeatable inhaled drug dose should be a continuing aim for aerosol scientists and physicians.

*

This thesis has contributed to the field of aerosol medicine by introducing a novel method for assessing the influence of breathing on drug delivery via spacer, where the simulated breathing can be recorded on subjects while they are using spacers, with minimum increase in dead space or resistance, and no physical alteration in the patient-device interface. Implementation of the method demonstrated that inhalation volumes and flows of young children using spacers are larger than expected, and therefore only a few tidal breaths are required for efficient drug delivery.

Furthermore, this thesis has contributed to our knowledge of inhalation therapy in preschool asthmatic children by illustrating the large variation drug delivery through pMDI-spacers due to differences in proficiency in spacer technique and adherence to prescribed medication, and by demonstrating that an incentive device, the Funhaler®, can improve spacer technique in very young children.

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APPENDIX

DECLARATION BY STATISTICIAN

This is to confirm that recruitment of the Funhaler study 933/EP was discontinued when 132 subjects were recruited. An interim data analysis at the time revealed that the recruitment of a further 28 subjects was extremely unlikely (probability approaching zero) to influence results with regards to the main outcome measures of the study.

Signed...   Date... 24/09/2009
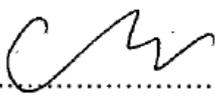
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