The Importance of Inhaler Technique in Measuring and Calculating Inhaler Adherence, and its Clinical Outcomes

AUTHOR(S)

Imran Sulaiman

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The Importance of Inhaler Technique in Measuring and Calculating Inhaler Adherence, and its Clinical Outcomes

Dr. Imran Sulaiman, MB BCh BAO (Hons), LRCSI, MRCPI, MRCPUK

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Submitted for the Degree of Doctor of Philosophy

Supervisors: Prof. Richard W Costello (Department of Medicine)/

Prof. Frank Doyle

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Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of Degree of Doctor of Philosophy, is my own personal effort. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that this work is original and to the best of my knowledge does not breach copyright law, and has not been taken from other sources except where such work has been sited and acknowledged within the text.

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Abstract

Depending on the population studied, cross-sectional observational studies suggest that between 14%-90% of patients do not use their pressurized metered dose inhaler correctly, while 50-60% misuse a dry powder inhaler. This means that unless incorrect technique is acounted for a significant underestimation of how much medication the person actually obtained may be made.

The aim of this thesis was to objectively determine the frequency and importance of inhaler technique errors and to combine these with inhaler use to provide an acurate method of calculating adherence. I then investigated different patterns of inhaler use, determinants of inhaler use and the impact of education directed at technique of inhaler use has on adherence and clinical outcomes.

To assess inhaler adherence the INhaler Compliance Assessment (INCA^{TM}) device was used. This device records digital audio of a patient using their inhaler to provide information on time and technique of use.

Firstly, Inhaler adherence was measured in a cohort of inhaler users recruited from a community care setting. Analysis of the audio recordings showed that these patients made several inhaler errors including generating insufficient inspiratory flow, exhalation into the inhaler mouthpiece after priming, multiple inhalation in one inhaler use, poor breath hold as well as frequntly missing doses. This identified the frequency of inhaler errors. Then I assessed the severity of these errors. Healthy volunteers performed common inhaler errors and drug plasma levels were measured. Results showed that of the errors identified above only poor inspiratory flow, exhalation into the mouthpiece and missed doses affected plasma drug levels. Based on these findings I developed a new method of calculating adherence that incorporated time of use, interval between doses and technique of use. I then prospectively related adherence calculated by this method with clinical outcomes in a cohort of patients with severe asthma. Among over 220 severe asthma patients followed for 3 months, adherence calculated in a way that accounted for time and technique of use, was more reflective of changes in clinical outcomes than current measures of calculating

adherence. With this method, I also assessed inhaler adherence in a cohort of Chronic Obstructive Pulmonary Disease patients being discharged from hospital. Adherence was poor in this population, due primarily to poor inhaler technique. Determinants of inhaler adherence were also evaluated leading to the identification of three clusters of inhaler use; those who took their inhaler regularly with good technique, those who took their inhaler regularly with poor technique, and those that took their inhaler irregularly and with poor technique. Finally an education program geared at inhaler technique was implemented in randomised control trial of asthma patients. Inhaler adherence was significantly higher in patients receiving inhaler training based on the individuals own time and technique of use.

These data highlight that both ineffective and irregular inhaler use are common in all users of inhalers and stress the importance of incorporating a measure of inhaler technique when assessing inhaler adherence.

Dedication

This thesis is dedicated to Siun; She has always been so supportive of my career. Her patience, understanding and help have got me through this large endeavour. With her unconditional love, positive attitude and constant reminder that there is light at the end of this long tunnel was I able to complete this thesis and I will be forever grateful to her.

I would also like to dedicate this to my parents Dusthy and Basheer, my sister Uzma and my sister-in-law Cliodhna, who have always been there for me and encouraged my pursuits, as difficult as they may seem. They have always supported me unconditionally and for this I will be ever grateful.

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I would also like to thank Ms Elaine MacHale who has been my counsel and inspiration for the last three years. Her patience, guidance, advice, encouragement and support have been ever present, and her direction and positivity have been inspirational in pursuing this PhD. I would also like to thank Dr Frank Doyle, Professor Anthony O'Regan and Professor Richard Reilly for their support and constructive criticism of my research for the past 3 years, constantly keeping me on my toes. A special thanks to Dr. Jansen Seheult who performed the salbutamol assay work described in Chapter 3 and was a great friend and collegue throughout this project.

I would like to thank all my colleagues in the Clinical Research Centre in RCSI, Beaumont Hospital for their constant support, sense of humour, friendship and patience. In particular, Ms Aoife Sartini-Bhreathnach for always willing to help however big or small the task, Ms Catherine Nora Moran, Dr Hannah McCarthy and Ms. Mandy Jackson for helping collect some of my data in such an organised and neat fashion, Dr Fiona Boland for her support and teaching in statistics, Dr Breda Cushen and Dr Matshediso Constantia Mokoka for their help, support and amazing friendship.

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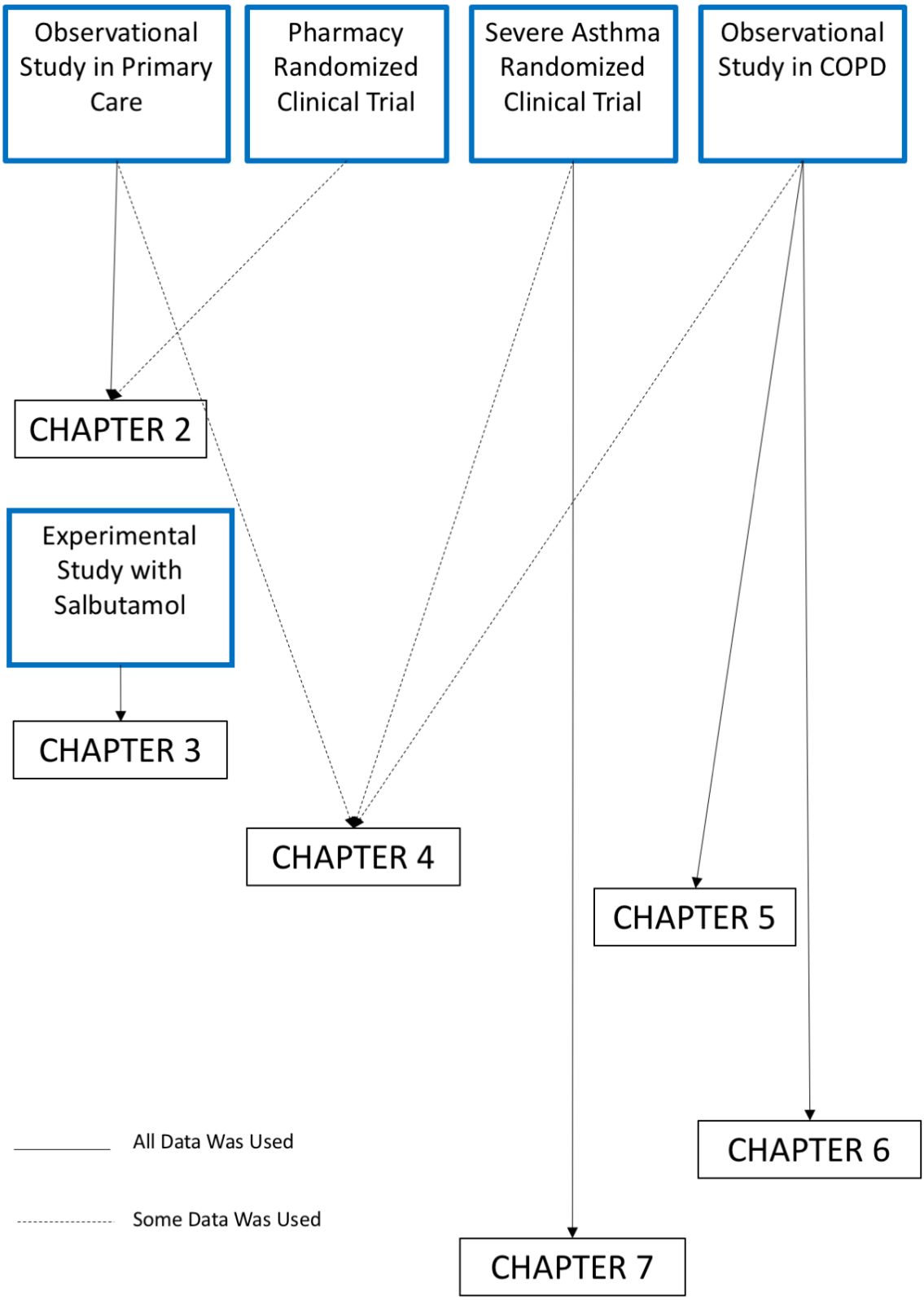

Summary of Data Allocation for All Chapters in Thesis

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Journal publications

1. **Sulaiman I**, Cushen B, Greene G, Seheult J, Seow D, Rawat F, et al. Objective Assessment of Adherence to Inhalers by COPD Patients. Am J Respir Crit Care Med. 2016 Jul. 13.

2. **Sulaiman I**, Seheult J, MacHale E, Boland F, O'Dwyer SM, Rapcan V, et al. A Method to Calculate Adherence to Inhaled Therapy That Reflects the Changes in Clinical Features of Asthma. Annals ATS. 2016 Jul. 28.

3. **Sulaiman I**, Seheult J, MacHale E, D'arcy S, Boland F, McCrory K, et al. Irregular and Ineffective: A Quantitative Observational Study of the Time and Technique of Inhaler Use. The Journal of Allergy and Clinical Immunology in Practice. 2016 Aug.; 4(5):900–909.e2.

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10. Taylor TE, Holmes MS, **Sulaiman I**, Costello RW, Reilly RB. Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2016 Feb. 9.

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Abstract Publications

1. **Sulaiman I**, Seheult J, Sadasivuni N, Cushen B. Inhaler Technique Errors Have An Impact On Drug Delivery. Am J Respir Crit Care Med 193;2016:A1715. 1715. *[under review for publication in the Journal of Aerosol Medicine and Pulmonary Drug Delivery]*

2. **Sulaiman I**, Seheult J, MacHale E, et al. INhaler Compliance Assessment (INCA). A37 COST. 2014. *[under review for publication in Thorax]*

3. **Sulaiman I**, Long D, Sehelut J, D'Arcy S. Changing a hospital inhaler policy to improve in-hospital inhaler use. European Respiraory Journal. 2014 Sep.;44(Suppl 58).

4. McCormack N, Costello R, **Sulaiman I**. Observational Study Of Patients Following An Acute Exacerbation Of COPD: Medication Adherence, Its Associations And Possible Consequences. Am J Respir Crit Care Med 191;2015:A2534. 2015.

5. Long D, Lyons AM, Byrne T, **Sulaiman I**, Costello R. Inhaler proficiency following the introduction of a new inhaler management policy for hospitalised patients. European Respiratory Journal. 2014 Sep. 1;44(Suppl_58):1298.

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7. Taylor TE, Holmes MS, **Sulaiman I,** D'arcy S, Costello RW, Reilly RB. An acoustic method to automatically detect pressurized metered dose inhaler actuations. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:4611–4614.

List of Presentations/Awards

Oral Presentations:

1. **ESPACOMP Conference, Prague, 2015**
    a. Adherence expressed as medication accumulation over time reflects changes in Clinical features of asthma

2. **Irish Thoracic Society, Ireland, 2015**
    a. INhaler Compliance Assessment (INCA) in an Asthma Cohort

3. **Irish Thoracic Society, Ireland 2014**
    a. Objective Quantification of both Time and Technique of Dry Powder Inhaler Use by a Community Based Population of Respiratory Patients

Poster Presentations (First Author):

1. **American Thoracic Society 2016 Poster Discussion**
    a. Feedback on Adherence and Inhaler Technique Using the INCA device: A Randomised Control Trial in Severe Asthma
    b. Determinants and Patterns of Adherence to inhaled therapy by patients with severe COPD
    c. Inhaler Technique Errors Have An Impact On Drug Delivery

2. **American Thoracic Society 2015 Poster Discussion**
    a. Observational study of patients following an acute exacerbation of COPD: medication adherence, it's associations and consequences

3. **American Thoracic Society 2014 Poster Discussion**
    a. INhaler Compliance Assessment in the Community (INCA GP)
    b. INhaler Compliance Assessment (INCA)
    c. A Change in Inhaler Policy to Reduce in Hospital Inhaler Errors

4. **European Respiratory Society 2015**
    a. A New Clinically Relevant Method of Calculating Adherence
    b. Inhaler adherence following an exacerbation of COPD.

5. **European Respiratory Society 2014**
    a. Changing a hospital inhaler policy to improve in-hospital inhaler use

6. **ESPACOMP 2015**
    a. INhaler Compliance Assessment (INCA) in an Asthma Cohort: A Randomized Control Trial to Improve Adherence
    b. Inhaler Compliance Assessment in a COPD cohort (INCA COPD)

7. **Irish Thoracic Society 2014 Poster Discussion**
    a. Inhaler Proficiency following the implementation of a New Inhaler Management Policy for Hospitalized Patients

Awards/Grants

1. Irish Thoracic Society Research Grant – primary applicant - €10,000 (2013)
2. Irish Thoracic Society – Best Oral Presentation (2014)
3. ESPACOMP – Best Poster Presentation (2015)
4. American Thoracic Society International Abstract Award (2015)
5. American Thoracic Society International Abstract Award (2013)

Glossary and Abbreviations

ACCP……American College of Chest Physicians

ACT……Asthma Control Test

Average Adherence…….Mean Possession Ratio Based on the Dose Counter

ALL……Acute Lymphoblastic Leukemia

AHT……Anti-Hormonal Therapy

AM……..Ante Meridiem (Morning)

AMT……Abbreviated Mental Test

ANOVA……Analysis of Variance

AQLQ……Asthma Quality of Life Questionnaire

AUC……Area Under the Curve

BIC……..Bayesian Information Criterion

BMI……Body Mass Index

BMQ……Beliefs in Medicine Questionnaire

CAT……COPD Assessment Test

C.I……Confidence Interval

COPD……Chronic Obstructive Pulmonary Disease

CPAP……Continuous Positive Airways Pressure

DMARD……Disease Modifying Anti-Rheumatic Drug

DOICS……...Directly Observed Inhaled Corticosteroids

DOT……Directly Observed Therapy

DPI……..Dry Powder Inhaler

EDTA…… Ethylenediaminetetraacetic acid

EHLS……European Health Literacy Survey

ESI……Electrospray Ionization

FA……..Formic Acid

FDA……Food and Drug Administration

FEV_1……Forced Expiratory Volume in 1 Second

FeNO……Fractionated Exhaled Nitric Oxide

FVC……..Forced Vital Capacity

GINA……..Global Initiative for Asthma

GOLD……Global Initiative for Chronic Obstructive Lung Disease

GP……..General Practitioner

HADs……Hospital Anxiety and Depression Score

HIV……Human immunodeficiency Virus

HPLC……High-performance liquid chromatography

HQC……Higher Quality Control

HR……...Hazards Ratio

IMS……Immunosuppressive

INCA……INhaler Compliance Assessment

INR……International Normalized Ratio

IS……Internal Standard

ICS……Inhaled Corticosteroids

IPS……Inhaler Proficiency Score

IQR……Interquartile Range

L……Liters

LABA……Long Acting Beta Agonist

LAMA……Long Acting Muscarinic Antagonist

LQC……Lower Quality Control

LTD……Limited

MCID……Minimally Clinically Important Difference

MDI……Metered Dose Inhaler

pMDI……pressurized Metered Dose Inhaler

MEMS……..Medication Event Monitoring System

MI……Multiple Imputation

MIN……Minute

MMAS-8……8-item Morisky Medication Adherence Scale

MMSE……Mini Mental Status Exam

MoCA……Montreal Cognitive Assessment

MPR……Mean Possession Ratio

MQC……Middle Quality Control

MS……Mass Spectrometry

NICE…….. National Institute for Health and Care Excellence

NPV……..Negative Predictive Value

OLS……..Ordinary Least Squares Regression

OR……Odds Ratio

OSA……..Obstructive Sleep Apnoea

PEFR……...Peak Expiratory Flow Rate

PIFR……Peak Inspiratory Flow Rate

PDC……..Proportion Days Covered

PM……Post Meridiem (Evening)

PPV……..Positive Predictive Value

QC……..Quality Control

RA……..Rheumatoid Arthritis

RAST……...Radioallergosorbent Test

RCTs……Randomized Control Trials

ROC……..Receiver Operating Curve

RR……..Relative Risk

RV……..Residual Volume

SD……..Standard Deviation

SLE……...Systemic Lupus Erythematous

TLC……..Total Lung Capacity

USB……..Universal Serial Bus

TORCH……..Towards a Revolution in COPD Health

WHO……..World Health Organization

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

In this chapter I will describe the importance of medication adherence for clinical outcomes in general medical conditions as well as respiratory disorders. Following this I will discuss the current methods for measuring adherence and how these can be used to calculate and describe adherence. I will then address the limits of the current methods, that they do not account for inhaler technique nor account for variations in medication use over time.

Following this, I will then evaluate the literature on predictors and determinants of inhaler adherence in general terms and specifically with respect to inhaler technique.
Lastly, I will review the literature on successful interventions to improve medication adherence and describe how a successful intervention will require a method of assessing adherence that incorporates the time of inhaler use as well as the technique of use.

1.2 THE IMPORTANCE OF ADHERENCE TO MEDICATIONS IN MEDICAL CONDITIONS

Records of patients not taking their medication are dated as far back as Hippocrates (400BC) who noted that patients who did not take their medication later complained that the treatment didn't work. Currently, medication non-adherence is recognized by the World Health Organization (WHO) as one of the most important and costly worldwide healthcare problems (1). The direct cost of non-adherence is estimated at $100 billion to $289 billion per year in the United States (2) and as the worldwide population ages, due to increased life expectancy, the prevalence of medication non-adherence will also increase. For any prescribed medication there are three crucial phases of adherence. The first phase, initiation; this phase follows the prescription of a medication from clinician to patient and encompasses whether the individual starts taking the medication. In this step patients may fail to retrieve their medication from their pharmacy, they may retrieve the medication but fail to start taking the medication. The second phase, execution/implementation; this phase is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen. For example, in a medication prescribed three times a day, does the patient stick to their prescription and take the medication within eight-hour intervals. In the cases where medication delivery is dependent on a device, such as insulin given through an insulin

pen or inhaled medication given through an inhaler device, technique of use plays an important role in the execution phase of adherence. The third phase, persistence; this is whether the patient continues to take their medication till an agreed date of continuation (discontinuation). This flow of patient adherence can be seen in Figure 1-1.

Adherence to medications is an important and crucial part of many disease management plans, particularly in chronic disease management. In a study of 184 adults with a history of chronic illness, only 64% were fully adherent to their treatment based on prescription refill records (3). The authors found several significant factors associated with poor medication adherence: the absence of a medical store within close distance, non-availability of drugs at the nearest pharmacy, inability to understand the doctor's explanation, failure to explain the consequences of not taking medicines by the healthcare provider, self-alteration of medicine dosage and fear that medicines will lead to the development of dependence to medicines. Interestingly, those who required special skills to take medicines, such as injections, or inhalers were more likely to be adherent. Broadly, these diverse drivers can be divided into socio-economic barriers, issues to do with communication between health care provider and patient as well as comprehension issues. Medication non-adherence is well published in several general medical conditions such as immunosuppressive therapy, treatments with narrow therapeutic indexes, treatment for oncological disorders, treatment for cardiovascular disease, treatment for obstructive sleep apnea and treatment of musculoskeletal conditions. In the following paragraphs I will describe examples of medication non-adherence and highlight its impact on some of these medical conditions before discussing medication non-adherence in respiratory disorders.

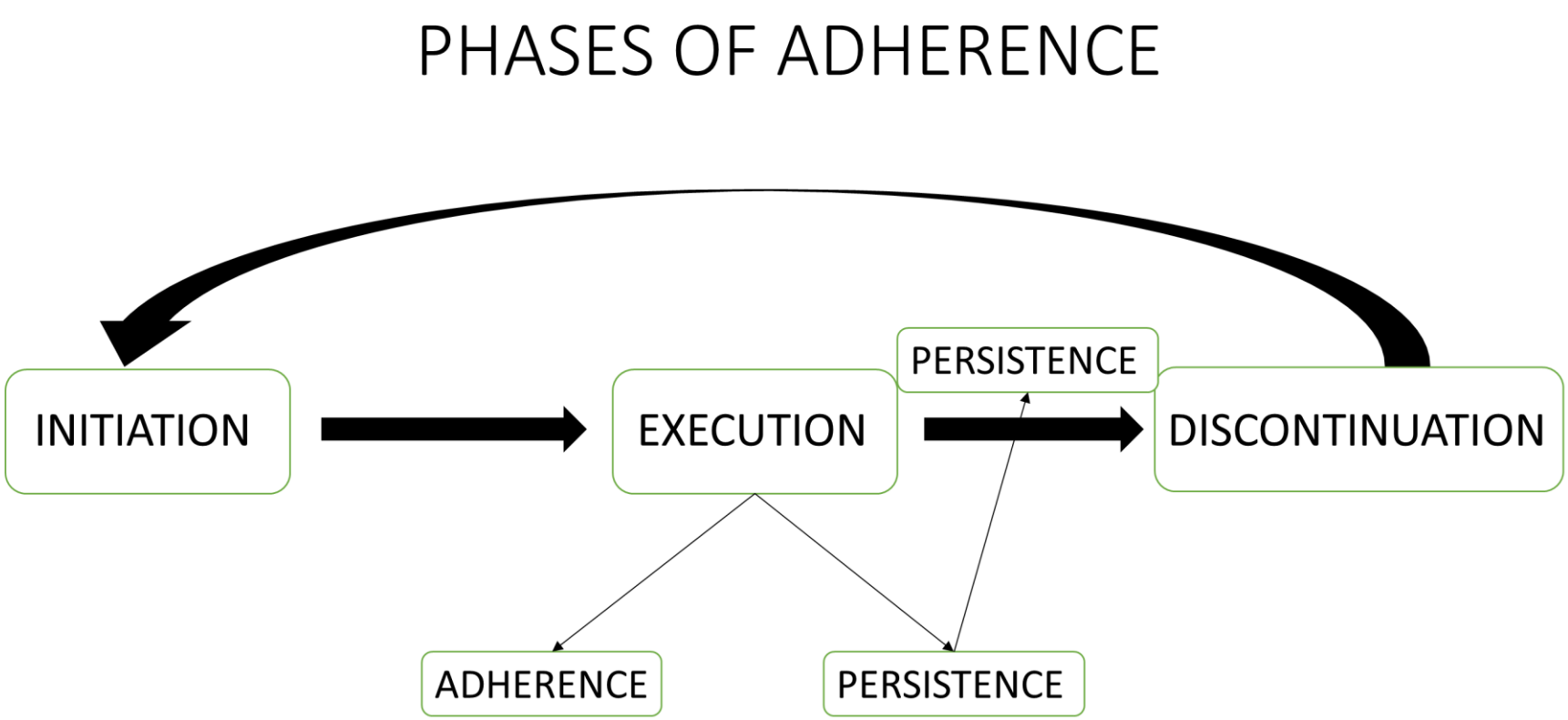
PHASES OF ADHERENCE
INITIATION
EXECUTION
PERSISTENCE
DISCONTINUATION
ADHERENCE
PERSISTENCE

Figure 1-1: Phases of Adherence:

There are three phases of adherence, initiation, execution/implementation and persistence which ends with discontinuation. Initiation starts with prescribing of medication in conjunction with the patient. Following this is execution/implementation. The patient has to collect their medication from their pharmacist (this may be assessed by pharmacy refill records). The patient then takes the medication, this can be assessed by electronic monitors and dose counters found on inhaler devices. With medications that are delivered by a specific device (i.e. inhalers) how the patient uses the device is crucial and therefore another component of execution. The next phase of adherence is persistence; does the patient continue taking their medication? Persistence continues till the prescribed medication is discontinued in conjunction with the patient.

1.2.1 Medication Adherence to Immunosuppressive Treatment

For patients post renal transplant, adherence to immunosuppressive treatment is essential to the long-term survival of the renal-graft. However, in a paper by Constantiner et al, this treatment was the class of drug that had the highest level of non-adherence in this cohort of patients (4). This reported non-adherence is extremely variable, with levels of adherence reported somewhere between 2% and 67% (5). In this group of patients non-adherence to immunosuppressive treatment can have disastrous consequences. In a systematic review published in 2004, it was found that 36% of graft losses were due to medication non-adherence (6). This level of non-adherence is also seen in lung and heart transplantation, 13% and 21% respectively (7). From these studies it is clear that medication adherence is poor in this patient population with important clinical implications.

1.2.2 Medication Adherence to Treatment with Known Therapeutic Indexes

As non-adherence is important for immunosuppressive therapies, it also has significant implications to medications with narrow therapeutic windows, such as the anticoagulant Warfarin, where the International Normalized Ratio (INR) guides dosing regimens. Non-adherence may lead to an INR below the suggested level and result in serious co-morbidities. On the other hand overuse may lead to a significant bleeding risk. Kimmel et al assessed warfarin adherence with the Medication Event Monitoring System (MEMS) (8). In this study 36% of patients missed more than 20% of their prescribed dose, while 4% had more than 10% extra doses. Importantly, missing one to two doses a week was associated with a near two-fold increase in the odds of a sub-therapeutic INR. Another medical treatment with a narrow therapeutic window is anti-epileptic treatment. Studies in this class of medication have shown that non-adherence to this therapy increases the risk of seizures (9), hospitalization (10) and increased mortality (11). Similar to immunosuppressive medication, these studies suggest that non-adherence has an important clinical impact.

1.2.3 Medication Adherence to Oncological Treatments

Another cohort of patients where adherence to treatment is crucial to disease management is the treatment of oncological disorders, such as acute lymphoblastic leukaemia (ALL). ALL treatment has changed dramatically in the last 50 years, originally with a survival rate of 10%, it is now greater than 90% and this is due to the advancements in medication treatment. One of the most important new treatments is the thiopurine 6MP. Adherence to this therapy has been assessed in a group of 742 children over a 6-month period (12). For this study, adherence was measured with an electronic monitor. The authors found that children who were non-adherent had a 2.7-fold increased risk of ALL relapse. Children who were adherent but had high intra-individual variability due to varying 6MP dose intensity and interruptions in drug delivery also had a significant risk of relapse, highlighting the importance of correctly capturing adherence, possibly in terms of the pharmacokinetic properties of the drug being studied (i.e. peak and troughs). Similarly with breast cancer, another oncological disorder, adherence to anti-hormonal therapy (AHT) ranges from 11% to 60% (13,14), while persistence rates range from 31% - 34% (15). This suggests that these patients may start their treatment but don't continue taking their treatment, which can be critical in certain types of breast cancer. Hence, these studies highlight that medication adherence, including persistence of adherence, is poor in patients being treated for oncological disorders, which also has significant clinical implications.

1.2.4 Medication Adherence to Cardiovascular Treatments

Medication adherence is also important in the management of cardiovascular disease. For patients with hypertension, high medication adherence improves blood pressure control. Similarly with cholesterol, a 25% increase in adherence to cholesterol lowering treatment leads to 3.8 mg/kl reduction in low density lipoprotein (LDL) cholesterol. Non-adherence to this class of medications leads to a significant increase in the relative risk for mortality by 12% to 25% (2). Munger et al published an excellent review article of non-adherence in cardiovascular disease (16). In this study the authors concluded that non-adherence is a significant risk factor for cardiovascular disease, particularly in relation to the treatment and its consequences.

1.2.5 Adherence to Obstructive Sleep Apnea Treatment

Adherence to medical devices can also be important in chronic disease management. For example, obstructive sleep apnoea (OSA) can be treated successfully with continuous positive airway pressure (CPAP), a device that a patient is asked to use every night for at least 4 hours to reduce sleepiness and cardiovascular risks (17). Therefore, adherence to this therapy has an impact on both morbidity and mortality for this condition (18). To study adherence in this patient population Wohlgemuth et al examined adherence patterns in 207 patients being treated for OSA using a latent cluster analysis (LCA). The authors identified three patterns of CPAP adherence (19). The first pattern showed that 38% of patients were 'Non-Adherers' and used their CPAP an average of 37 minutes a night. The second pattern showed that 32% of patients were labelled 'Attempters,' these patients used their CPAP an average of 156 minutes a night. The remaining 30% of patients were labelled 'Adherers' using their CPAP an average of 392 minutes a night. The authors also found that self-efficacy, OSA severity (based on the apnoea-hypopnea index), insomnia, time since CPAP was initiated and the prescribed CPAP pressure predicted group membership. Hence, it is clear that there are different behaviours of adherence and again, non-adherence to 'treatment' has significant clinical implications

1.2.6 Medication Adherence to Musculoskeletal Disease Treatment

Medication regimens are built around the pharmacokinetic properties of the drug to provide the most effective treatment. Musculoskeletal diseases such as rheumatoid arthritis (RA) and systemic lupus erythematous (SLE) have strict medication regimes known to facilitate disease remission. RA is a chronic inflammatory disease that leads to progressive joint damage, functional disability, increased morbidity and mortality. Treatment for this conditions has greatly improved in the last two decades with new disease modifying anti-rheumatic drugs (DMARDS). Nevertheless, studies have reported poor medication adherence in this patient population, ranging from 30% to 80% (20-22). Even with patient self report, 32-40% of patients with RA report poor adherence to their DMARD prescription (20). These reports of low medication adherence are similar in SLE. Using Medicaid data, Feldman et al (23) reviewed medication adherence of 9,600 users of hydroxychloriquine (HCQ) and 3,829 users of immunosuppressive medications (IMS) for SLE. The mean adherence rate was 48% for the HCQ users and near 43% for IMS users. Astonishingly, 79%

of HCQ users and 83% of IMS users were non-adherent (adherence <80%) and the non-adherent patients had significantly higher acute care utilization. Similarly to the previously highlighted studies, these studies highlight the importance of medication adherence and the role non-adherence has in disease progression and increased health costs.

1.2.7 Medication Adherence in Randomized Control Trials

To test the effectiveness of any medical treatments randomized control trials (RCTs) are considered the gold standard. However, it is not clear if medication adherence is considered in trial protocols and data analysis. In a 2007 paper reviewing RCTS, only 33% of 192 papers reported adherence results during the study period (24). In a follow up study published in 2014, only 46% of 111 oral therapy based RCTs published adherence (20)(20) (25) results. Interestingly, those papers that reported adherence data were more likely to be negative studies (25). Also of relevance, excluding non-adherent patients from analysis lead to biased results. This is the rationale for intention-to-treat analysis suggested by the Food and Drug Administration (FDA) as it avoids selection bias of the adherent subgroup and is more reflective of a real-world population (26,27).

Furthermore, poor or intermittent adherence is a major contributor to variable drug response, which can lead to poor interpretation of clinical trial results and poor drug development. In a review article by Blaschke, the author lists several problems due to poor or absent measurements of adherence. These include: failed treatment, inappropriate dose escalation, overestimated dosing requirements, emergence of drug resistant microorganisms (for anti-microbial drug trials), hazardous rebound, misdiagnosis, type II errors (for efficacy), underestimated adverse events related to medication dosing and poor pharmacoeconomic understanding (28). These issues are particularly relevant to Phase II, III and IV of large drug trials. Unmeasured under dosing may lead to incorrect dosing regimens for a new drug or even lead to discontinuation due to perceived ineffectiveness. Incorrect dosing regimens, due to unmeasured adherence, may even lead to drug toxicity and increased adverse events. In a paper by Cross et al, it was estimated that 20-30% of drugs registered between 1980 and 1999 went through dose changes and 60-80% of these were dose reductions (29).

It is fair to say that in drug trials where medication adherence is not measured, investigators assume 100% adherence. However, this is far from true as reported in several studies using robust methods of measuring adherence. In their review paper, Blaschke et al analysed a cohort of 16,907 patients from 95 clinical trials. The authors found that over time medication adherence progressively decreased, so much so that by 100 days nearly 20% of patients had discontinued their treatment and 12% of patients still taking the treatment were not fully adherent. At 365 days, 40% of patients had discontinued their treatment and 15% of patients were missing doses. They concluded that less than 70% of patients were fully adherent to the study protocol-dosing regimen (28). The safety and efficacy of any new drug needs to be related to the actual doses taken, not to a presumed 100% adherence, therefore the measurement of adherence is crucial in any clinical trial. It is also important to acknowledge that randomized control trials may not reflect a real-world population due to strict inclusion and exclusion criteria. In fact, in a 2007 paper published by Travers et al, the authors found that randomized clinical trials exclude over 90% of real-world asthmatic patients (30). Based on these findings a subsequent paper published in 2011 suggested more observational approaches to provide data that would be relevant to a real-world population (31).

Measuring adherence also has implications in regards to future patient management as different adherence patterns lead to different treatment strategies. For example, a patient with poor adherence, by not taking their medication daily and regularly, would need help integrating their dosing regimen into their daily routine. Whereas, a patient who discontinues their medication would need re-motivation and direct discussion with their healthcare provider to discuss barriers to optimal adherence. It is suggested if a patient is not benefiting from their medications, always consider non-adherence (32).

All these studies highlight the importance of medication adherence in general medical conditions and how non-adherence has both health care cost and clinical implications.

1.3 MEDICATION ADHERENCE IN RESPIRATORY DISORDERS

Having shown the importance and clinical implications of medication non-adherence in several general medication conditions, I will now describe the complications and implications of medication adherence in respiratory disorders. First I will discuss the common mode of treatment in these conditions.

1.3.1 Aerosol Drug Delivery

Treatment of respiratory disorders, such as asthma and Chronic Obstructive Pulmonary Disease (COPD), are dependent on adherence to prescribed therapies. The most common prescribed treatment in respiratory disorders are inhaled medications. These treatments are inhaled as aerosols, which lead to a potentially high dose drug delivery to a targeted area, with few side effects. The targeted area is made up of approximately 23 airways generations. These aerosols, once inhaled, deposit on the airways surface initially by impaction. In this process, which is dependent on the mass and velocity of the aerosol, the particles impact onto the airways. This process of deposition tends to occur in the first 7 airways generations. Sedimentation occurs in the more distal airways where air velocity is slower. As this process takes time, breath holding when using an inhaler device has been suggested to increase sedimentation and therefore drug delivery. Diffusion occurs in extremely small particles and is only a minor method of aerosol deposition. It is suggested that before inhalation of an aerosol that the user exhales to residual volume (RV), then inhalation should be slow and steady till total lung capacity (TLC) is reached. This will reduce drug lost to the pharynx and upper airway. To compare aerosol particles of different sizes and shapes the mass median aerodynamic diameter (MMAD) is used. Smaller particles (1-3 um) are more likely to reach the peripheral airways, however particles <1 um are largely exhaled. (33). The study of drug absorption and distribution is the basis of pharmacokinetics. This method of analysis is important when studying any medication as it provides information on drug dosing, toxicity and the best route of administration (34). Important variables in pharmacokinetic studies include peak concentrations (C_{MAX}), peak time (T_{MAX}), terminal half-life ($t_{1/2}$) and Area Under the Curve (AUC). Traditionally the AUC is used to estimate the maximum concentration of the drug in the plasma, to represent the exposure of the drug to the body (35-37). Pulmonary delivery of medications (other than

those used specifically to treat airways diseases such as asthma) is becoming increasingly attractive due to fast absorption, the large surface area provided by the lungs, abundant vasculature and thin air–blood barrier, with avoidance of first pass metabolism (38). However, in using medical devices such as inhalers to deliver medication appropriately there also come specific instructions of use, which I will discuss for two such devices now.

1.3.2 Inhaler Technique

As discussed previously, with any inhaled medications, to reach therapeutic effect in patients, there needs to be reasonable deposition of drug in the medium and small airways. To achieve this amount of drug deposition with inhaler devices there needs to be a sufficient level of inhaler technique (39,40). The two most commonly used categories of inhaler devices are the pressurized metered dose inhalers (pMDI) and the dry powder inhalers (DPI). A newer type of inhaler device is the soft mist inhaler. I will now describe the differences between the two common inhaler devices, with particular attention to inhaler technique.

1.3.2.1 The Pressurized Metered Dose Inhaler (pMDI)

The pressurized metered dose inhaler (pMDI) was previously the most commonly used inhaler device to treat airways disease, see Figure 1-2. The aerosol of a pMDI has particles sizes of 0.5-10 um. Even with small particle sizes it has been reported that only 55-60% of the inhaled dose reaches the airways, even with good inhaler technique (41). It is suggested for maximum drug delivery with the pMDI devices, patients should inhale deeply for 5 to 10 seconds, activate the inhaler just after the onset of inspiration and breath hold for 6 to 10 seconds (42), refer to Table 1-1. Therefore, critical errors include breathing in too quickly, stopping inhalation immediately after activation, activating the inhaler more than once in one inhalation, poor breath hold and poor coordination between activation and inhalation. Some of these errors can be reduced with the use of a spacer device, such as co-ordination between acctuation and inhalation. In an previously published experiment, 8 patients with obstructive airways disease used a Teflon marked terbutaline pMDI (40). In this study, only 8.8% of inhaled drug reached the lungs, while 80% was deposited in the mouth. It has been reported that slow inhalation reduces deposition in the oral cavity and larynx and leads to better deposition in the lower airways by gravity and diffusion (40).

Table 1-1: Pressurized Metered Dose Inhaler:

Bellow are the recommended steps for using a pMDI device.

1	Remove the cap from the inhaler mouthpiece
2	Hold the inhaler upright
3	Exhale fully away from the mouthpiece
4	Place the mouthpiece between your lips (keep tongue down and out)
5	Start to inhale slowly and deeply
6	Actuate the inhaler right after inhalation starts
7	Continue to breath in till your lungs are full
8	Remove the inhaler from your mouth and hold your breath for 10 seconds
9	Exhale

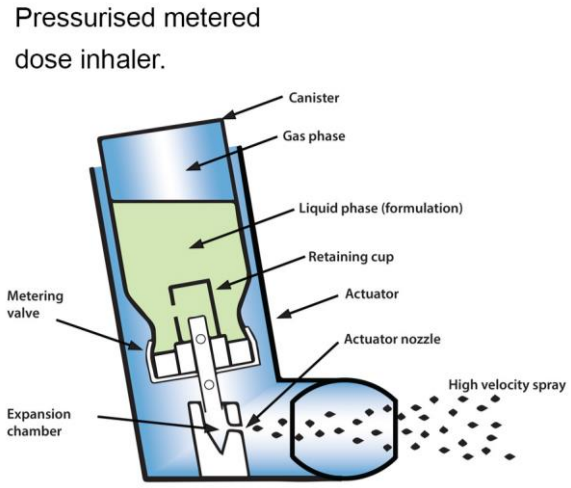

Figure 1-2: The Pressurized Metered Dose Inhaler:

A schematic of a pressurized metered dose inhaler (pMDI), taken from the Global Asthma Report 2014 (43)

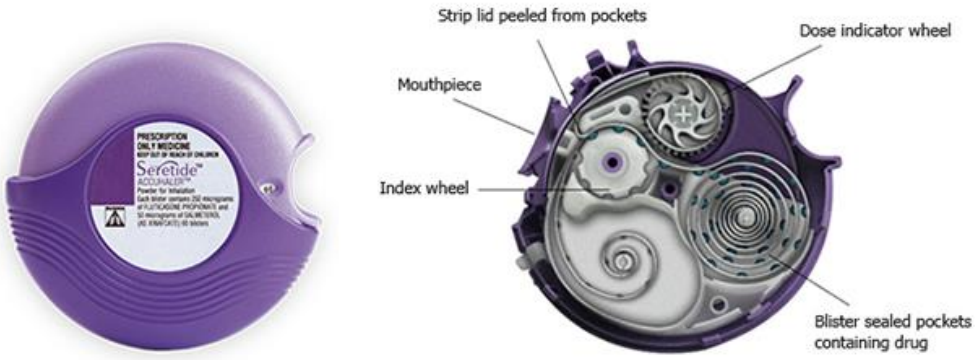

Figure 1-3: The Dry Powder Inhaler:

The outside appearance and inner workings of a Dry Powder Inhaler (DPI). This is the Diskus type of DPI device. Image retrieved from the Seretide website (GSK, New Zealand) (44)

1.3.2.2 The Dry Powder Inhaler (DPI)

pMDI's are said to be the most difficult device to use (45) and due to some patients having difficulty coordinating an actuation with a slow inhalation, the dry powder inhalers (DPI) have come more into fashion (46). The drug formulation of DPIs has better chemical stability than the pMDIs consisting of micronized drug particles (1–5 µm) combined with an inactive excipient (i.e. lactose) of larger sizes (40 µm) which help in deagglomeration and powder flow (47). The DPIs are breath-activated and come in two types. The first type houses a single-dose rigid capsule and the inhaler is activated when the capsule is pierced. With perforation and the patient's own rapid and forceful inhalation, the drug is de-aggregated and aerosolized. The second type contains multiple doses in a reservoir (i.e. Turbohaler) or a foil strip (i.e. Diskus^{TM}, see Figure 1-3) that is transported through the device. Particle deposition with the DPI devices is dependent of the velocity of the airflow during inspiration and each device has its own airflow resistance. The challenge in DPI design is the balance between inhaler resistance and air flow (38). In an experimental paper by Yokoyama et al, the authors hypothesized that inspiratory flow can effect drug distribution in a lung model. In this experiment there was a positive relationship between inspiratory flow and drug delivery to the modelled airways with an r^2 value of 0.899,

p<0.001 (48). The In-Check device (Clement Clarke International LTD.) can be used to educate patients in regards to the appropriate flow required for each DPI device (resistance can be altered to match that of the specific DPI device). Borgstrom et al showed that patients with asthma (including severe asthma) and COPD were able to generate enough flow to operate a DPI correctly (49). In addition to potential errors with low inspiratory flow DPIs are affected by humidity, which can lead to de-aggregation of the dry powder mix and reduced drug deposition (50). Of course failure to prime the drug is also a critical inhaler error. It is therefore suggested that for DPIs, patients prime the drug, exhale fully away from the device before taking a hard and fast inhalation and then breath hold for 10 seconds, refer to Table 1-2. In addition to these errors listed, capsule based DPI's require the user to load a capsule into the device and then peirce the capsule to release the dry powder.

As we can see inhalers can be difficult to use correctly and with these choices in inhaler devices guidelines published by the American College of Chest Physicians (ACCP) have made suggestions when selecting an aerosol delivery device; physicians should consider the following: device availability, the clinical setting, patient age, a patient's ability to use the device, cost, drug administration time, convenience of the device and patient and physician preference (51). Even though it has been reported that physicians are poor at recognizing improper inhaler technique (52) and may not even know the correct technique for the inhaler device (53), it is important to thoroughly assess and correct inhaler technique to ensure patients are receiving maximum therapy. Good training in inhaler technique requires effective communication of proper technique (and its purpose) and longitudinal monitoring to confirm that these skills are understood and maintained (54). As previous reports have shown that inhaler technique falls over time, periodic re-training is also required (55,56). These studies clearly describe the many barriers in using an inhaler correctly. I will now outline inhaler adherence in two common respiratory disorders, asthma and COPD.

Table 1-2: Dry Powder Inhaler:

Below are the recommended steps for taking any DPI device.

1	Expose the Mouthpiece
2	Hold the inhaler in recommended position for specific inhaler device
3	Prime the inhaler
4	Exhale fully away from the mouthpiece
5	Place the mouthpiece between your lips (keep tongue down and out)
6	Inhale Rapidly and forcefully
7	Continue to breath in till your lungs are full
8	Remove the inhaler from your mouth and hold your breath for 10 seconds
9	Exhale
10	Cover the Mouthpiece

1.3.3 Inhaler Adherence in Asthma

In asthma there are effective treatments that control symptoms and prevent acute events, thus reducing morbidity and (5)(5) mortality associated with the condition (57). The National Asthma Education and Prevention Project (NAEPP) have advised greater use of anti-inflammatory medications to control symptoms and better use of rescue-medication for immediate to short-term relief (58). However the main therapy for asthma remains inhaled corticosteroids (ICS) and adherence to this therapy is poor. In 2009, Gamble et al reported on the prevalence of non-adherence in difficult asthma. Of the 182 patients reviewed in a difficult asthma clinic, 35% filled out 50% or fewer prescriptions for ICS, 45% filled out somewhere between 50% and 100% prescriptions and only 21% filled out 100% of their prescriptions for ICS (59). In another study conducted in Leicester, 65.2% of asthmatic patients on inhaled corticosteroids had <80% prescriptions filled out (60).

When disease stability or symptom control is not achieved while on ICS treatment it may be due to several causes, such as poor adherence, poor inhaler technique ongoing exposure to environmental factors/triggers, or other co-morbid conditions. This relationship between inhaler adherence and asthma control has been explored previously. Ismalia et al (61) conducted an observational retrospective cohort study looking at the relationship with

inhaler adherence and asthma exacerbations in 19,126 Canadian asthmatic patients treated with salmeterol/fluticasone (a commonly prescribed inhaled medication for asthma). For the purpose of this study adherence was calculated as the mean possession ratio (MPR) from the dose counter, with >80% indicative of adherent behaviour. The outcome measure was the incidence of an asthma related exacerbation in the follow up period. In this study only patients with an adherence rate greater than 80% had a reduced rate of asthma related exacerbations (p=0.006). Adherent patients had lower rates of steroid use, emergency room visits, general practitioner visits, hospitalizations and respiratory specialist reviews. Patients that were persistent with this level of adherence also had a lower rate of asthma related exacerbations (0.19 vs. 0.23, p<0.001). The adjusted odds ratio for asthma exacerbations with adherence to salmeterol/fluticasone was 0.48 (p<0.001), which translates to a 52% reduction in risk for adherent patients versus those that were non-adherent. Similarly with persistent patients, the odds ratio for an asthma exacerbation was 0.48 (p<0.001). Adherent patients also had a lower adjusted risk for oral corticosteroid use, emergency room visit, hospitalization, ICU admission, respiratory specialist review and general practice review. Overall the authors showed a 24% increased risk in having an exacerbation when non-adherent with salmeterol/fluticasone treatment (61)

In a similar study, Williams et al published a paper on inhaler non-adherence in asthma and its impact on exacerbations (62). In this paper the authors calculated a moving average of adherence to inhaled corticosteroids using electronic pharmacy refill records. The authors reported a baseline adherence of 26.3% in 298 patients with asthma and noted increased inhaler adherence prior to an exacerbation. Controlling for asthma severity (both current and historic), adherence to inhaled corticosteroids was protective against exacerbations. A 25% increase in adherence was associated with an 11% risk reduction for an asthma exacerbation (Hazard Ratio (HR) 0.89, 95% CI 0.81–0.97, p=0.009). In patients whose asthma was not controlled at baseline (i.e. Asthma Control Test <19), inhaler adherence >75% lead to a significant reduction in the risk of an exacerbation. The authors estimated that almost 25% of exacerbations reported could have been avoided through improved inhaler adherence. These findings were similar to this groups previous retrospective study published in 2004 where the authors found inhaler adherence (measured as the number of days between refils and the total days of treatment gap/number of days between refils) was

significantly and negatively correlated with the number emergency room visits, number of fills for a course of oral corticosteroids and total number of days supply of oral corticosteroids in a cohort of 405 adult patients with asthma (57). Each 25% increase in time without inhaled corticosteroids led to a doubling in the rate of asthma-related hospitalization. In another study looking at prescription use of inhaled corticosteroids (prescription re-fill records), the authors found a clear association with adherence and improved clinical outcomes. Comparing non-users to even just the moderate users, the authors found a lower risk of death and or near-death in the moderate users of ICS. (63). A paper published in 2012 by Murphy et al looked at the clinical outcomes of medication non-adherence (calculated as the number of doses issued divided by the number of expected doses) in 115 patients with difficult-to-control asthma (64). Sixty-five percent of these patients had an adherence level less than 80% (based on prescription refill data). These patients with poor inhaler adherence had significantly lower forced expiratory volume (FEV_1) and higher sputum eosinophils. Interestingly, the authors found an association between poor inhaler adherence and risk of being ventilated previously; each 10% decrease in adherence lead to a 1.35 odds of being ventilated previously.

With regards to inhaler technique, Giraud et al studied 3,955 asthmatic patients in a community-based setting (65). In this study patients were on a pMDI device, had their inhaler technique assessed by their general practitioner and information on asthma stability was recorded. Seventy-one percent of patients misused their pMDI and 47% of these were due to poor co-ordination. The authors also found that misusers of the pMDI had less stable asthma.

As I have shown, inhaler adherence has a clear relationship to asthma control. However, in cases of poor asthma control while on ICS therapy, patients may be labelled as either treatment resistant or refractory and it is normal to escalate therapy with the addition of other agents such as long acting beta agonists (LABA) or even monoclonal antibody treatment (i.e. omalizumab). However, before escalating therapy in severe asthma, to what are often costly medications with increased side effects, it is essential that medication adherence is measured and accounted for. The WHO statement on severe asthma suggests

three situations where severe asthma maybe considered: untreated severe asthma (treatment not available), difficult to treat severe asthma (non-adherence or co-morbidities may be the cause of poor control) and treatment-resistant severe asthma (where adherence has been proven adequate) (66). However, the method by which adherence is measured is not discussed. Five percent of asthmatics have true severe treatment-refractory asthma; some have severe treatment refractory disease, others may have an alternative diagnosis and some may appear to have severe disease due to poor adherence (67). A systematic assessment with a planned series of investigations and assessments can elucidate the pathway of persistent symptoms, and importantly confirm the diagnosis of asthma, identify comorbid conditions, and review adherence to asthma therapy. This individualized assessment has the potential to personalize treatment and drug therapy that may lead to improved symptoms, asthma control and quality of life. This approach also has a crucial role in appropriately highlighting patients suitable for alternative and costly therapies (67). Hence, there is a need for longitudinal monitoring of inhaler use and technique in this patient population.

1.3.4 Inhaler Adherence in COPD

Similar to asthma, treatment for COPD revolves around the use of inhaled medication. However, unlike asthma, there is little literature regarding inhaler adherence in this population.

In a landmark paper published in 2009 Vestbo et al (68) assessed the impact of medication adherence (measured from the inhaler dose counter) in the Towards a Revolution in COPD Health (TORCH) study. The TORCH study was a randomized study comparing salmeterol, fluticasone propionate, the combination of salmeterol with fluticasone propionate and placebo. The primary end point in this study was mortality over a 3-year follow-up. Adherence was measured and calculated from the dose counter on the inhaler device. Good adherence was defined as an average adherence greater than 80% over the whole study period. Of the 6112 patients in this study, 79.8% had an adherence level greater than 80%. The authors found no associations between COPD severity (Based on GOLD stage) and adherence. The overall mortality for the study period was 14.3%. Of the patients with good

adherence, 11.3% died, compared to 26.4% in patients with poor adherence. Adjusting for region, age, sex, smoking status, FEV_1, BMI, MRC dyspnoea score, previous use of inhaled corticosteroids, previous myocardial infarction and treatment arm, good adherence was associated with a 60% lower risk of death (HR: 0.40, p<0.001). In a similar model adjusting for region, age, sex, smoking status, FEV_1, BMI, prior exacerbations and treatment, good adherence was associated with a 44% reduction in the rate of severe exacerbations (rate ratio 0.5, p<0.001). Specifically looking at the arm that received salmeterol and fluticasone together, there was a 6.6% relative risk reduction in death for those with poor adherence and 21.2% for those with good adherence. In this paper it is important to note that the documented survival benefit was independent of the study treatment. Therefore, even those with good adherence and on the placebo arm had a survival benefit. This finding might highlight a healthy survivor benefit or "the healthy adherer effect", being that patients who exhibited a high adherence behavior to the study drug or placebo were likely to be adherent to other medications or treatments (such as physiotherapy/rehabilitation). These were unmeasured confounding variables in this study.

In another paper, Blee et al looked at the association between COPD readmission and adherence. In this paper, the authors examined a cohort of COPD patients being discharged from hospital with a proposed intervention: The intervention was a multi-dose medication dispensing system on discharge. Patients before and after the intervention were compared. With this intervention patients were considered adherent as they were given the remaining doses of their multi-dose inhaler on discharge. Patients were followed for up to 60 days and the authors found significantly more readmissions at 30 days (p<0.01) and at 60 days (p<0.01) in the patients who didn't receive the multi-dose medication dispersion (69), suggesting poor adherence is associated with COPD readmissions, as we have seen in asthma. However, unlike asthma, there are no known studies assessing inhaler use and technique in this patient population.

It is evident that adherence to medications is important in both general medical conditions and respiratory disorders. It is therefore crucial that medication adherence is measured accurately. I will now describe several methods of measuring medication adherence.

1.4 MEASURING ADHERENCE

As described by Heaney in 2012, the first step in studying non-adherence is the identification of non-adherence, a review of the literature on how adherence can be assessed is outlined below (70).

1.4.1 Direct Methods

Measuring adherence has been divided into two broad categories, direct and indirect methods (1). Direct methods involve such techniques as measuring blood levels of the medication in question. This measurement gives information on medication adherence, if the drug is within the therapeutic index or if the patient has toxic levels of the medication. However, this method is prone to variations in drug metabolism, potentially high costs for sampling and analysis as well as inconvenience to the patient. Additionally, the presence of drug in an assay dose not necessarily mean the patient was adherent, they may have just taken one or two recent doses. Neither dose lack of drug in the assay mean the patient was non-adherent, they may have just missed one or two recent doses. Another example of a direct method is directly observed therapy (DOT). This is commonly used in *Mycobacterium tuberculosis* treatment. Due to its highly infective state and therefore implications for public health and safety, adherence is crucially important. Again with this method there is inconvenience to the patient and the potential for factitious results (i.e. the patient could hide the medication in their mouth while being observed and discard it later). Neither of these methods are practical in a busy out patient service tending to a common clinical condition such as asthma or COPD. In an attempt to make DOT less inconvenient for the patient, Video/Virtual observed therapy (VOT) has become possible in recent years with the availability of smartphones and tablets (71). This may be a technique used in the future to assess adherence.

1.4.2 Indirect Methods

Indirect methods of assessing adherence don't involve measuring drug levels or directly observing medication been taken. This category includes self-reported adherence (72), pill counting (or dose counter results for inhaler devices), pharmacy refill records, and in recent years, electronic monitors. Self-report is in itself biased by poor self-recall or

misinformation to please a healthcare provider (73-78). Currently there are approximately 58 different tools for capturing self-reported adherence. In a recently published systematic review of self-reported adherence scales, only 16 of these 58 had any published data on reliability (79). Pill counting or dose counter measurements are simple and cheap methods of assessing adherence. However, these values give no information on when the medication was taken and are open to manipulation, such as dose/pill dumping (80,81). In a cohort of 216 patients taking low-dose phenobarbital (a commonly used treatment for epilepsy), 161 (75%) appeared to have good adherence based on pill counting (80). Using a direct method of measuring adherence, 51 (32%) had low plasma phenobarbital concentrations, suggesting poor adherence. The authors concluded that pill counting grossly overestimates medication adherence. It is important to note that cut-offs for good and poor adherence are often chosen arbitrarily, and variations in this cut off will significantly effect the sensitivity, specificity and accuracy of the adherence method, i.e. high cut-offs will increase sensitivity and decrease specificity while low cut-offs will increase specificity but decrease sensitivity (82). Even with the widely used Moriskey Medication Adherence Scale (MMAS-8) sensitivity has been reported as low as 26% with a corresponding specificity of 75% (83). In this same study, with a multivariate regression model MMAS-8 was not predictive of non-adherence. Similarly with pharmacy refill records (84), no information on when the medication or even if the medication was taken is provided. For example, a patient may collect their prescription and take all their medication in the first week due to symptoms and then take nothing for the rest of the treatment period. With this indirect measure of medication adherence, the only information collected is if the patient collected their medication from the pharmacy (2) and no information on the pattern of usage. Additionally, not all countries have fully integrated and complete pharmacy registries, which may make this method of measuring adherence un-attainable.

Another example of an indirect measure of adherence used in a select asthma population is Fractional Exhaled Nitric Oxide (FeNO). FeNO has been established as a non-invasive surrogate marker of airway inflammation (85) in a subset of asthma patients as it correlates with eosinophilic inflammation (86). The test is a simple exhaled breath test that can be performed quickly and either in the patient's home or in the hospital. A study published by McNicholl et al (87) assessed the utility of FeNO in identifying non-adherence in difficult

asthma. In this paper the authors reviewed 146 new referrals to a difficult asthma clinic. There was no significant relationship between baseline FeNO levels and previous ICS prescription refill adherence. Patients with a high FeNO level (>45ppb) were then followed for 5 consecutive days receiving directly observed inhaled steroid therapy (DOICS). Patients who were deemed non-adherent (based on previous pharmacy refill records) had a significantly greater reduction in their FeNO level than those who were adherent, suggesting that FeNO may be used to differentiate patients with difficult asthma who are adherent and those who are not. To validate their findings the authors then performed concordance interviews in 40 patients. Interestingly, 3 patients who were deemed adherent based on prescription refill records were identified as non-adherent by the FeNO suppression test (5 days of DOICS). Through the interview process these three patients admitted to not taking their medications regularly, and two patients also had incorrect inhaler technique. Therefore, it is reasonable to suggest that FeNO can be used to identify patients who fill prescriptions for treatment but don't actually take them (a pitfall in pharmacy refill record analysis). However, FeNO is not readily available in all centres, is costly and is only applicable to a small subset of asthma patients (e.g. those who have high FeNO, don't smoke and have mild sinus disease).

1.4.3 Electronic Monitors

Several studies have shown that patient self-report and even health-care worker assessment are inaccurate in quantifying medication adherence (88,89). As mentioned previously, indirect methods such as pill counting, or dose counting can be falsely elevated in cases of dose dumping, an attempt to hide poor adherence. While direct methods have their shortcomings as well, electronic monitors are slowly becoming the gold standard in measuring adherence (90). Electronic monitors provide a more realistic description of medication adherence particularly when compared to self-report. Zeller et al compared self-reported adherence of cardiovascular medication to an electronic monitor (the medical event monitoring system (MEMS) for pill based medication) (91). Seventy-eight patients were evaluated and adherence was monitored for a mean of 75 days. In this study, the majority of patients (79%) over reported their medication adherence; therefore there was no correlation between self-reported adherence and adherence recorded by the electronic monitor. Another group compared self-report to electronic monitoring of medication

adherence in a cohort of patients taking anti-hypertensive treatment (92). In this paper only 21% of patients admitted to missing doses, however through the electronic monitor 42% of patients were identified as missing doses. Electronic monitors also have the added advantage of promoting adherence. Demonceau et al examined factors that influenced adherence and found that the greatest impact on medication adherence was when electronic adherence monitoring combined with feedback from the patients healthcare provider and their individualized adherence pattern was utilized (93).

There are several different groups of electronic monitoring devices available. Electronic diaries, although dependent on the patient using them, automatically record and store information on the date of time of each diary entry. There is also electronic detection of package entry. With these devices micro circuitry is embedded into the drug packaging and doses are recorded with the time and date when the drug is released from the packaging (94). There are also a number of ingestible smart sensors. For these medications the micro circuitry is incorporated into the tablet/medication itself and becomes active once contact with gastric acid is made. From there a radio signal is emitted to a detector worn on the patient's skin to identify the drug ingested and the time of the dosing (95). The most effective method of measuring adherence with an electronic monitor will be a monitor with the least demand from the patient (i.e. no additional work for the patient).

Electronic monitors are also commonly used for monitoring inhaler adherence. The Doser (96), one of the oldest electronic monitors, records the number of inhaler actuations without recording the time of use. The MDILog, SmartTrack (97), SmartTouch, SmartDisk (98), SmartTurbo, SmartFlow, SmartMist, SmartSpray and Propellor sensors record the date and time of each inhaler actuation and this data is uploaded remotely to a webserver (99,100). These devices also have on-board reminders for missed doses based on the patient's treatment regimen. Julius et al tested the accuracy of the Doser, MDILog and the SmartMist in recording actuations (101). All devices had high levels of accuracy, however the SmartMist was 100% accurate. The Doser and MDILog occasionally recorded additional actuations. A recent article by Chan et al (102) reviewed the currently available electronic inhaler monitors for inhalers. Most available monitors for inhalers are built for the metered dose inhaler (MDI) and all electronic inhaler monitors are able to record the time and date

that the inhaler was used. Some can also record inspiratory flow during inhalation. A few devices are able to upload data to a webserver or to a cell phone via Bluetooth, which reduces the potential for data being lost. The accuracy of some of these devices, when compared to written diaries is between 90% and 100%, with failure rates ranging from 0% to 21%. The temporal data collected from electronic monitoring aids in the management of asthma patients by identifying different patterns of inhaler use. Chan refers to patients with poor adherence needing either more intensive interventions or reduced/intermittent treatment.

As mentioned previously, another advantage of electronic monitors is its use in adherence promotion. With respect to this, two themes have been identified in the literature: face-to-face health professional to patient adherence feedback and direct to patient reminders for missed doses. Face-to-face feedback tended to be in the form of discussions around printouts of inhaler use, however the outcomes, change in asthma control and emergency department visits has not been consistent between studies. Most of these studies were limited by high levels of adherence in both active and control groups of the intervention, perpetuated by free medication, frequent study visits and the fact patients were aware their adherence was being monitored. Direct to patient reminders are used to establish good habits in medication taking. In a randomized control trial published in 2007, the authors of this paper were able to show an almost 20% higher level of inhaler adherence in patients that received a reminder by way of a beep up to an hour after a dose was due, $p<0.0001$ (103).

In the review paper by Chan et al, the authors identify that more evidence is required regarding the feasibility and cost-effectiveness of electronic monitors and their relationship with clinical outcomes in different patient populations (102). The authors also identify a lack of studies looking at real-life use of electronic monitors to highlight their acceptability and feasibility outside of research settings. Another area lacking research with electronic monitors is different patterns of inhaler use and their impact on adverse events. It is clear from the literature that larger and longer-term studies are needed to determine if adherence improvements can be sustained and how that relates to clinical outcomes. The authors of this review paper identified three main areas for electronic monitor use:

Firstly, for personal patient-driver use. Feed back of personalized inhaler adherence to patients may lead to increased inhaler adherence and better self-management. Secondly, for clinical management of difficult to treat disease (i.e. asthma); with reliable patient adherence data clinicians can make informed treatment decisions. For example, by accurately monitoring inhaler adherence in asthma, clinicians can identify poorly controlled patients due to poor inhaler adherence, rather than unnecessarily escalating treatment to potentially high-cost add-on treatment. The cost of electronic monitors could be offset by savings made by avoiding this escalation treatment. It has been suggested that an adherence program that increases adherence by 50% could be as low as US $130 per person annually to be cost-effective; electronic monitors are already in this price range (104). The final practical use for electronic monitors is in clinical research.

Adherence to medications questions how well a patient adheres to a treatment plan. It is adherence to therapy, good or poor, that leads to specific clinical outcomes based on the drug in question. For example, taking treatment for epilepsy is most effective at preventing seizures when the plasma level of the medication is within a set range. For medications taken in pill form this information is simply related to if and when a patient takes their medication. For medications that require a device for drug delivery, there is an added component to medication adherence and drug delivery, which is how well the patient takes their medication. An example of this would be an inhaler device.

As discussed in the previous section, each commercially available inhaler device has a set of instructions that lead to maximum drug delivery and therefore maximum effect. Although the drivers for if (sometimes referred to as intentional adherence) and how (sometimes referred to as un-intentional adherence) a patient takes their medication may be different, the end result of medication adherence is the clinical effect of the medication. Therefore, for devices such as inhalers, where technique of use is also a crucial part to drug delivery and clinical effect, medication adherence has to account for technique of use. The electronic monitors discussed above collect data on when an inhaler is used, however none can tell the user how well the inhaler was used.

I will now describe a new and novel solution to measuring inhaler adherence, the INCA™ device.

1.4.4 INCA Device

The INhaler Compliance Assessment (INCA™) device, developed by our team, is a novel electronic monitor that was designed for the Diskus™ DPI and sits on top of the inhaler. Unlike the previously mentioned electronic devices, the INCA device can measure inhaler technique longitudinally by recording audio of inhaler use, a presumed improvement on the current electronic monitors, however as there is no definite gold standard to measuring adherence, or a device similar to this, diagnostic accuracy is difficult to measure. The device is removable and audio files are downloaded from the device onto a computer via universal serial bus (USB) (see Appendix Figure A-1). Analysis of the acoustic data allows identification of the critical steps in inhaler use, for the Diskus™ inhaler: 1. Open the inhaler, 2. Push the lever back completely, 3. Exhale away from the inhaler, 4. Place the mouthpiece between teeth and lips and inhale deeply, 5. Hold breath for at least 5 seconds and 6. Exhale away from the mouthpiece (105-109). Audio analysis identifies whether the inhaler was opened, if the lever was moved, if the user inhaled, along with the acoustic data associated with the inhalation (duration, peak inspiratory flow (PIFR)). This also allows for classification of some other pre-identified inhaler errors such as exhalation after drug priming, or multiple actuations or multiple inhalations. A full description of the device can be found in Appendix A.

With all the different methods that I have described for measuring adherence, there are also methods used to calculate adherence, which I will describe now.

1.5 CALCULATING ADHERENCE

There is no gold standard in calculating adherence and as I have shown adherence to medication therapy remains a complicated process. Currently used methods of calculating adherence such as the mean possession ratio (MPR) and the proportion of days covered (PDC) don't account for some of these intricacies of adherence.

$$\text{Ü Ũ'Y} \text{ سٍ} \frac{\text{òéòŏà èóáŨ̃Ωì é'Ω Ω̈ŏώí íóηὰώ éŨ̃òŏΩὲ'ΩΩ Ωóì⁇è'Ω éŨ̃íΩìùŏò⁇éè ὴΩì⁇é'Ω}}{\text{òéòŏà èóáŨ̃Ωì é'Ω Ω̈ŏώí Ωóì⁇è'Ω éŨ̃íΩìùŏò⁇éè ὴΩì⁇é'Ω}}$$

or

$$\text{Ü Ũ'Y} \text{ سٍ} \frac{\text{òéòŏà èóáŨ̃Ωì é'Ω ΩéíΩí ŏòòΩáὴòΩΩ ⁇è éŨ̃íΩìùŏò⁇éè ὴΩì⁇é'Ω}}{\text{òéòŏà èóáŨ̃Ωì é'Ω ΩéíΩí Ωώὴ Ω̃ŨòΩΩ ⁇è éŨ̃íΩìùŏò⁇éè ὴΩì⁇é'Ω}}$$

$$\text{Ũ'Oŏ} \text{ سٍ} \frac{\text{''Yéòŏà Ω̈ŏώí ŏàà Ωì ó'Ω ŏùŏ⁇àŏŨ̃à'Ω}}{\text{Oŏώí ⁇è 'Oéàéú óὴ Ũ̃Ωì⁇é'Ω}}$$

With electronic monitors, information on exact time of use can be acquired which can be used to predict plasma drug concentrations. This relationship has been tested and proven with electronic monitors for pill-based medications that record events when a pill container is opened. These studies centred around retro-viral treatment for Human Immunodeficiency Virus (HIV) and compared predicted plasma concentrations based on time of dose captured from the electronic monitor and periodic directly measured plasma concentration from the patient's own blood samples (110,111).

It has been suggested that calculating medication adherence over a defined interval of time include: 1. The proportion of prescribed drug taken, 2. The proportion of days with the correct number of doses taken, 3. The proportion of doses taken on time, in relation to a prescription-defined time interval between successive doses, 4. The distribution of inter-dose intervals, 5. The number of drug holidays and 6. The longest interval between doses

(112). There is no current method to calculate adherence as a direct relationship to the drug (in question) profile and its expected clinical outcomes. A method that is non-invasive, low cost and can model individuals own drug exposure is required to quantify adherence and pharmacokinetics. Vrijens rightfully states that the clinical power of data obtained through pharmacometric analysis can be greatly improved (113).

I have described several methods of measuring and calculating adherence. I have also shown that mediation adherence is poor in several patient populations, with important clinical implications highlighting its importance in respiratory disorders. I will now discuss the predictors of non-adherence in patients with respiratory disorders.

1.6 PREDICTORS OF INHALER ADHERENCE

In order to design interventions to promote adherence, it is necessary to understand why people are not adherent. A reliable model to predict adherence will in theory help physicians intervene even before the beginning of non-adherence, therefore much research has gone into identifying factors that predict medication adherence, particularly in terms of inhaler adherence. Over 15 years ago Balkirshnan et al examined predictors of inhaler adherence in a cohort of elderly patients with COPD (114). The authors performed a retrospective longitudinal cohort study from 1995 to 1997 of 1595 patients who were over the age of 65 and had a diagnosis of asthma, COPD, chronic bronchitis, chronic airways obstruction or emphysema. As defined by the authors, 60% of this population had poor inhaler adherence. Patients with good adherence were more likely to be female, with more chronic medications (including short acting beta-agonists), non-government based health insurance and lower health care utilization.

In the next few paragraphs I will describe known predictors of inhaler adherence by specific subheadings. That is, those specifically related to the disease, those related to the patient himself or herself, those related to socioeconomic factors and lastly factors related specifically to inhaler technique.

1.6.1 Disease Related Determinants of Adherence

For this review disease factors include disease severity and disease burden. In a paper by Diette et al, the authors found a strong correlation with the asthma symptom index and B-agonist overuse, a marker of disease severity and control. This would suggest that symptoms may have a pivotal role in overuse of inhaled medications (115). While Gamble et al found low adherence to ICS was significantly associated with female sex, quality of life and hospital admission in the previous year (59). Balkirshnan et al also found a relationship with inhaler adherence and comorbidity (114). Using the Charlson Co-morbidity score (116), the authors found that a 1 unit increase in this score reduced the risk of good adherence by almost 22%. Importantly, good adherence was associated with a significant reduction in hospitalization and physician visits. It is clear that both disease severity and disease burden influence medication adherence.

1.6.2 Personal Factors as Determinants of Adherence

Personal factors relate specifically to the patient and include factors such as age, gender, comprehension and personality. In a systematic review of observational studies looking at inhaler adherence, Dima et al divided inhaler adherence into its three main phases (117), as discussed previously. Focusing on the initiation phase the authors found non-initiation was associated with younger age and female gender.

Important to the execution/implementation phase is comprehension. A marker of comprehension, cognitive function, has previously been reported as a potential determinant of good inhaler technique with a pMDI (118-120). In these papers, the authors used the abbreviated mental test (AMT) and found that patients with an AMT score of <8 were unable to use a pMDI. In a follow up study, Allen et al (121) looked at 30 inhaler-naïve inpatients receiving active rehabilitation with a variety of surgical or medical illnesses. These patients were elderly with a mean age of 85 years and had a baseline AMT score of 8 to 10. During the study period patients received training in the use of the MDI and Turbohaler. A previously published 10 point scale for MDI technique was used (122), see Table 1-3 . This scoring system also identifies the potential inhaler errors associated with the MDI (A checklist for a DPI device can be found in Appendix E). In this study the authors found a significant correlation between this inhaler technique score for the MDI and Mini-Mental Status Exam (MMSE). The authors also found that impaired frontal executive function, (assessed with the validated EXIT25 test) was also associated with poor inhaler technique, suggesting that the executive domain is important in self-administering technique. With the 10-point analogue score, the authors found that the most common inhaler errors with the MDI were failure to actuate the device during inhalation, stopping inhalation upon actuation and exhaling after actuation. However, for the Turbohaler, the most common errors were failure to prime the device and exhaling through the device.

Table 1-3: Inhaler Checklist for pMDI:

Below is the Metered Dose Inhaler (MDI) Score used in assessing inhaler technique for the MDI.

Typical Errors Observed	MDI score
A Perfect Technique	10
Breath Hold <5 seconds	9
No Breath Health	8
Actuates Inhaler Slightly Late in Inspiration	7
Actuates Late but well Before Full Inspiration	6
Actuates Too Late/Too Early	5
Poor Inspiratory Effort with Late/Early Actuation	4
Very Poor Co-ordination of Inspiration/Actuation	3
Failure to Actuate or No Inspiration	2
Little Idea How to Use the Inhaler	1
No Idea What to do with the Inhaler	0

Included in personal factors, Axelsson et al hypothesized that personality traits have an impact on medication adherence (123). For this paper, the authors collected data on 180 asthma patients based in Sweden. Information on adherence and personality were collected through questionnaires, therefore adherence was self-reported. The authors found that female patients tended to report higher levels of adherence. Men with higher levels of neuroticism were less likely to follow treatment regimens, whereas those who scored higher in agreeableness and conscientiousness domains were more likely to be adherent. Similar findings in smaller cohort of asthma patients (n=35) was published by Emilsson et al (124).

These studies have demonstrated that inhaler adherence is complicated and is influenced by several factors related to the patient directly. This may even include income and socioeconomic class.

1.6.3 Socioeconomic Factors as Determinants of Adherence

In the systematic review published by Dima et al, three studies found that higher income was associated with higher levels of inhaler adherence (117). Apter et al (125) looked at the influence of socioeconomic and health-belief on inhaler adherence. Patients were initially interviewed with a script of standard questions assessing socioeconomic status, asthma severity, current medications, and a health locus of control questionnaire was filled. For this analysis, adherence was measured with an electronic monitor (Chronolog, Medtrac Technologies, Inc., Lakewood, CO) on an MDI and calculated as the number of actuations recorded divided by the number of doses prescribed. Adherence was categorized as good and bad based on a 70% cut-off for good adherence. Of the 50 asthmatic patients studied, 54% had an adherence level greater than 70%. Initially, in a univariate analysis the authors of this paper identified several socioeconomic factors that influenced inhaler adherence; these included less than 12 years of formal education ($p<0.001$), Spanish as a primary language ($p=0.005$), household income less than $20,000 ($p=0.002$) and minority status ($p=0.007$). The authors suggest that this relationship with lower socioeconomic class may explain the increased asthma morbidly seen in this population cohort. In a multivariate logistic regression model, less than 12 years of education (OR: 6.72) and poor patient-clinician communication (OR: 1.2) were associated with poor adherence. Mean inhaler adherence for high-school graduates was 89% and only 43% in those who did not complete high school. In this paper the authors also identify four different patterns of poor inhaler adherence. One group of patients they describe as typical non-adherence, where the patient either remembers fully to take their medication or forgets completely. Another group were the patients that didn't use their medication at all. The third group described were patients who take their inhaler regularly but take fewer doses than prescribed per day. The fourth group both under use and overuse their prescribed medication.

Some qualitative research in inhaler adherence has also been performed. In Canada, Pelaez et al performed 1 hour interviews with 24 subjects with asthma (or parents of children with asthma) revolving around asthma perceptions, use of asthma medications, current self-management, prior changes in self-management and patient-physician relationship (126). Examples of questions used in the interview included: "Why do you take/not take your medications? What would you think/do if your doctor recommends that you take long-term

controller medication?" The authors divided the barriers to inhaler adherence into three groups, patient related, patient-physician interaction related, and health-care system related. Patient related barriers included cognition, motivation (attitudes and preferences towards medications), practical implementation (i.e. inconvenience of having to take a medication more than once a day) and parental support (for children with asthma). Patient-physician interaction related barriers included communication and the patient-physician relationship. Barriers related to the health-care system included resources and services. The authors suggest patient's adherence to a treatment plan is a multi-level phenomenon.

In a systematic review published in 2009 Drotar and Bonner reviewed 27 articles pertaining to inhaler adherence in children with asthma (127). Several factors related to inhaler non-adherence included minority status, single-parent status, and socioeconomic status (including parental education and income). In regards to psychological factors the authors identified medication side effects, lack of efficacy, low expectations of asthma control and parental psychosocial status were all related to inhaler non-adherence. Hence, reinforcing the idea that medication adherence is a multi-level phenomenon.

1.6.4 Inhaler Technique

An added complication to inhaler medication adherence is the required skill and technique to use the device correctly, resulting in maximum benefit from the medication. It is therefore important, when discussing predictors of inhaler adherence, that predictors of inhaler technique also be discussed. Wieshammer et al sought to report inhaler errors for four commonly used inhalers (Aerolizer, Diskus, Handihaler and Turbohaler) while also identifying risk factors for inhaler errors (128). The authors included 224 patients in their analysis. Almost 31% of the patients had poor inhalation technique and this error was significantly more common with the Handihaler and Turbohaler. Significant associations were found with age and level of airways obstruction (based on lung physiology); older patients and worse airways obstruction lead to higher levels of inhaler errors. The authors also did a further analysis looking at the impact inhaler training had and found the odds ratio of ineffective inhalation fell with training. Goodman et al looked at inhaler technique with the pMDI in 58 patients (129). The authors of this study used a sensor to measure the

inhalation flow and found that only 58% of patients had correct inspiratory flow. The authors looked at gender, age and diagnosis (asthma or COPD) as predictors of poor inhaler technique, and only found gender to be significant; females were more likely to have correct inhalation flow.

These studies would suggest there are several determinants of inhaler adherence. Such determinants of adherence include lower co-morbidity, good patient cognition, certain personality traits, higher socio-economic class and good patient beliefs. Having identified these predictors of medication non-adherence, I will now discuss possible interventions to promote medication adherence.

1.7 METHODS TO PROMOTE MEDICATION ADHERENCE

It is clear that non-adherence to medicines is a world wide problem (130) particularly in relation to chronic disease management and therefore interventions are needed to improve adherence. Identifying problems with adherence is the first step which health care professionals are poor at. In a recently published large multinational cross sectional survey across Europe, Clyne et al surveyed 3196 healthcare professionals (855 doctors, 1047 nurses and 1294 pharmacists) (131) using a 50-item questionnaire regarding adherence-enhancing interventions. The primary outcome of this study was participant's response to the question "I ask patients if they have missed any doses of their medication." The authors found that only 50% of health care professions ask their patients if they have missed any doses of their regular medications. This represents a missed opportunity to intervene in patients with poor medication adherence. Schlender et al examined the effects of adherence interventions using an Archimedes model, a simulation model that includes anatomic, physiologic, clinical and administrative factors, to predict outcomes in an asthma population. In their model the authors suggested that adherence interventions could reduce annual asthma related hospitalizations by one million, reduce emergency department visits by four million, and cut down unscheduled doctor visits by almost nine million in the United States (132).

Several studies have looked at different interventions aimed at improving medication adherence and clinical outcomes in different disease states. A systematic review published in the Annals of Internal Medicine examined interventions to improve adherence for chronic diseases in the United States (133). In this paper the authors reviewed 73 articles that met their inclusion criteria, 69 were randomized control trials and 4 were observational studies (to examine the effectivness of policy interventions not seen in clinical trials). The authors found several pathways to improve medication adherence with little evidence linking good adherence with other outcomes such as morbidity, mortality, quality of life, patient satisfaction, health care use or costs. Of the 33 trials that reported improvements in adherence only 18 (29%) reported an improvement in at least one health outcome, 8 (13%) reported no improvements and 7 (11%) did not collect data on health outcomes. Improved health outcomes with good adherence were mostly found in studies that tested their

interventions in hypertension, heart failure, depression and asthma. Examples of interventions that improved medication adherence were blister packaging, case management, education with behavioural support, reminder calls, pharmacist-led multicomponent interventions, collaborative care, self-management and shared decision making. Asthma studies that lead to an improvement in adherence used self-management with strong educational components and shared decision-making tools. In one study shared decision-making lead to improvements in symptoms, pulmonary function, health care use and quality of life (134). I will now discuss the following adherence interventions used in some general medication conditions (such as cardiovascular disease) and respiratory disorders: adherence reminders, adherence education, and the behavrioural component of adherence, including motivational interviewing.

1.7.1 Adherence Reminders & The Formation of Habit

Reminders are a suggested adherence intervention. In a cluster-randomized trial to test the benefits of reminders in patients being treated for tuberculosis, the authors randomized 4,173 patients into 4 arms: control, text messaging, medication monitor and combined (139). Patients were followed up for 6 months and all patients took medications out of a monitor box, which recorded when the box was opened. This electronic monitor only gave reminders in the medication monitor and combined arms. The endpoint of this study was the percentage of patients who missed more than 20% of their anti-tuberculosis treatment. In the control arm almost 30% of patients missed more than 20% of their treatment, 27% in the text messaging arm, 17% in the medication monitoring arm and only 14% in the combined arm missed more than 20% of their treatment. In a meta-analysis examining the benefits of mobile phone text messaging in adherence interventions, the authors found 16 randomized clinical trials where text messaging was used to improve medication adherence (140). In this pooled analysis of 2472 patients, text messaging significantly improved medication adherence with an odds ratio of 2.11 leading to an absolute increase of almost 18% in adherence rates. This therefore provides evidence for reminders as a method of promoting medication adherence. It would therefore seem that the formation of a regular habit is an important tool in improving adherence (141). In a randomized clinical trial among stroke survivors, 62 patients were randomized to usual care or a two-session

adherence intervention with the recognition of environmental cues to form a regular habit of medication taking (142). Adherence to anti-hypertensive medication was monitored with an electronic pill bottle monitor for up to 3 months. In this study the intervention group had higher adherence rates for doses taken on schedule. This translated to a 10% increase in doses of anti-hypertensive medication taken on schedule, thus identifying habit formation as another tool in promoting medication adherence.

1.7.2 Adherence Education

Adherence education is another intervention used to improve medication adherence. In a study examining the impact of education on medication adherence, 160 patients with heart failure were randomized into usual care or an experimental group that received health education booklet and telephone follow-ups in an attempt to improve medication adherence (135). Both groups had a decline in medication adherence over the study period, however the experimental group had a significantly higher level of adherence throughout the study. In addition, the experimental group had better quality of life scores and less anxiety and depression. Similarly, in a study of asthma patients randomized to person-centred education including inhaler technique or written information-only education; those with the person-centred education had improvements in asthma control, inhaler adherence and quality of life with reduced exacerbations (136). With regards to COPD, the lung health study followed patients with COPD for 5 years to evaluate the efficacy of an intensive smoking cessation intervention and bronchodilator therapy (137). Included in this study was an ancillary study of inhaler adherence (138). Two hundred and thirty-one patients had adherence data recorded with an electronic monitor for the study period and were randomized to either receive feedback regarding their adherence (readings of actuation dates and times from the electronic monitor were used as feedback during the 1st and 10th weeks) or usual care. Inhaler adherence was significantly higher in the feedback group for each of the follow up intervals. However, for both groups, inhaler adherence decreased rapidly during the first 8 weeks. The usual care group had a larger decline in the first four months. Interestingly, both groups increased inhaler adherence directly after a trial visit. These studies highlight that education interventions can promote medication adherence.

1.7.3 The Behavioral Component of Non-Adherence

It has been suggested that non-adherence be treated as a variable behaviour as opposed to it being a trait characteristic, meaning that not only does adherence differ between individuals but is also variable within the one individual. It is therefore important to understand the individual when assessing adherence and consider their motivation and ability. A meta-analysis of 93 studies, published in 2009, showed that medication adherence is related to how an individual judges their own need for the medication and their concerns regarding the negative effects of the medication (143). Several papers have examined the impact patient beliefs have on medication adherence. Using the beliefs in medicine questionnaire (144), Chapman et al performed a cross-sectional study of people with epilepsy receiving treatment (145). Poor adherence was associated with negative beliefs (doubts regarding necessity) and concerns about potential side effects. The authors found these predictors of non-adherence to be more significant than clinical and demographic variables. The NICE Medicines Adherence Guidelines (143) consider the three most important variables in medication adherence to be patients' beliefs and concerns, satisfaction with involvement in treatment decision and practical support with using medication. It is known in asthma that asthma education empowers patients and patients with positive attitude towards controlling their disease are more likely to adhere to prescribed treatment (146,147).

1.7.4 Motivational Interviewing

Motivational interviewing is an example of a patient-centred communication tool that focuses primarily on enhancing the patient's intrinsic motivation to engage in good self-management. Lavoie et al conducted a randomized controlled trial of brief motivational interviewing to improve adherence to inhaled medications in asthmatics (148). The authors of this paper recruited and finished follow up on 40 adult patients with a confirmed diagnosis of asthma that was uncontrolled. These patients were all on inhaled corticosteroids and non-adherent (<50% based on pharmacy refill records). Patients were then randomized to either the usual care arm or motivational interviewing arm. Those in the motivational interviewing arm underwent three to four 14-30 minute individual sessions over four to six weeks with a specialist in motivational interviewing. Briefly the interview process included strategies that explored ambivalence, supported self-efficacy, "rolling with

resistance" and eliciting "change talk." Patients in the active arm had a 13% increase in inhaler adherence, while the usual care patients only had a 6% improvement. Interestingly, improvement in asthma self-efficacy was more pronounced in the active arm, however neither of these differences were significantly different.

These broad variables of patients' beliefs and concerns, satisfaction with involvement in treatment decision , adherence reminders, adherence education and practical support with using medication provide an excellent framework for the development of adherence interventions. Such education methods used in inhaler training for asthma include written instructions, illustrations, interactive computer programs and audio-visual feedback (149). An example of such an intervention was published by Charles et al in 2007 (103). In this randomized open-label parallel group study of 110 asthmatics, patients were randomized to receive 24 weeks of fluticasone propionate 250 mg twice daily via a pMDI with or without audio-visual reminder function. All pMDI's had an electronic adherence monitor. The patients randomized to the audio-visual reminder function had significantly better inhaler adherence particularly in the last 12 weeks of the study protocol.

Recently the Hospital Information and Quality Authority in Ireland published a systematic review which included over 2,000 randomized control trials involving self-management support interventions in chronic diseases (150). The strongest evidence was for disease specific interventions. Specifically for asthma, 12 systematic reviews (90 randomized control trials) were evaluated. It was suggested that self-management interventions in asthma should include patient education, skills training, behavioral interventions and the use of written action plans. Interestingly, behavioral interventions lead to improved medication adherence and a reduction in symptoms. The authors also noted that in non-disease specific interventions, those that included motivational-interviewing lead to improved medication adherence. Specifically for COPD the authors of this document reviewed 16 systematic reviews (185 randomized controlled trials). In this review it was found that education lead to reduced COPD-related admissions while complex self-management support interventions (including education and exercise) and some telemedicine interventions lead to improved health-related quality of life.

From all these studies, it is evident that to promote medication adherence an effective intervention requires several factors such as reminders, cues to help develop habits, education and factors related to an individuals personal motivation and ability.

1.8 FINAL REMARKS

In this chapter I have shown that medication adherence is an important factor in chronic disease management with both clinical and health cost implications in general medical conditions and respiratory disorders. Specifically in respiratory disorders, such as asthma and COPD, I have shown that inhaler adherence is complicated by the technique required to achieve maximum drug delivery for each inhaler device. I have also described different ways of measuring adherence and different methods to calculate adherence and have shown with these tools and methods most studies report low levels of medication adherence. However, there is still a lack of published evidence in the literature regarding the importance of inhaler technique in measuring and calculating inhaler adherence, how inhaler technique is measured longitudinally, as well as its impact on clinical outcomes and most importantly how it can be optimized effectively.

1.9 AMS AND INTENTIONS

The aim of this thesis is to determine the importance of inhaler technique in measuring and calculating inhaler adherence in various respiratory disorders. In order to gain a better understanding of how inhaler technique impacts on inhaler adherence the following intentions were set:

1. To review inhaler adherence in a real-world population and identify the prevalence of common inhaler technique errors using the INCA^{TM} device that records audio each time a patient uses their inhaler (Chapter 2). From this I can identify the frequency of specific inhaler errors.

2. To assess the impact the specific inhaler errors, identified in the previous section, have on drug delivery (Chapter 3).

3. To develop a new method of calculating adherence that accounts for both inhaler use and technique, and compare the relationship this method has with clinical outcomes over current methods of measuring adherence (Chapter 4).

4. To describe inhaler adherence, using this new method of calculating adherence, in a large cohort of respiratory patients (Chapter 5)

5. To identify predictors of inhaler adherence, when technique of use is included (Chapter 6).

6. To examine the effect an education program targeting inhaler technique has on inhaler adherence in a cohort of severe asthma patients (Chapter 7).

Chapter 2 :

A PILOT STUDY TO DETERMINE THE FREQUENCY OF ERRORS IN INHALER TECHNIQUE AND INHALER USE IN A UNSELECTED COHORT OF RESPIRATORY PATIENTS RECTUITED FROM PRIMARY/PHARMACY CARE

2.1 INTRODUCTION

In the previous chapter (Chapter 1) I described the importance of medication adherence, in particular inhaler adherence in respiratory patients. Specifically with respiratory patients and inhaler devices, I highlighted the need to know the intricacies of inhaler adherence including missed doses as well as the frequency of inhaler errors, which is difficult to measure with current methods. I then introduced a new electronic monitor (INCA^{TM}) which can longitudinally and objectively monitor inhaler adherence while accounting for both missed doses and inhaler technique errors. In this chapter I will use the INCA^{TM} device to report the frequency of inhaler technique errors in a cross-section of respiratory patients.

2.2 BACKGROUND

For inhaled treatments, incorrect technique may have a significant effect on the measurement of adherence during the implementation phase of adherence when combined with time of use. Depending on the population studied, between 14%-90% of patients reportedly do not to use their pressurized metered dose inhaler (pMDI) correctly, while 50-60% misuse a dry powder inhaler (DPI) (65). A major limitation of the methodology employed to assess inhaler technique of use, direct observation, is that it involves a subjective visual assessment of the individual's technique during inhaler use. Hence, this method cannot assess how well the patient uses their inhaler when not under observation. Electronic adherence monitors have been developed for clinical research, including those specifically for inhaler therapy (102,151,152). These monitors provide the opportunity to give insight into adherence, in particular the implementation period (as described in Chapter 1), however at present none assess technique of inhaler use in conjunction with time of use.

The purpose of this study was to use the INCA^{TM} device to assess the frequency of errors in inhaler use including the time and technique of use, in a cross section of respiratory patients prescribed a twice daily preventer inhaler.

I hypothesized that by making an audio recording of an individual using their dry powder inhaler (DPI), an objective assessment of inhaler user technique can be captured which would enable physicians to properly assess adherence, including unintentional non-adherence due to poor technique in a real world population.

2.3 METHODS

This was a prospective cross-section observational study in a primary/pharmacy care setting designed to obtain a sample size that would recruit 100 patients and provide at least 3000 audio recordings 50% of prescribed inhalations over the month. Six general practice (GP) clinics and twelve community pharmacies in urban areas of Dublin, Ireland participated in this study. The 6 GP practices across Dublin were chosen as they represented a diverse range of socioeconomic classes. The pharmacies were chosen at random from a cohort of national chain pharmacy sites (Boots Pharmacy Inc.) as part of a pilot study of a randomized control trial (NCT02203266).

2.3.1 Primary and Secondary Endpoints

The primary endpoint for this study was to quantify inhaler adherence and the incidence of inhaler errors, in a cross-section of respiratory patients.

Secondary endpoints included reporting the frequency of common inhaler errors and identifying potential patient factors related to poor adherence.

2.3.2 Ethics and Consent

This study was approved by the Ethics committee of the Irish College of General Practitioners (Inhaler Adherence in Real Life General Practice) and the Royal College of Surgeons in Ireland (Registered on ClinicalTrials.gov NCT02552472).

2.3.3 Participants

The databases for the GP practices and community pharmacies were initially screened and flagged for potential patients. In an attempt to reduce selection bias, over a 2 to 4-week period, general practitioners and pharmacists were asked to recruit consecutive patients with any history of respiratory illness (i.e. Asthma, COPD) already prescribed a salmeterol/fluticasone Diskus™ inhaler.

The inclusion criteria required patients to have an established respiratory condition (diagnosed by their general practitioner) and already be on a salmeterol/fluticasone Diskus™ inhaler. The only exclusion criterion was if a patient was not already on a salmeterol/fluticasone Diskus™ inhaler. Once identified patients were asked to participate in the study and gave written informed consent. Patients were fully aware that their adherence was being monitored with an electronic monitor during the study period, however neither patients nor clinicians had any reservations regarding the monitoring used in this study.

Once consented, patients were given an INCA™ enabled 60-dose salmeterol/fluticasone Diskus™ inhaler for 1 month of use. Unless patients specifically requested to be shown how to use their inhaler, inhaler technique training was not performed, since the purpose of the study was to assess inhaler adherence in a real world setting.

Patients were asked to use the inhaler as they normally would and to return it at the end of one month. On collection of the inhaler the number of doses used in the study period, as per the mechanical dose counter, was recorded in the study file. Retrospective data collected from general practices and pharmacies included information on age, sex, clinical diagnosis, smoking history, education, socio-economic class, number of exacerbations, hospital admissions and GP use in the last year.

2.3.4 INCA™ device

The design and validation of the INCA™ device has been described in Chapter 1 and has been previously published (106,153). Briefly, analysis of the acoustic data allows identification of the critical steps in inhaler use. This includes, whether the inhaler was opened, if the lever to load the drug was moved, if the user inhaled, along with the acoustic data associated with the inhalation (duration, peak inspiratory flow) and if an error occurred. Details of the relationships between the acoustic data and each of these features have been reported in other papers (105-109).

Each audio file, representing each time the inhaler was used, was assessed by two separate trained raters who used a commercial software analysis program (Audacity ® version 2.04 from the Audacity Team. Retrieved from http://audacity.sourceforge.net/) , to visualize and

listen to inhaler sounds. Agreement between the two raters was 81% (with a kappa score of 0.625) and disagreements were reconciled by consensus agreement. Most of the differences observed between the raters were due to the classification decision of insufficient inhalations. While objective thresholds were established for classification purposes, the exact identification of these thresholds from the audio track was subjective. In light of this, an automated acoustic analysis algorithm was used to assess the precise peak inspiratory flow rate achieved by the participant for each event (106).

2.3.5 Adherence Outcomes Measured

Through analysis of the audio data, files with evidence of drug priming suggested the patient attempted to take their inhaler, attempted doses. Inhaler errors were also identified through a very detailed acoustic analysis of each recorded audio file. Adjusting doses based on the presence or absence of inhaler errors (identified by the inhaler device manufacturer, (154) allowed for the calculation of the actual doses. Adherence for all different measures was calculated as the mean possession ratio (MPR, (112)), described in Chapter 1. Expected doses were calculated as the number of doses prescribed for the number of days the patient was in the study. For example, a salmeterol/fluticasone Diskus™ inhaler is prescribed as a twice-daily (12 hourly) medication. Over a 30-day period, a patient prescribed this treatment would be expected to take 60 doses.

Average Adherence was calculated as the number of doses recorded as taken by the dose counter divided by the number of doses expected. "Attempted" MPR was calculated as the number of doses recorded by the INCA™ (audio files with evidence of drug priming), divided by the number of doses expected (the term "Attempted" was used to indicate that the patient attempted to take their inhaler, regardless of how well they took it) "Actual" MPR was calculated as the number of actual doses recorded from the INCA™ (doses with inhaler errors were removed from the total number of doses) divided again by the number of doses expected (the term "Actual" was used to indicate that the patient had taken their inhaler with correct technique leading to a full, actual, dose being delivered to the airways).

2.3.5.1 Correct Technique

Correct inhaler technique for the Diskus™ inhaler has been previously described (155), see Chapter 1. Initially the user has to open the Diskus™ which reveals the mouth piece and drug lever. It is then suggested that the user move the lever to prime the drug into the mouth piece. Each time the lever is moved the dose counter on top of the device moves one digit lower (i.ie from 60 to 59). The user then has to exhale fully to residual volume and away from the mouth piece. Following this, the user needs to create a tight seal around the mouth piece and take a strong deep inhalation. Once inhalation is complete the user has to hold their breath for at least 5 seconds. Lastly the user must close the device, covering the mouth piece and concealing the drug lever.

2.3.6 Follow up with the General Practitioner

After the acoustic data analysis was completed and adherence was calculated, each patient's month of adherence was discussed directly with his/her GP. This provided more detailed patient-specific information relevant to explaining each patient's pattern of adherence, errors in adherence and possible methods to address these.

2.3.7 Statistical analysis

Descriptive statistics were used to describe the patient characteristics and the errors in inhaler use. Mean and standard deviation (SD) was used to describe continuous variables and proportions for any categorical variables. For this study, missing data was omitted from analysis. A comparison between recruitment site (general practice or community pharmacy) was performed with a paired t-test.

2.3.7.1 Regression Analysis

A negative binomial regression model was used to determine trends in technique errors. The number of attempted doses was used as the offset term and age, gender, smoking history, education (primary/secondary), GP use, exacerbations and hospitalizations were included as fixed effects in the model. The Bayesian Information Criteria (BIC) was used to

compare models. An ordinary linear regression model was used to determine trends in the Actual MPR. P-values <0.05 were deemed statistically significant. Stata version 12 was used for statistical analysis. (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

2.4 RESULTS

2.4.1 Study population

Patients were recruited between 2013 and 2014. During this period one hundred and twenty-three patients were given an INCA™ enabled Diskus™ inhaler. Of the 123 devices distributed, 12 (10%) were not returned by patients and there were 8 (6.5%) device failures, with no salvageable audio recordings.

The majority of patients recruited had a clinician diagnosis of asthma. The mean age for the entire population was 57.2, while COPD patients tended to be slightly older (mean=66.0, $p<0.01$) with a larger proportion of male patients (57%). Understandably there were more patients with a smoking history in the COPD cohort (88%). As these were patients managed primarily in the community there were few hospital admissions in the previous year to recruitment (mean=0.5). Most patients had a primary level of education (42%). Although the majority of COPD patients had only primary level education (62%) and almost all COPD patients had government sponsored health insurance (81%). Baseline demographic data of these patients is presented in Table 2-1. I will now describe several different measures of adherence in this patient population.

Table 2-1: Clinical Characteristics:

Patient demographics for patients with available acoustic data. *p<0.05 comparing COPD and Asthma populations.

	ALL	***ASTHMA (n=82)***	***COPD (n=21)***
Mean Age (range)*	57.2 (22-86)	54.8 (22-78)	66.0 (54-86)
Gender	46 (45%) Male	34 (41%) Male	12 (57%) Male
	57 (55%) Female	48 (59%) Female	9 (43%) Female
Smoking History*	41 (40%) Never	46 (56%) Never	3 (12%) Never
	41 (40%) Current	21 (26%) Current	13 (63%) Current
	21 (20%) Ex	15 (18%) Ex	5 (25%) Ex
Mean no of Exacerbations in the previous year (SD)	1.9 (1.3)	1.9 (1.0)	1.8 (1.7)
Mean no of Hospital Admissions in the previous year (SD)	0.5 (1.1)	0.3 (0.6)	0.8 (1.6)
Mean No. Visits to General Practice in the previous year (SD)	7.1 (5.5)	6.3 (5.1)	8.4 (6.0)
Education Level	43 (42%) Primary	25 (30%) Primary	13 (62%) Primary
	43 (42%) Secondary	37 (45%) Secondary	8 (38%) Secondary
	17 (16%) College	20 (25%) College	
Level of Health Insurance*	43 (42%) Self-paying (Private)	40 (49%) Self-Paying (Private)	4 (19%) Self-Paying (Private)
	60 (58%) Government Sponsored	42 (51%) Government Sponsored	17 (81%) Government Sponsored

2.4.2 Doses Used

Among the 103 patients for whom an inhaler device was collected, there were 5228 doses taken according to the dose counter. From these inhalers an INCA^{TM} device was collected, audio files were downloaded and analyzed. There were 5045 audio files in which the individual opened the inhaler, primed the device and attempted to inhale ($p<0.001$, comparing the dose counter doses to the attempted doses recorded to the INCA^{TM}) of an expected 6180 doses. The discrepancy between the dose counter and the number of audio files with evidence of drug priming is explained by multiple drug priming and drug dumping. Although multiple priming and drug dumping are identified by the acoustic analysis, the exact number of multiple priming in one audio file is difficult to calculate.

2.4.3 Errors in time of use of the inhaler

2.4.3.1 Over Dosing

Twenty (19%) individuals took more than 2 doses in a day for at least two consecutive days; leading to 66 episodes of cluster overdosing, see Table 2-2 and Figure 2-1 (b). Over the study period the mean (SD) overdoses per patient was 4.7 (7.0).

2.4.3.2 Missed Doses

There were 1861 total missed doses. Thirty-eight (37%) individuals missed taking 4 doses over two days, leading to 97 episodes of cluster-missed doses, see Table 2-2 and Figure 2-1 (c). The mean (SD) missed dose per patient was 18.1 (7.1). Comparing patients by respiratory diagnosis there was no significant difference seen.

Table 2-2: Breakdown of different measures of adherence:

Values of doses expected to be taken over the study period (30 days), the number of doses actually taken during the study period judged from the dose counter, the number of doses attempted (attempted doses), based on the number of audio files, and the number of doses successfully taken (actual doses), audio files judged to have been taken correctly are presented in this table. Out of the 6180 doses prescribed to this cohort of patients only 82% were taken. And of those taken only 76% were taken correctly. Clusters of missed dosses were defined as 2 or more consecutive days of missed doses (i.e. >4 doses missed over >48 hours) and cluster of over doses were defined as taking more than 2 doses in one day over 2 consecutive days. There were a large number of cluster of missed doses (97) and over doses (66), suggesting different possible patterns of inhaler use.

	Total	***All Mean (95% CI)****	***Asthma Mean (95%CI)****	***COPD Mean (95% CI)****
Number of Expected Doses	6180	60	60	60
Mean Number of Counter Doses	5228 (85%)	55 (53-57)	55 (52-59)	57 (55-60)
Mean Number of Attempted Doses	5045 (82%)	49 (46-52)	49 (45-54)	51 (46-57)
Mean Number of Actual Doses	3823 (76%)	34 (30-38)	37 (30-44)	29 (18-41)
Number of episodes of significant clusters of missed doses	-	97	49	48
Number of episodes of significant clusters of overdoses	-	66	43	23
Mean Number of Errors	1204 (24%)	12 (9-15)	11 (6-16)	18.3 (10-27)

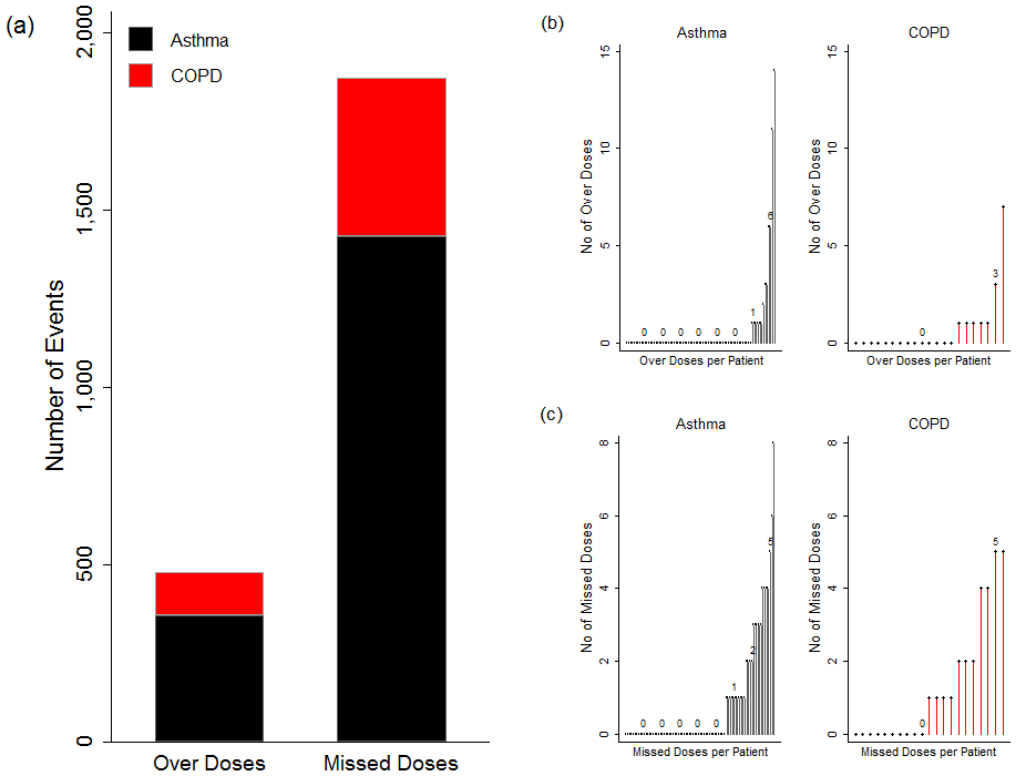

Figure 2-1: Over Dosing and Missed Doses:

Figure (a) illustrates the total number of missed doses and over doses in this patient population, and separated by clinician diagnosis (asthma or COPD). Figures (b) and (c) show the distribution of overdoses and missed doses, respectively, per individual in a primary/pharmacy care cross-section of patients, showing the large variation in errors in timing across patients.

2.4.4 Errors in inhaler technique

Analysis of the audio data identified that only 3823 (76%) inhalations followed the correct procedure for inhaler use (155). A visual and audio example of correct inhaler technique is seen in Figure 2-2 (d) and Appendix B.

2.4.4.1 Errors in Drug Priming

In order of correct inhaler use, errors in drug priming (i.e. Multiple priming), the first step in inhaler use, accounted for 11% of all errors.

2.4.4.2 Exhalation into the mouth piece

Exhalation into the inhaler after dose actuation and prior to inhalation (see Figure 2-2 (f) and Appendix B) was identified in 217 (18%) events.

2.4.4.3 Errors in Inhalation

Errors in inhalation accounted for 46% of all errors and the most common inhaler technique error identified was low peak inspiratory flow rate (PIFR). In total, 325 (27%) incorrect inhalations were performed with a PIFR< 35L/min (156). A visual audio example of low PIFR is seen in Figure 2-2 (e). The volume of this inhalation profile is significantly smaller than that of a normal inhalation, as seen in Figure 2-2 (d). Drug blister/priming present with no inhalation was present in 229 (19%) audio files. These events were where the patient blistered the drug and either forgot to take the medication or blistered as a method of drug dumping.

2.4.4.4 Multiple Inhalations

Multiple inhalations, where the patient blisters the drug and takes several consecutive inhalations (i.e. no breath hold and possibly exhaling directly into the mouthpiece) were recorded in 301 (25%) inhalations. This was the only inhaler error that was significantly more common in the COPD population cohort compared to asthma. See Table 2-3 for a breakdown of all the inhaler errors identified.

While errors were common, ranging from 100% (i.e. a patient who made persistent technique errors) to 0% it is noteworthy that among the studied cohort there was a wide variation in the frequency of inhaler technique user errors (see Figure 2-3) and the mean number of errors per person was 12 per 60-dose inhaler (20%).

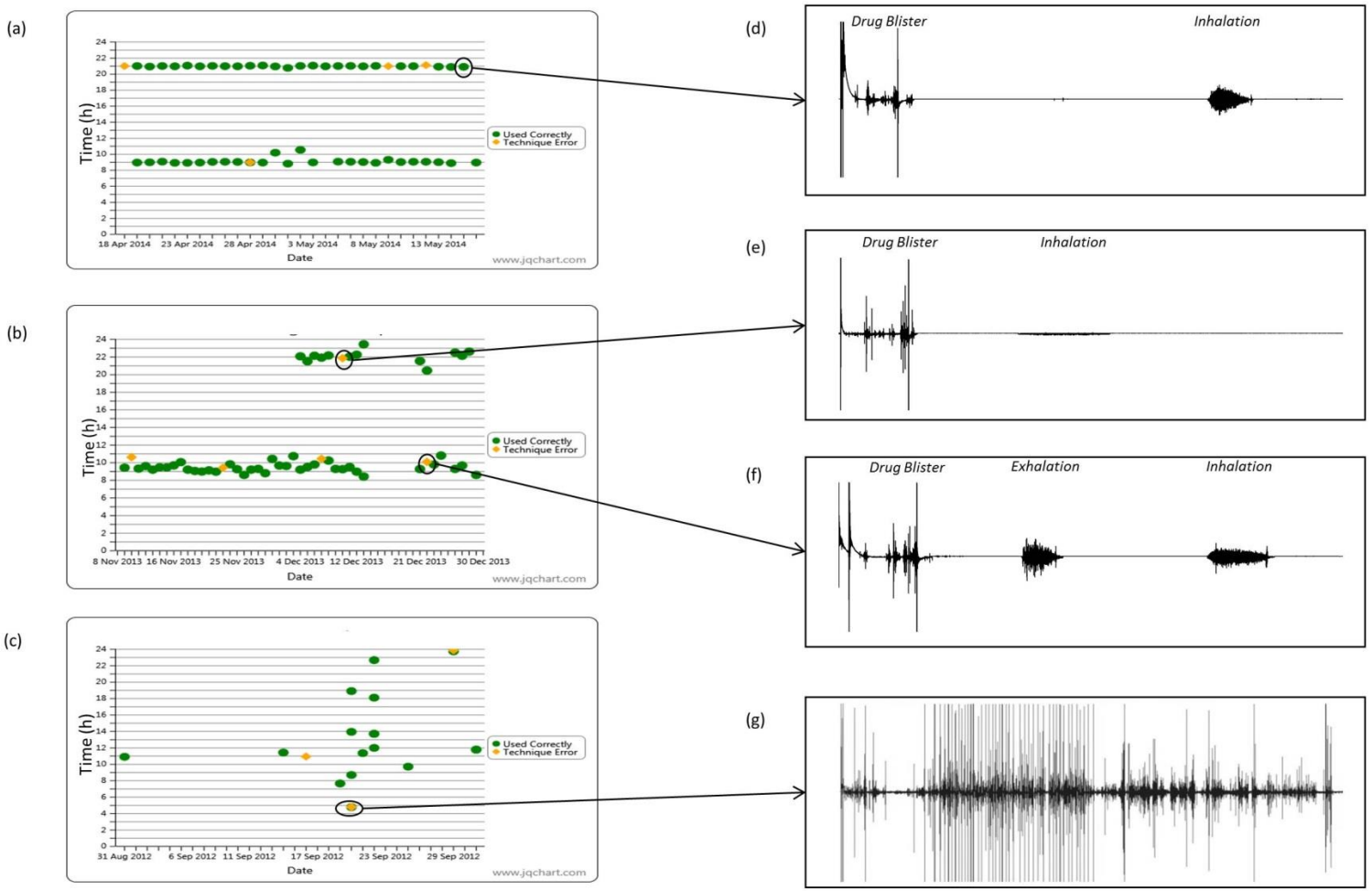
(a)
(b)
(c)
(d)
(e)
(f)
(g)
Time (h)
Date
Used Correctly
Technique Error
www.jqchart.com
Drug Blister
Inhalation
Exhalation

Figure 2-2: Patterns of Inhaler Use and Audio Samples:

Figures (a) to (c) are calendar plots of inhaler use over time with days on the x axis and time of day on the y axis. A green dot indicates good technique for that dose, while a yellow diamond indicates poor technique. Figure (a) is an example of a patient who uses their inhaler regularly and with good technique. Figure (b) identifies a patient with good inhaler technique but poor timing, leading to a cluster of overdosing. Figure (c) shows a patient with good technique and somewhat good timing, but has a cluster episode of missed doses. Examples of different audio files heard in analysis of INCA™ devices are seen in figures (d)-(g); (d) An example of good inhaler technique with adequate inhalation (visual pattern of correct technique); (e) An example of poor inspiratory effort, compare, the inhalation profile is barely visible; (f) An example of an exhalation prior to an inhalation, note the different waveform of the exhalation profile; (g) An example of a patient priming the inhaler over 20 times with no actual inhalation of drug, drug dumping

Table 2-3: Inhaler Technique Errors:

The frequency of errors in inhaler handling among the 103 patients is shown. The most common error for both patient populations was Low Peak Inspiratory Flow Rate (PIFR). There seemed to be more of these events in the COPD population (6.5 vs 4.1), however this was not significantly different. Other common errors included multiple inhalations, drug priming/blister present but no inhalation and exhalation into the mouth piece prior to inhalation. *p<0.05, comparing Asthma to COPD.

Instruction	Audio Error	Frequency (% of all errors)	Mean per Any patient (range)	Mean per Asthma patient (range)	Mean per COPD patient (range)
Total number		1204 (24%)	12 (0-60)	11 (0-52)	18 (0-60)
INHALER PREPERATION					
DRUG PRIMING					
	No Priming, Inhale Detected	24 (2%)	0.23 (0-4)	0.11 (0-1)	0.21 (0-4)
	Multiple Priming	72 (6%)	0.68 (0-23)	0.68 (0-9)	1.2 (0-23)
	Dose Dumping	36 (3%)	0.34 (0-23)	0.28 (0-4)	1.2 (0-23)
BREATH OUT DEEPLY AWAY FROM THE INHALER					
	Exhalation into inhaler	217 (18%)	2.17 (0-46)	3.13 (0-46)	2.1 (0-10)
INHALATION					
INHALE DEEPLY					
	Priming present, No Inhale	229 (19%)	2.28 (0-47)	1.0 (0-35)	0.21 (0-2)
	Low PIFR (<35L/min)	325 (27%)	3.25 (0-60)	4.1 (0-47)	6.5 (0-60)
HOLD BREATH FOR > 5 SEC					
	Multiple Inhalations*	301 (25%)	3.05 (0-50)	1.7 (0-31)	6.6 (0-30)

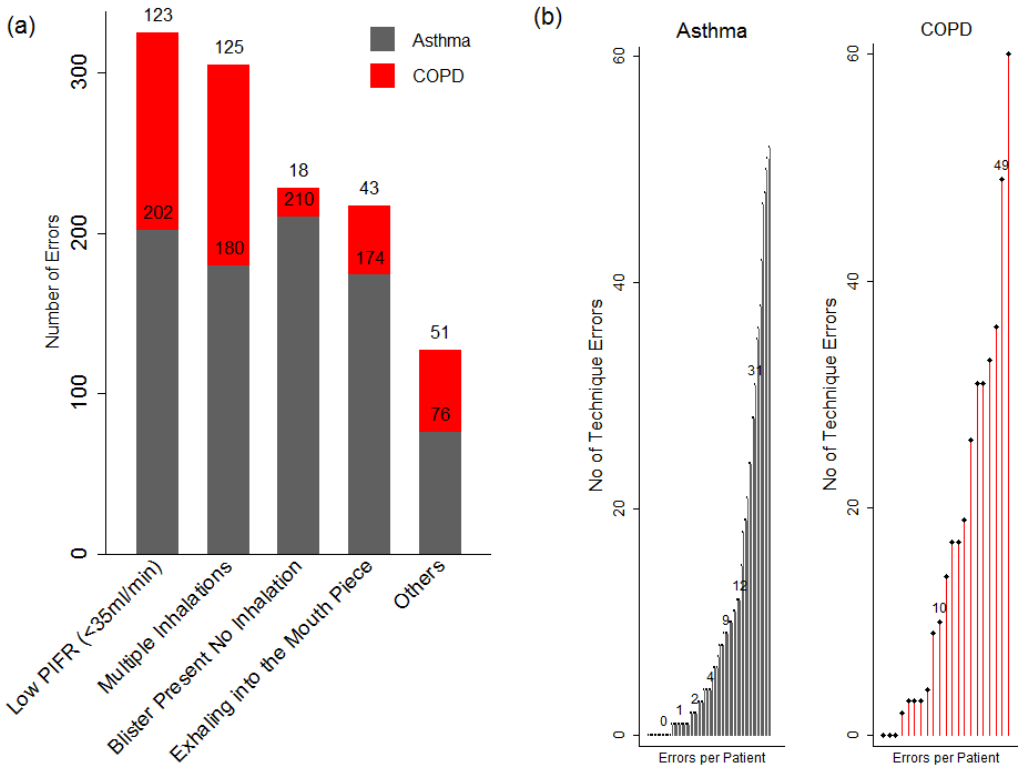

Figure 2-3: Inhaler Technique Errors:

Figure (a) The most common inhaler errors were low peak inspiratory flow rate (PIFR), drug priming without a subsequent inhalation, exhalation prior to inhalation and multiple inhalations. Figure (b) shows the distribution of inhaler user technique errors per individual in a community care cross-section of patients.

2.4.5 Impact of errors in technique of inhaler use and missed doses on calculating adherence

2.4.5.1 Dose Counter—Average Adherence

The dose counter provides no information on when and how a patient uses their inhaler. The mean number of doses taken in a month, measured by the dose counter was 55 doses. The mean possession ratio (MPR) using information from the dose counter was 92.7% (100% represents perfect adherence), Table 2-2. Eighty-seven percent of patients had an adherence rate above 80%, using this method of assessing adherence.

2.4.5.2 Attempted MPR

With the INCA^{TM} device specific information on when a patient attempts to take their inhaler can be measured. Acoustic analysis of recorded audio files identified only 5045 attempted doses and the MPR using the number of audio files with evidence of drug priming, was 81.6% (5-100%) and only 71% of patients had an attempted MPR above 80%. This was significantly lower than the adherence rates calculated from the dose counter ($p < 0.001$). This difference explained by dose dumping and errors in loading the device.

2.4.5.3 Adherence accounting for Technique Errors—Actual MPR

With detailed analysis of each audio file from the INCA^{TM} device technique errors are identified and actual doses (discounting technique errors) can be calculated. Discounting audio files with evidence of a technique error, the "Actual" MPR was 56.7%. This was significantly lower than the adherence measure based on the dose counter ($p<0.001$) and the Attempted MPR ($p < 0.001$). Only 41% of patients had an "Actual" MPR above 80%, see Figure 2-4 (d). There was no significant difference in any measure of adherence between COPD and asthma.

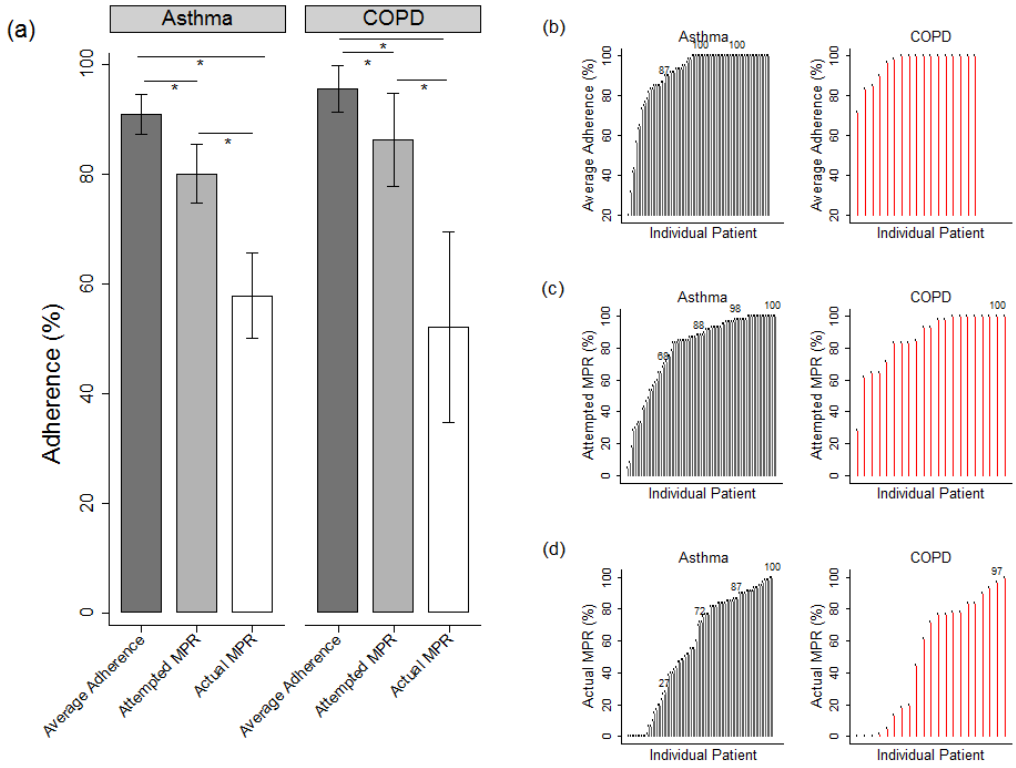

Figure 2-4: Comparing Average Adherence, Attempted MPR and Actual MPR:

Figure (a) is a bar graph comparing cumulative expected doses, to attempted doses and actual doses (where technique errors are accounted for). Figures (b), (c) and (d) illustrate the large variation and distribution of average adherence (dose counter), attempted and actual mean possession ratio, respectively, per individual patient. *p<0.001.

2.4.5.4 Cumulative Drug Accumulation

Medications with longer half-lives, such as preventer inhalers, are dependent on the individual building up a certain resting level of the medication to continue its prescribed clinical effect. Over a 30-day period, patients prescribed a twice daily (12 hours apart) medication are expected to take 60 doses (30*2) total. Therefore, there is a linear increase in cumulative doses (2 dose increment per day). The mean number of attempted doses for the study period was 49 doses per patient (3-67) and the mean number of actual doses taken was 34 doses (0-60) out of a potential 60 doses ($p<0.05$). The mean cumulative attempted doses over time was significantly lower than what was expected and the mean cumulative actual doses over time was significantly lower than both the expected and attempted doses, see Figure 2-5.

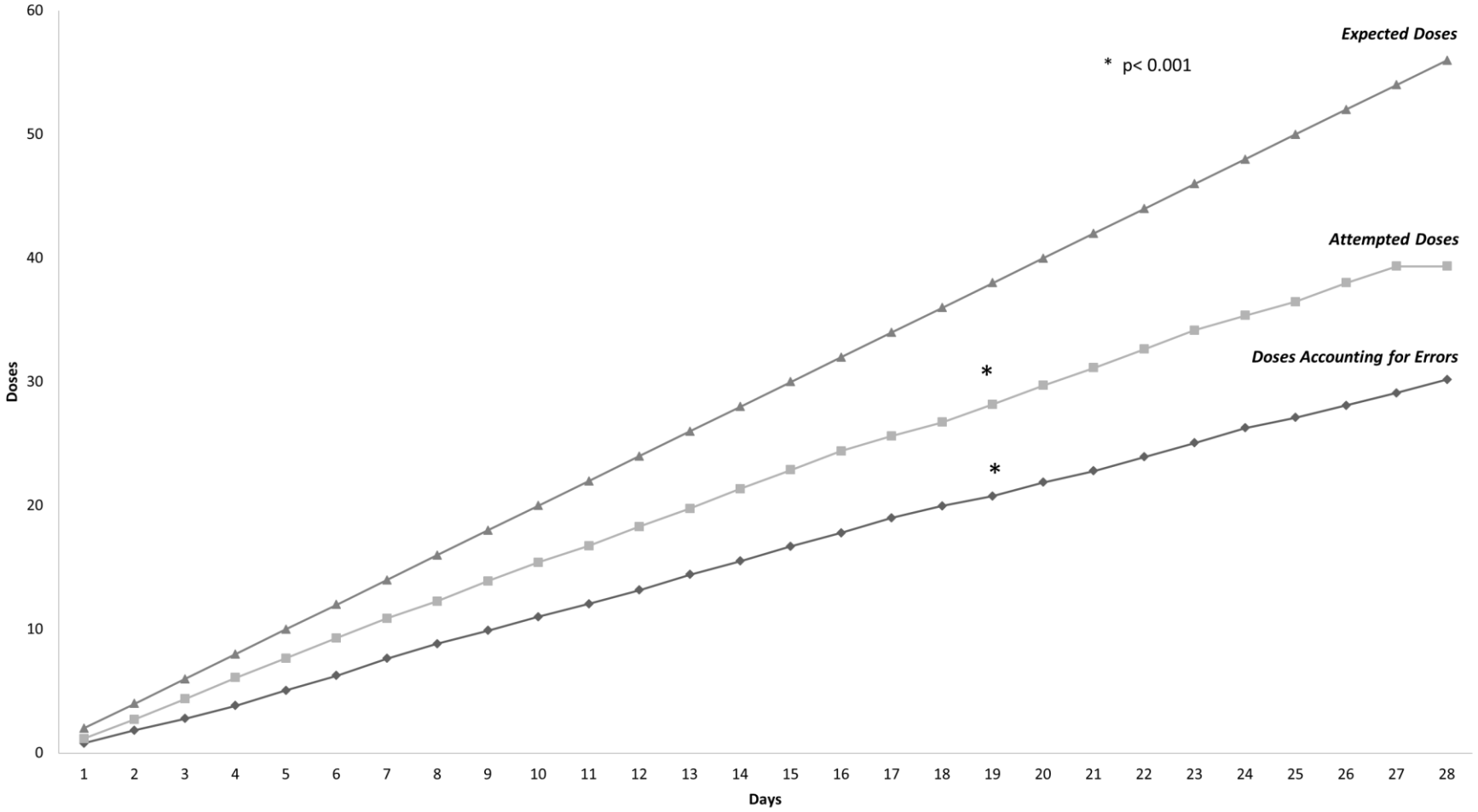
Expected Doses
* p< 0.001
Attempted Doses
Doses Accounting for Errors
*
*
Doses
Days
0
10
20
30
40
50
60
1
2
3
4
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Figure 2-5: Cumulative Expected, Attempted and Actual Doses:

Patients in this study were prescribed salmeterol/fluticasone twice daily. Therefore with 2 doses a day, over 30 days this, in a linear pattern, accumulates to 60 doses. Attempted doses, evidence of drug priming on the audio analysis, were averaged over all patients for each day enrolled in the study. Actual Doses, doses account for inhaler technique errors, were averaged over all patients for each day enrolled in the study. Each slope of the cumulative dose graph was compared using an ANOVA method. The cumulative attempted doses was significantly lower than what was expected. The cumulative actual doses was significantly lower that what was expected and also what was attempted. This figure illustrates the impact technique errors have on drug accumulation over time.

2.4.6 Variations in inhaler use over time

As I have shown the rates of attempted and actual MPR varied considerably. Examining the trajectory of inhaler adherence over the 4 weeks and calculating the slope of that trajectory allowed for the identification of some trends in inhaler use (see Figure 2-6). Firstly, there was a group of patients who started with good attempted and actual MPR (based on an 80% cut-off for good and poor adherence) and ended with poor adherence (slope < -0.05). Secondly, there was a group who had poor attempted and actual MPR throughout the study (slope between -0.05 and 0.05). Thirdly there was a group with good attempted and actual MPR throughout the study (slope between -0.05 and 0.05). Finally, there was a group that started with poor attempted and actual MPR but ended with good adherence (slope > 0.05). Errors in technique lowered the adherence calculation over time (Figure 2-6: compare the solid line with the hatched line in (a)-(d)). There was no significant difference in the baseline demographic information between these four groups of patients.

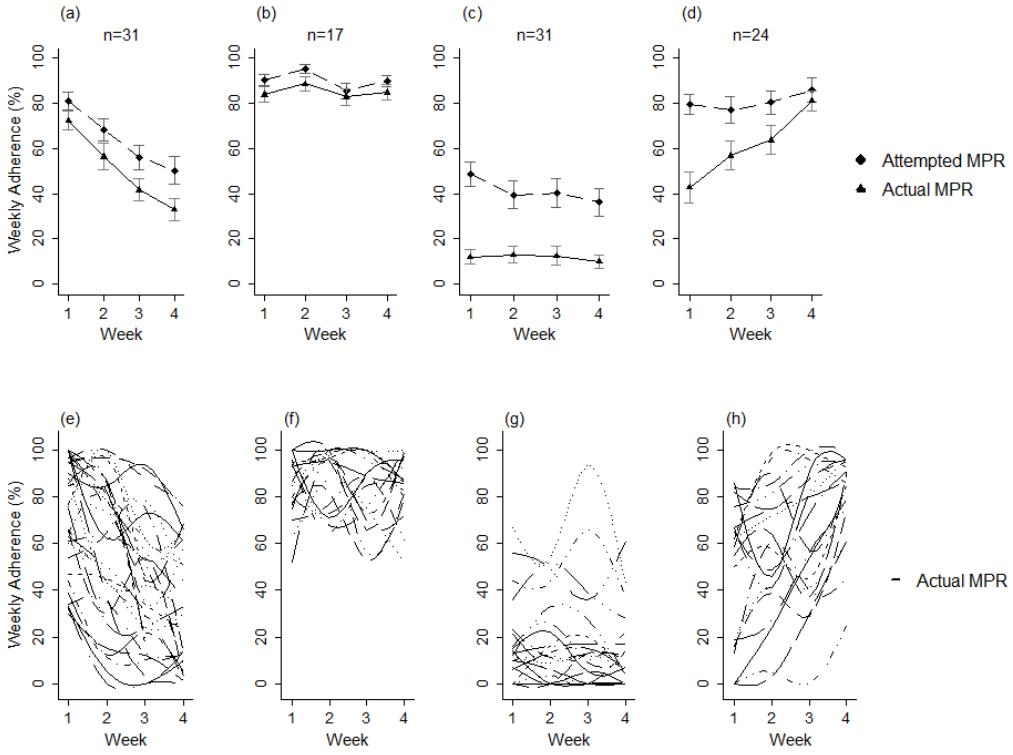


Figure 2-6: Weekly Patterns of Adherence:

Reviewing combined adherence rates, patients fell into 4 groups; (a) Patients whose adherence declined during the study period, (b) Patients whose adherence was good and remained good, (c) Patients whose adherence was poor and remained poor, (d) OÁÔÉÅÎÔïÓ ×ÈÏÓÅ ÁÄÈerence improved during the study period.

2.4.7 Factors related to adherence

Rates of inhaler adherence were similar between a general practice and community pharmacy population, see Figure 2-7. In trying to identify factors that may predict inhaler adherence, only socio-economic class correlated well with inhaler technique errors. Therefore, patients without private health insurance were more likely to make inhaler technique errors ($p<0.01$). With the Actual MPR (incorporating inhaler technique errors), patients with secondary education level had better adherence ($p=0.014$). Furthermore, better Attempted MPR correlated with better Actual MPR ($p<0.01$).

2.4.8 Feedback to General Practitioner

Once the audio data was analyzed feedback was provided to the GPs for each of their patients. In particular, there were two patients who had poor user technique but had attempted to take their medication at the correct time. Upon discussing these two patients with the general practitioner it was discovered that these individuals were frequently unwell and ended up having their inhaler therapy changed. In the audio analysis from this group of patients two cases of drug dumping were identified. This is where the patient blisters (drug priming) the inhaler over and over again to bring the dose counter down without actually using the inhaler (an example of this is shown in Figure 2-2 (g) and Appendix B). Both of these patients rarely used their inhalers during the month of the study prior to returning the device and both patients dumped over 20 doses of drug. In both cases the GP knew from their electronic medical record that the patients had a tendency to both manipulative behavior and to prior non-adherence to other therapies.

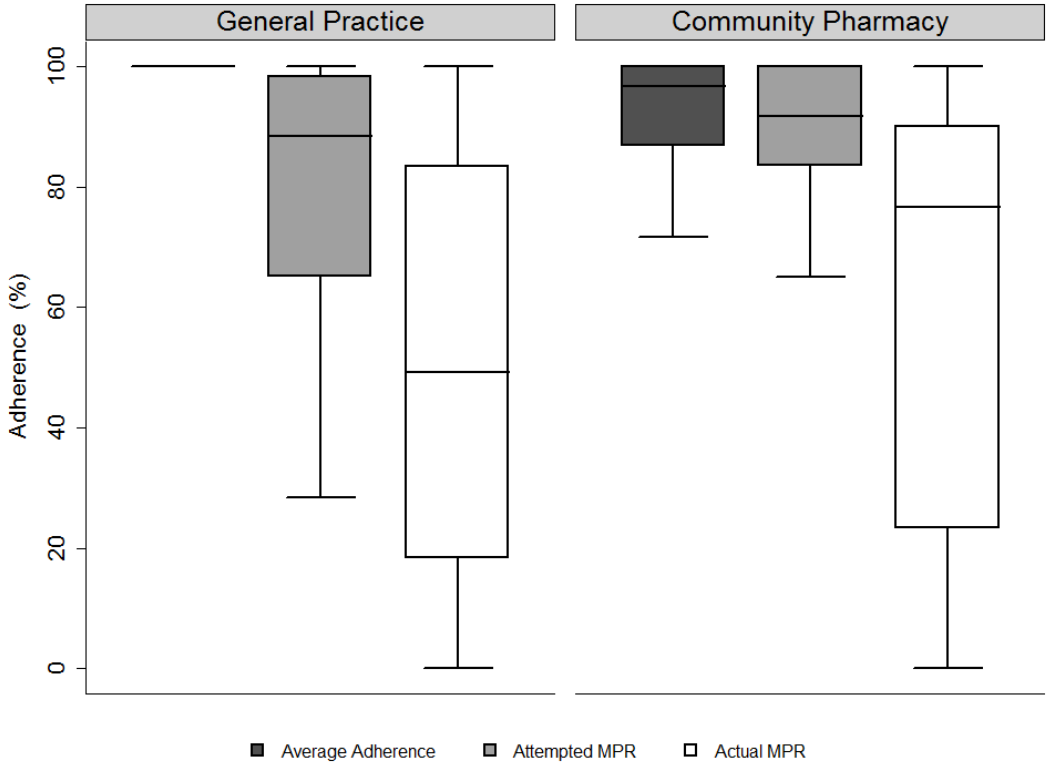


Figure 2-7: Adherence comparing General Practice and Pharmacy Cohorts:

This study looked to quantify adherence levels in a cross-section of respiratory patients. Patients were recruited from general practice clinics and community pharmacies. Comparing patients recruited from general practice and those recruited from community pharmacies there was no significant different in any of the adherence measures calculated: Average adherence from the dose counter, Attempted Mean Possession Ratio (MPR) and Actual Mean Possession Ratio (MPR).

2.5 DISCUSSION

Clinicians need a variety of methods to objectively identify poor adherence since, before escalating therapy in patients with airway disease, all practice guidelines suggest that both adherence to inhaled therapy and inhaler technique are addressed (157). While there are many reasons for poor adherence, these can be grouped as a failure to initiate, implement or persist with the medication, as described in Chapter 1 and a recent taxonomy of adherence (112). The initiation and persistence phases can be assessed using pharmacy refill records. There is little information, outside of clinical trials, that describes adherence to inhalers during the implementation phase (158,159), particularly with regard to inhaler technique.

The purpose of this study was to quantify, over time, the variation in adherence to a regularly prescribed inhaled therapy during the implementation phase in a cross-section of patients. To address this question I used the novel INCA^{TM} technology that digitally records objective information on both the point in time and the user technique each time an individual uses their inhaler. The results of this study suggest that errors in overuse, underuse and errors in inhaler handling are equally common and that this is irrespective of the underlying clinical condition. When both of these errors (in timing and technique) are combined they significantly lower the calculation of adherence compared to simply using the average adherence, from the dose counter.

Recently, a number of methods to assess adherence have been developed, including monitoring changes in biomarkers as well as electronic monitors (87,159-162). However, these do not assess an individual user's inhaler technique. Most studies that report inhaler technique employ direct visualization of the user to assess this component of adherence. These checklist-based methods offer the advantage that they are easy and quick to use and detect major errors in inhaler handling. However, they are limited in that direct observation only gives a cross-sectional rather than longitudinal assessment of user technique adherence, which means that careless errors are not detected and inhaler flow rate is subjectively assessed. To address this issue the INCA^{TM} device was used to capture

electronic audio recordings of an inhaler being used. The INCA™ device was attached to a Diskus™ inhaler because the dry powder inhaler is considered to be easier to use than a metered dose inhaler and salmeterol/fluticasone has a fixed dosing regimen. Recordings were made each time the inhaler was opened by the patient. Hence, it was possible to record precisely when and how the inhaler was used. In prior studies my research group have identified and objectively related the audio features to the correct use of a Diskus™ inhaler (106,107). In particular, the following inhaler events can be objectively quantified: the inhaler is opened, the device is primed, the patient exhales after the drug has been primed or breathes out directly after inhaling (106). Furthermore my group have investigated the relationship of the acoustic profile of inhalation to drug delivery (108). Analysis of the acoustic energy of inhalation is directly related to the inhalation flow rate, thereby providing a quantitative and objective measure of the precise inhalation flow rate each time the inhaler is used (105,107,108). Hence, audio analysis of inhaler use done in this study, provides objective quantitative assessment of the most critical steps involved in inhaler use, which would be extremely useful in daily clinical practice (e.g. patients attending a severe asthma clinic).

There were several novel findings in this study. The frequency of critical errors in inhaler use made by the patients was quantified. The most common error was failure to achieve a sufficient inspiratory flow rate. This was identified by examining the acoustic profile of each recorded inhalation. This particular error may lead to significant reductions in drug delivery, therefore reducing the clinical impact of the inhaler. Another inhaler error identified, drug priming with no subsequent inhalation; this is similar to low inspiratory flow rate, in that drug priming with no inhalation leads to no drug delivery and will therefore reduce the clinical effect of the drug. However, reasons for this error may differ in comparison to low inspiratory flow rate. Patients with severe hyperinflation (i.e. In COPD) may not be able to achieve a sufficient inspiratory flow rate. While patients who drug prime with no inhalation, may have forgotten to inhale or this may be an example of multiple priming/drug dumping. Exhalation of humid air into the dry powder inhaler mouth piece and rapid exhalation after inhalation (seen in multiple inhalations); together these critical errors were made regularly by most patients. Analysis of the data indicated that errors in inhaler handling were not

binary, simply confined to some patients, but rather many patients regularly but not all the time demonstrated poor inhaler technique. This is the first study to quantify such a haphazard nature of inhaler adherence within this population. Interestingly, four different inhaler users were identified. There were some patients that used their inhaler well and some that used it poorly throughout the study period. While other patients started with good adherence and ended with poor adherence, suggestive of the Hawthorne effect as these patients knew they were being observed and another group who started with poor inhaler adherence but ended with good inhaler adherence, without any inhaler education. This again highlights the variable nature of inhaler adherence. This detailed information on inhaler adherence may have significant clinical impact. For example, in a patient who is forgetful a method based on reminders may be the most appropriate mechanism to improve adherence, as discussed in Chapter 1. Whereas patients with poor inhaler technique may require specific training using information from an electronic monitor that records technique, such as INCA^{TM}. This may even lead to a change in inhaler device if particular errors cannot be corrected, such as inadequate inspiratory flow.

Accounting for technique errors, such as low inspiratory flow rate, lead to a significant reduction in adherence calculated as the mean possession ratio. This was significantly lower than adherence calculated by the dose counter, emphasizing the importance technique of use has on inhaler adherence. In addition, discounting doses with a technique error, lead to a significant reduction in the total cumulative doses in the study period. This has particular significance to the expected clinical effect of a treatment that is dependent on a certain baseline level of medication, only acquired by taking the medication regularly (and correctly for inhalers).

There are many factors associated with poor adherence to inhaler therapy and they involve healthcare structures such as cost of medication, patient factors (e.g. health beliefs) and healthcare provider factors (e.g. where poor communication and failure to address health literacy issues are all implicated) (68,163-165). This study was not designed to address the drivers or predictors of adherence behavior. However, in this study poor technique was

associated with overall poor inhaler use, lower education levels and lower socio-economic status.

Interestingly, in this study, two patients known to their practitioner as having borderline personality disorder demonstrated drug dumping (see Appendix B, Figure B-6/Audio). Hence, objective assessment of adherence provides an insight into patient behavior, an insight previously reported by Emilson and colleagues (123,124,166).

2.5.1 Limitations

This study has several limitations; this was an observational study restricted to those recruited in primary and pharmacy care and may not reflect those typically enrolled in clinical research studies or those attending secondary care services. Nevertheless, I was able to describe adherence in a large group of patients, who represent the most common users of inhalers. Patients enrolled in this study were aware that their inhaler use was being monitored, as covert monitoring was not permitted by the ethical review committee. This may have an impact on how patients used their inhaler; that is patients may be more adherent when under observation than in a 'real world' environment. Additionally, information on the patients that did not return their inhalers was not collected; we can however assume that prior adherence is poor in these patients. Nonetheless, despite these limitations, four different types of inhaler users were identified. This highlights the variable rates of adherence seen in this patient population.

Another limitation in this study is the lack of a disease outcome measure such as changes in the patients' symptoms over the observation period and disease severity. Additionally some of the data was collected retrospectively (i.e. Smoking History, Diagnosis) from general practitioners and community pharmacists, potentially leading to recall bias (i.e. there were a few non-smoking COPD patients in this study). However, as this was a relatively short observation period and the primary outcome was to observe adherence in a real-world population, the value of recording possible changes in clinical symptoms may not be relevant. This was a cross-sectional observational study and so, included both older and younger patients with either asthma or COPD with varying disease severity, socio-economic

status and education history. There are likely to be differences in inhaler handling, attitudes to medications and understanding of the requirements between patients of different ages, disease states and disease severity. However, this study did not have enough statistical power to investigate these differences.

Another limitation of the study is that not all errors in inhaler use were examined, such as wrong inhaler position, nor other types of inhalers, for example the pMDI or other DPI devices. The INCA^{TM} device is currently being developed for several other inhaler devices. While there would be differences between devices there is no reason to believe that the critical message of this study, namely that poor inhaler technique is common, and not restricted to a few patients would be different.

2.6 CONCLUSION

This observational study of inhaler adherence from a cross-section of patients recruited from primary and pharmacy care shows that poor inhaler technique is present in one fourth of all inhalations. This means that one fourth of doses from a DPI were effectively wasted, incurring a preventable cost and potentially exposing patients to a risk, by falsely reassuring them that they have taken their medicines.

The purpose of this study was to objectively quantify the frequency of inhaler technique errors in a group of respiratory patients. The most common errors identified included:

1. Exhalation into the inhaler after drug priming and before inhalation (18%)
2. Low inspiratory flow rate (27%)
3. Multiple Inhalations with no breath hold (25%)
4. Missed Doses (30%)

Being that these errors are so common it will be important to understand how exactly these specific inhaler errors with the Diskus^{TM} inhaler affect drug delivery. This will be explored in Chapter 3.

This study also highlights that patients miss about 25% of doses. When combined together, errors in inhaler technique along with missed doses account for almost half of prescribed doses. This was particularly seen when calculating the cumulative doses taken for the study period. The current method for calculating adherence is an average of doses taken (MPR), therefore does not take into account the pharmacokinetics of the drug studied and the impact inhaler errors have on drug delivery. It is worth noting that MPR refers to the amount of medication a patient possesses and is therefore not the appropriate term when calculating adherence based on the amount of medication a patient actually uses. In Chapter 4 I will explain a new method of calculating inhaler adherence that takes into account both the missed doses and doses taken incorrectly with a more appropriate nomenclature (Actual Adherence).

Chapter 3 **:**

THE IMPACT OF COMMON INHALER ERRORS ON DRUG DELIVERY

3.1 INTRODUCTION

In the prior chapter I identified several common inhaler technique errors with a Diskus™ inhaler in a cohort of respiratory patients. With the high frequency of these errors, it is important to fully understand how, when objectively measured with an electronic monitor, these errors effect drug delivery. In this chapter I will evaluate each of these inhaler technique errors and their impact on drug delivery in a cohort of healthy volunteers.

3.2 BACKGROUND

Respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD) are a consequence of airway injury leading to inflamed and constricted airways. These pathological changes in the airway lead to specific symptoms such as shortness of breath, cough and with bronchoconstriction, wheeze (167). Treatment is driven by targeting this inflammation and bronchoconstriction in the airways. The best mode of delivering medication to the airways is directly through inhalation (33,38). For asthma and COPD there are two main types of inhaler medications. For symptomatic relief there are 'reliever' medications, which provide immediate relief of bronchoconstriction (e.g. Salbutamol/ Ventolin). The other group of inhalers, the 'preventer' inhalers, are aimed at reducing the chronic inflammation and some bronchoconstriction. Long-term preventer inhalers include long acting beta agonists (such as salmeterol), which helps in reducing bronchoconstriction, and inhaled corticosteroids (such as fluticasone), which aid in reducing airways inflammation. These medications must be taken regularly and at set intervals (based on the drug-half life) to build a resting constant level of medication effect on the airways (34,37). All these inhaled therapies are administered through various inhaler devices. Unlike the oral route where the technique of administration doesn't matter, to achieve maximum drug delivery, technique is vital in inhaled therapy.

As I have shown in my previous chapters, non-adherence to these medications (without even considering technique of use) is a problem with patients, and an estimated 30-70% of asthmatic patients are non-adherent (168). Usually, when studies record adherence, they

use pharmacy records or electronic diaries and these methods are not able to take into consideration the technique of the patients using inhalers. Some authors have used checklists to assess inhaler technique (155), however these checklists only provide a snapshot of inhaler use. The previously described INCA^{TM} device can quantify both inhaler technique and adherence over time. With this device several common inhaler technique errors among a group of respiratory patients in a real world setting regularly taking inhaled medications were identified (Chapter 2). These identified inhaler errors included:

1. Exhalation into the inhaler after drug priming but before inhalation
2. Low Peak Inspiratory Flow Rate (PIFR)
3. Multiple Inhalations
4. Breath Hold Less than 10 seconds (also seen in multiple inhalations where the patient takes exhales and inhales directly after the first inhalation).
5. Missed Doses

Having described the frequency of these errors it is important to assess their impact on drug delivery and whether any of these should be considered 'critical' technique errors. I hypothesize that, previously identified, common inhaler errors lead to poor inhaled drug delivery and may therefore impact on how we calculate adherence.

3.3 METHODS

The aim of this study was to evaluate the impact of commonly observed inhaler technique errors. Trough and peak plasma salbutamol levels were compared between correctly taken events and when the inhaler was taken incorrectly.

3.3.1 Ethics and Consent

The ethics committee of the Royal College of Surgeons in Ireland and Beaumont Hospital approved this study. All participants provided written informed consent.

3.3.2 Pilot Study

For this study it was decided to measure trough and peak plasma levels of salbutamol to reduce the number of blood samples needed. However, prior to doing this I needed to determine the accurate time of sampling to get results most reflective of peak and trough levels for salbutamol. Therefore, a pilot study was done with two healthy volunteers. Participants were instructed on how to correctly use the salbutamol Diskus™ inhaler and asked to take 10 doses 6 hours apart over 3 days. Blood samples were taken at dose 6 and dose 10 and specific times in relation to the dose: time zero, 5 minutes after dose, 10 minutes after dose, 20 minutes after dose, 30 minutes after dose, 60 minutes (1 hour) after dose, 120 minutes (2 hours) after dose, 180 minutes (3 hours) after dose and 240 minutes (4 hours) after dose.

3.3.3 Study Design

After identifying the best sampling times for peak and trough levels the primary study comparing correct technique and incorrect technique began. Initially all participants were instructed on the correct use of the salbutamol Diskus™ inhaler. Correct technique starts with opening the inhaler device, followed by priming the drug by moving the drug lever, exhaling away from the mouth piece, holding the device at a horizontal position and creating a tight seal around the mouth piece, taking a deep strong inhalation, breath holding for at least 10 seconds, exhaling away from the inhaler and ends with closing the device. To ensure participants knew what an adequate inspiratory flow rate was each participant

demonstrated inspiratory flow with the Clement Clarke Inspiratory flow meter (set to Diskus™) until they comfortably reached above 60 L/min.

3.3.3.1 Control Phase (correct technique)

After ensuring adequate inhaler technique each participant was assigned to do one "control phase." In the control phase, participants were asked to use the salbutamol Diskus™ inhaler correctly (as taught). Participants took 6 doses, 6 hours apart over two days.

3.3.3.2 Error Phase (incorrect technique)

A minimum of 5 days after completing the control phase (as a washout phase), participants commenced the error phase of the study.

Similar to the control phase, participants were asked to use the salbutamol Diskus™ inhaler, 6 doses 6 hours apart over two days. However, in this phase participants were asked to purposely make a consistent and pre-defined error each time the inhaler was used.

Inhaler Errors

Pre-defined inhaler errors (identified in Chapter 2) assessed in this study included:

Exhaling into device: To simulate this inhaler error, participants were asked to first prime the drug by moving the lever then to breathe out fully into the inhaler mouthpiece. Following this participants were asked to take an adequate inhalation.

Low peak flow: Prior to starting this specific error phase, participants were given a demonstration on how to perform a low inhalation flow. To do this participants were asked to demonstrate low inhalation with the Clement Clarke In-Check DIAL (Clement Clarke International LTD.) until a flow below 35 L/min (48) was measured. Once participants were comfortable recreating a low inspiratory flow, they were instructed to take each of the 6 doses with a purposeful low flow.

Multiple inhalations: For this inhaler error participants were asked to take more than two inhalations for each drug blister. Participants would blister the drug, take a

deep inhalation, and straight away exhale and take another inhalation This error is a combination of low breath hold and potentially exhalation into the device.

Low breath hold: Although most recommendations suggest breath holding for at least 10 seconds after inhalation, some studies have suggested 5 seconds is sufficient (42). Therefore, for this study, participants were asked to hold their breath for no more than 4 seconds after an adequate inhalation.

Missed dose: To simulate missed doses, a common error in real life patients, participants were instructed to miss the fourth and fifth doses out of their six-dose regimen. This allowed for the participants to develop an initial rise in drug levels (seen when a patient initially start taking an inhaler) followed by a fall in drug levels.

Wrong inhaler position: According to the manufacturers of the Diskus™ inhaler device the correct way to use the DPI is to hold it parallel to the ground while inhaling (169). For this error participants were instructed to hold the inhaler device perpendicular to the ground while inhaling the drug.

3.3.3.3 Blood Sampling

To assess salbutamol drug levels, serum samples were required. Preivously published studies have shown there is good correlation between measured plasma salbutamol and lung deposition (170-173). Based on the results of the pilot study blood samples were taken before (time zero) and after (25 minutes after dose) dose one and dose six of each phase (4 samples per phase). The timing of blood sampling allowed for measurement of trough (time zero before dose 6) and peak (time 25 minutes after dose one and dose 6). Samples at time zero before dose one acted as a further control. A 22-gauge butterfly (winged) needle was used to acquire blood samples. Samples were initially collected in an Ethylenediaminetetraacetic acid (EDTA) blood bottle.

Each sample sat vertically for at least 30 minutes after venepuncture. Samples were then placed in a centrifuge and spun for 10 minutes at 1500g. Following this 1ml samples of

plasma were pipetted out of the blood bottle in to 1ml capsules and frozen at -30¯C. Each sample was labelled with a unique identifier and coded information on the subject number, the dose (one or six), the time of the sample and the error (or no error for control samples).

Samples were then batch shipped on dry ice to a lab in Pennsylvania Medical University. The salbutamol assay described below was perfomed by Dr. Jansen Seheult (mentioned in the aknowledgements).

Figure 3-1: Blood Sampling Schedule:

This figure illustrates the blood sampling schedule for this study. Based on the results of the pilot study, participants had a blood sample taken before dose one (a pre-dose baseline level) and then a sample taken 25 minutes later (a peak level). Participants then took 5 more doses of salbutamol. Prior to the 6th dose another sample was collected (a trough level) and then a final sample was taken 25 minutes after dose 6 (a steady peak level). This blood sampling schedule was the same for the control phase and error phase of the study.

3.3.3.4 Salbutamol Assay - external

Serum salbutamol concentration was measured using a well published method adapted from Sidler-Moix et al (174). Salbutamol sulphate was purchased from Sigma Aldrich [St. Louis, MO, USA] and salbutamol-d4, the internal standard (IS), was purchased from Toronto Research Chemicals [Toronto, Ontario, Canada]. All chemicals and solvents were of analytical grade and used as received. Protein precipitation was used to prepare samples for subsequent analysis.

The high-performance liquid chromatography system was a Waters Alliance 2795 separation module with quaternary pump and autosampler, controlled by Waters MassLynx software [Waters Corporation, MA, USA]. The separations were carried out on a 2.1x50mm Atlantis T3 3 µm analytical column [Waters Corporation, MA, USA]. The chromatographic system was coupled to a Waters Quattro Micro triple quadrupole mass analyzer with an Electrospray Ionization (ESI) source.

The mobile phase consisted of 10mM ammonium formate in ultrapure water containing 0.1% FA (= solution A) and Acetonitrile with 1% FA (solution B). The following stepwise gradient elution protocol was used (see Table 3-1)

Table 3-1 Stepwise Gradient Protocol:

Gradient elution protocol for measurement of serum salbutamol by HPLC-ESI-MS/MS. Solvent A = 10mM ammonium formate in ultrapure water containing 0.1% FA; Solvent B = Acetonitrile with 1% FA

Time (min)	Flow Rate (ml/min)	Solvent A	Solvent B
0.0	0.3	95	5
3.0	0.4	95	5
7.0	0.4	20	80
8.0	0.4	20	80
9.0	0.3	95	5
10.0	0.3	95	5

ESI was set in positive ionization mode and operated at a capillary voltage of 3.5kV. The source temperature was set at 120°C, the desolvation temperature was set at 350°C and the desolvation gas flow was 650 L/h. The cone voltage was 30V, the extractor voltage was 2V and the RF lens voltage was 0.1V. MS1 and MS2 low and high mass resolutions were set at 15. Ion Energy 1 was 1.2 and Ion Energy 2 was 1.0. Entrance potential was -2V and exit potential was 2V. The multiplier potential was 650V. Mass spectra were acquired in the Multiple Reaction Monitoring Mode. The optimal potential settings and the MS/MS transitions were determined by direct infusion into the MS/MS detector of salbutamol and IS solutions separately at a concentration of 10µg/mL in methanol (see Table 3-2).

Table 3-2: Optimal Potential Settings:

Instrument method for determination of salbutamol and salbutamol-d4 by ESI-MS/MS.

Analyte	Precursor (m/z)	Product (m/z)	Collision Energy (eV)	Retention Time (min)
Salbutamol	240.1	147.8	25	4.54
Salbutamol-d4	244.1	151.9	23	4.52

Method imprecision was determined by performing 5 replicates per day for 5 days at all 3 levels of QC. The limit of detection for the assay was 0.01ng/ml and the limit of quantification was 0.04ng/ml.

3.3.4 Participants and Sample Size

Over a three-month period, healthy volunteers were identified by word of mouth. Patients attending the adjacent hospital (Beaumont Hospital) were not recruited to this study. The inclusion criteria allowed for recruitment of healthy participants and non-frequent users of any inhaler. The exclusion criteria consisted of any history of sensitivity to salbutamol or refusal of consent. I planned to have at least 5 participants perform each of the inhaler errors listed above.

3.3.5 INhaler Compliance Assessment (INCA™)

The inhaler device used in this study was the DPI Diskus™ inhaler and the drug administered to the participants was salbutamol. Salbutamol was chosen for this study as measuring blood levels have been tested and validated previously (174-177). Also due to its short duration of action, participants would not have to take the medication for extended periods of time. To ensure participants used the inhaler as directed and to provide an accurate measure of peak inspiratory flow rate (PIFR) the INCA™ device was used. The audio was downloaded and analysed for each participant.

3.3.6 Outcomes Measured

Plasma salbutamol levels for each time point (pre-dose, peak dose, trough steady state and peak steady state) were measured and control levels were compared to each specific pre-defined error.

3.3.7 Statistical Analysis

Descriptive statistics were used to present basic patient details for those included in this analysis. Means and standard deviations (SD) are presented for continuous variables. Paired t-tests were used to compare the means of salbutamol levels at different times between different error phases and the control phase. All statistical analysis was conducted using Stata Release 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3.4 RESULTS

3.4.1 Pilot Study

Prior to commencing the primary study two healthy volunteers were recruited for a pilot study and took 10 doses of salbutamol over 3 days, 6 hours apart and with correct inhaler technique, see Figure 3-2. By dose 6, the mean salbutamol level was 0.565 ng/ml (0.39 for participant 1 and 0.74 for participant 2). This level steadily increased after the dose was taken, reaching its maximum between 20 and 30 minutes. At 20 minutes the salbutamol level for participant 1 was 0.82 ng/ml and 1.59 ng/ml for participant 2. At 30 minutes it was 1.15 ng/ml for participant 1 and 1.46 ng/ml for participant 2. Following this peak there was a steady decline. By dose 10, the average salbutamol level was 0.52 ng/ml (0.36 for participant 1 and 0.68 for participant 2). Again there was a steady increase reaching a peak between 20 and 30 minutes. At 20 minutes the salbutamol level for participant 1 was 1.04 ng/ml and 1.22 ng/ml for participant 2. By 30 minutes it was 0.96 ng/ml for participant 1 and 1.27 for participant 2, see Figure 3-2.

Based on these results, blood samples were taken at dose 1, time zero and time 25 minutes and again at dose 6 time zero and time 25 minutes (i.e. pre-dose, peak level, trough at steady state and peak at steady state) in the primary study.

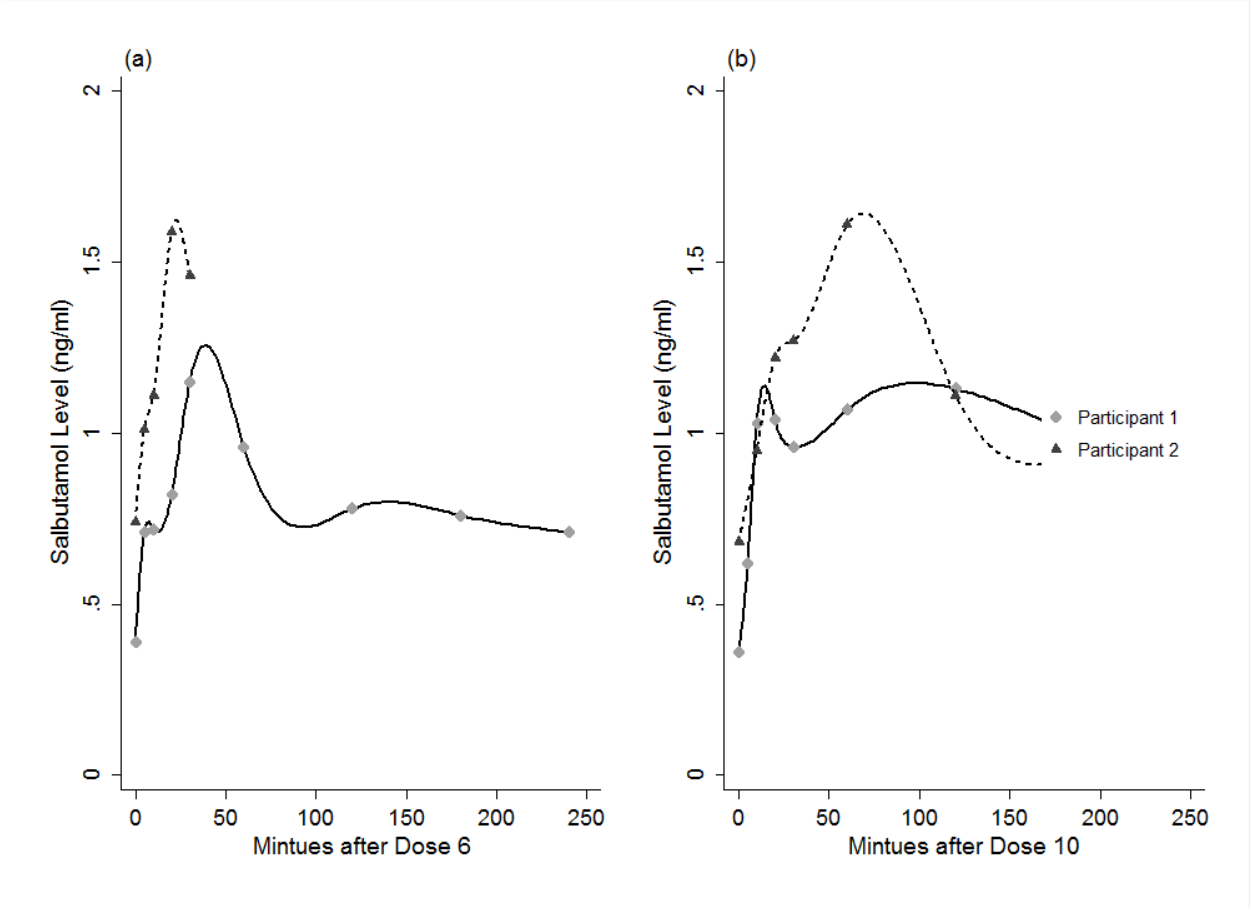


Figure 3-2: Pilot Study of Salbutamol Assay:

Figure (a) is a plot of the salbutamol levels for Dose 6. There is an initial peak in both participants around the 30-minute mark, followed by a steep fall and plateau between 100 and 250 minutes after Dose 6 was taken. Figure (b) is a plot of the salbutamol level for Dose 10. Again there is an initial peak in the salbutamol level. Participant 2 has an initial peak at around 30 minutes but has another increase at 60 minutes. Although Participant 1 had an initial peak and fall of salbutamol there was a small increase in salbutamol levels at around 60 minutes after Dose 10. Both of those later increases in salbutamol levels are related to gastrointestinal absorption of salbutamol and ingestion, which occurred in both participants.

3.4.2 Participants

For the primary study, between June 2015 to August 2015, 15 healthy volunteers were recruited. One participant dropped out of the study due to difficultly with venipuncture. Ten participants were male while the remaining four were female. The mean (95% Confidence Interval) age for these participants was 25.8 (20.7, 30.8)

3.4.3 Control Phase

All 14 participants completed the control phase of the study. Two runs of the salbutamol assay were completed for each sample received. For Dose 1, all participants had a baseline salbutamol level of near 0, (mean=0.01). Twenty-five minutes after the dose, there was an increase in salbutamol levels for all participants with a mean (SD) increase of 0.50 (0.14) ng/ml for the first run and 0.54 (0.16) ng/ml in the second run. This was not significantly different, p=0.51.

By dose 6, the mean (SD) trough level for all participants was 0.82 (0.11) ng/ml. Twenty-five minutes after dose 6, all patients, bar two, had an increase in salbutamol levels with a mean (SD) increase of 0.58 (0.30) ng/ml for run 1 and 0.61 (0.26) ng/ml for run 2. The two patients that had a decrease in salbutamol levels both had good inhaler technique, objectively assessed with acoustic data from the INCA^{TM} device; one had a mean (SD) drop of 0.36 (0.01) ng/ml and the other participant's salbutamol level fell by 0.12 (0.01) ng/ml for the two runs. Despite good inhaler technique these subject data were removed from all subsequent analyses. It is important to note, including these subjects in the following analysis lead to the same results. Due to the non-significant difference between run 1 and run 2 the mean of the two assessments was used for the rest of the analysis.

See Figure 3-3 for a summary of the control phase results.

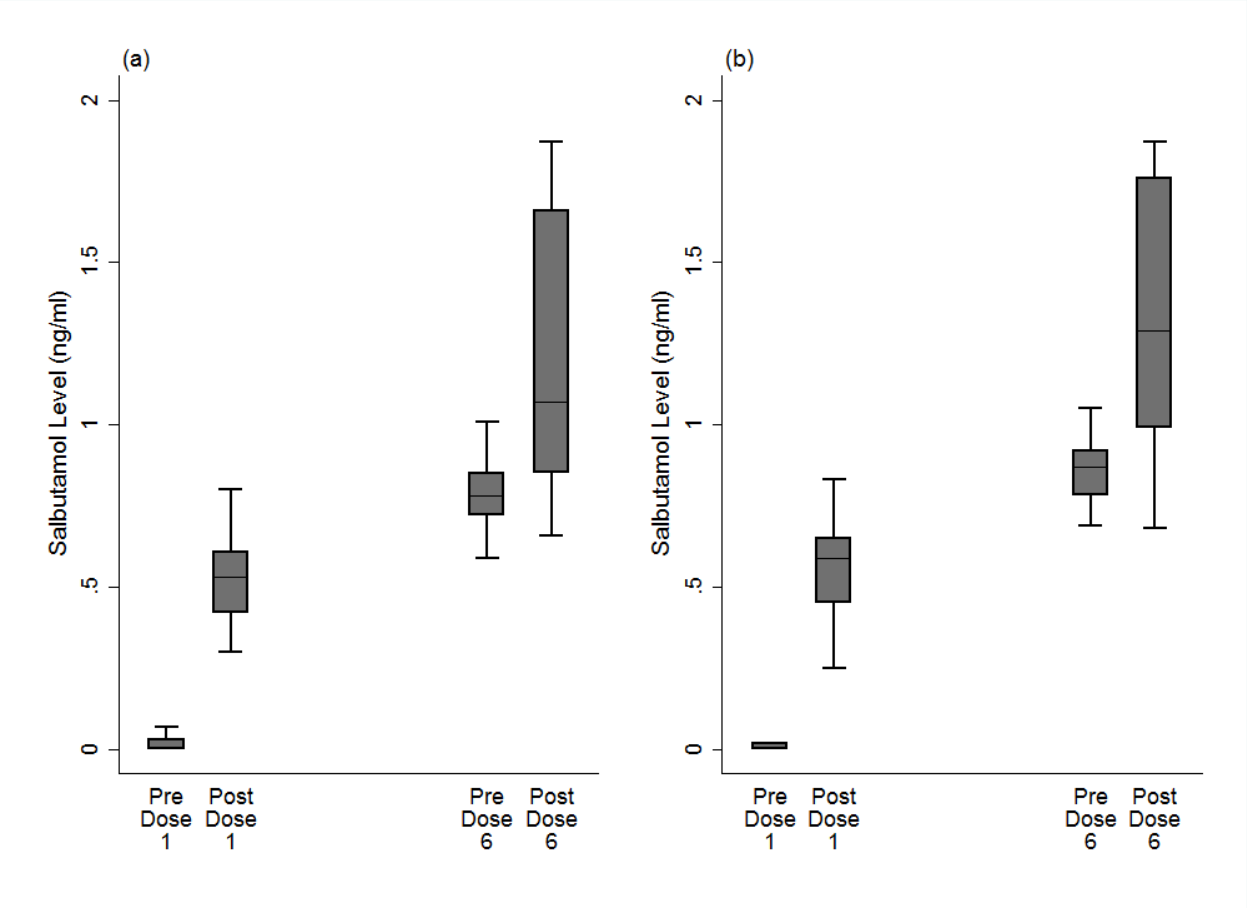


Figure 3-3: Control Phase Salbutamol Level Changes:

All 14 participants completed the control phase. All samples were assessed with 2 sample runs. Figures (a) represents the first run and Figure (b) represents the second run. Baseline levels (pre-dose 1) of salbutamol were as expected near zero. Twenty-five minutes after taking a salbutamol dose all patients had an increase in their salbutamol level. After taking 4 subsequent doses 6 hours apart with correct technique, pre dose 6 all participants now had a resting level of salbutamol, higher than baseline, $p<0.001$. Twenty-five minutes after taking dose 6, all patients, except for two had a rise in their salbutamol levels.

3.4.4 Error Phase

All participants completed both the control phase (correct technique) and at least one error phase (incorrect technique), see Figure 3-4. I will now describe the impact each of the errors had on drug delivery, when compared to the matched control.

3.4.4.1 Exhalation Error

With at least 5 days between the control phase and error phase, the mean (SD) baseline salbutamol level for patients performing this error was 0.00 (0.00). Participants (n=5) then performed the exhalation inhaler error (see Figure 3-5 (a) and (b), described above, and a blood sample was taken 25 minutes later. Salbutamol level rose to a mean (SD) 0.21 (0.29) ng/ml. This was not significantly different than the control phase, 0.53 (0.25) ng/ml ($p=0.12$). Participants then continued this error for the next 4 doses; prior to taking dose 6 the mean (SD) salbutamol level was 0.44 (0.35) ng/ml. This trough level was lower than the matched control phase, 0.79 (0.05) ng/ml, however this was not significant ($p=0.10$). Participants then took dose 6 with an exhalation error, and 25 minutes later the mean (SD) peak salbutamol level was 0.53 (0.40). This final peak level was significantly lower than the matched control, $p<0.01$. (see Figure 3-6 (a) and Table 3-3)

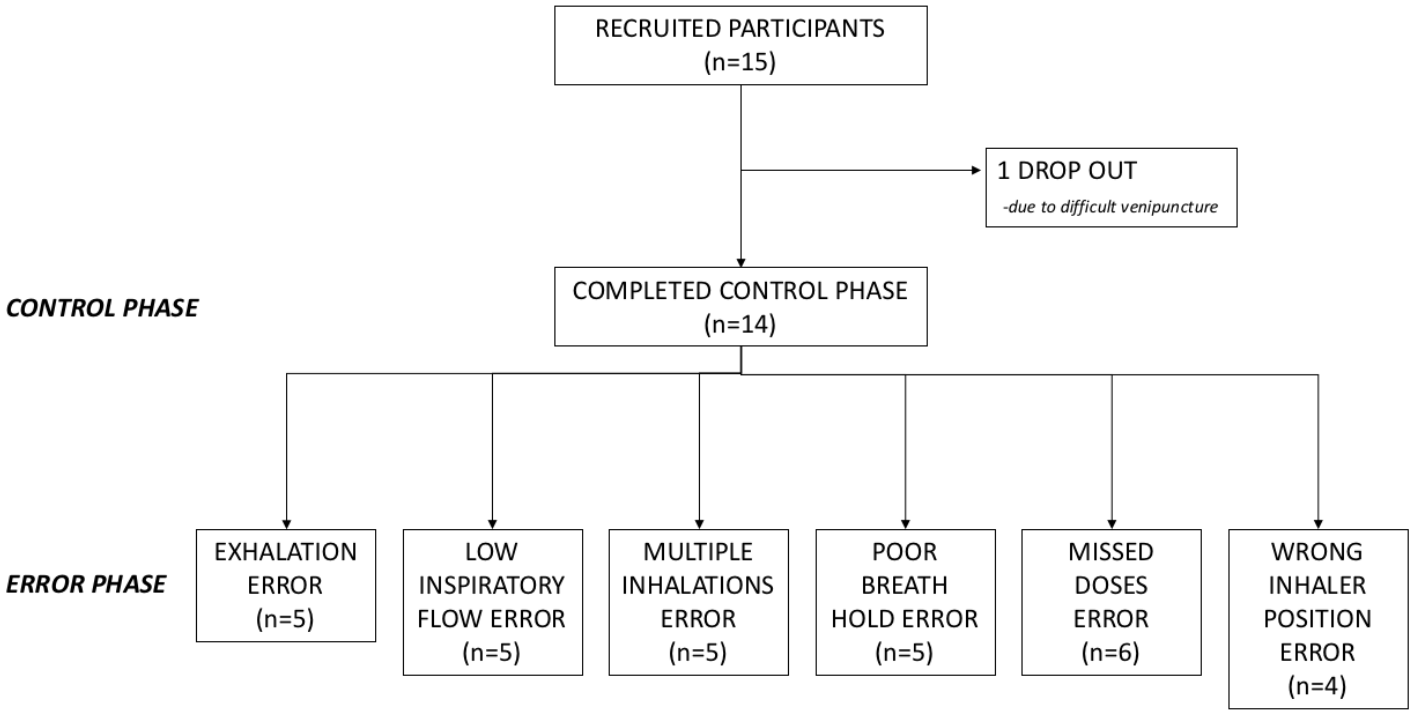


Figure 3-4: Study Flow:

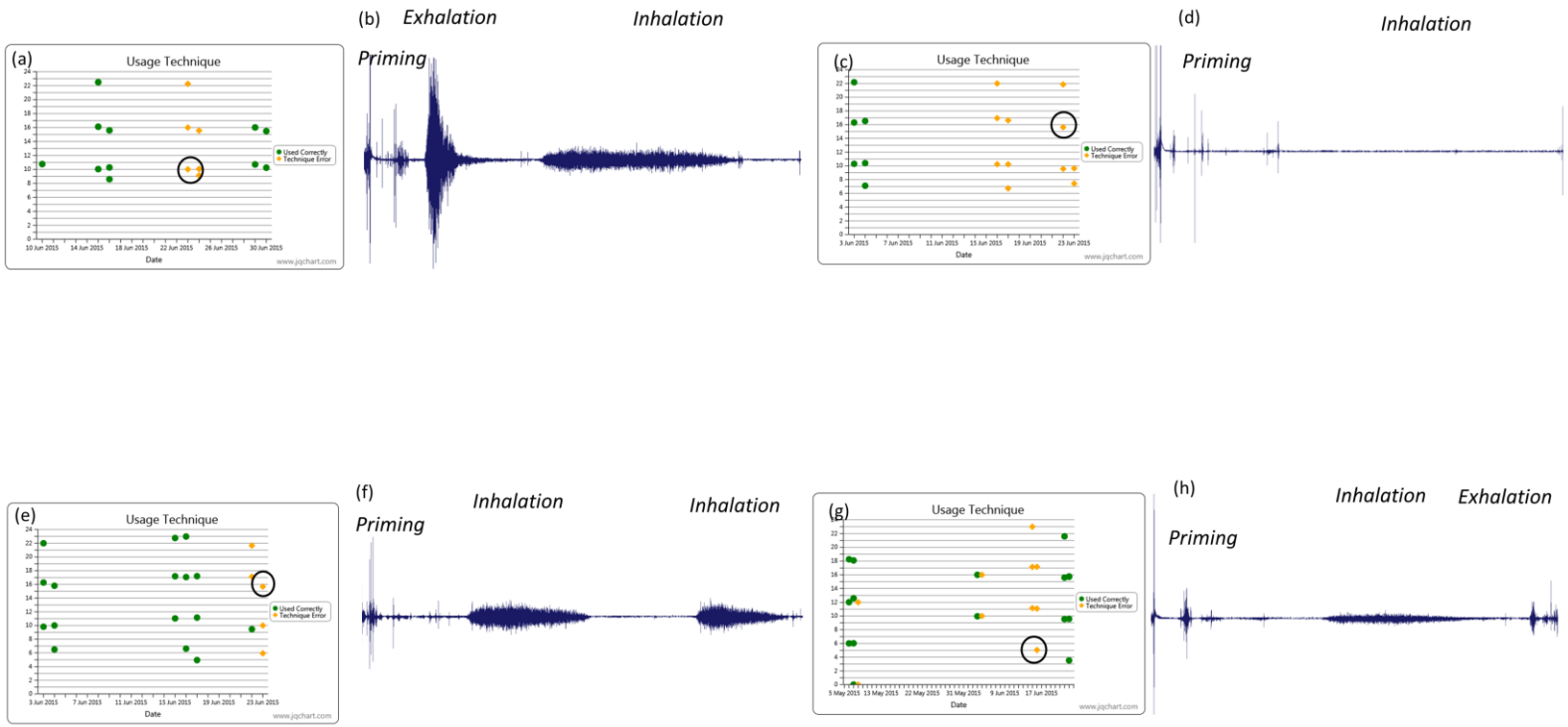
This is a diagram of the study flow. Fifteen participants were recruited overall, with just one drop out. All 14 participants completed the control phase. Five participants completed the exhalation error, low inspiratory flow error, multiple inhalations error and poor breath hold error. Six participants completed the missed doses error and only four participants completed the wrong inhaler position error. Due to low recruitment, some participants completed more than one error, however between errors there was always a minimum 5-day gap to allow enough time for salbutamol levels to return to normal/not detectable

3.4.4.2 Poor Inspiratory Flow Rate

Similarly, the baseline level of salbutamol was near zero in this error phase. Participants (n=5) generated a low inspiratory flow (see Figure 3-5 (c) and (d)) and twenty-five minutes after completing this error, the mean (SD) salbutamol level was 0.27 (0.13) ng/ml. This was significantly lower than the matched control of 0.58 (0.12) ng/ml (p=0.02). Before the sixth dose, the mean (SD) salbutamol level was 0.14 (0.09) ng/ml. This trough level was also significantly lower than the matched control, 0.74 (0.06) ng/ml (p<0.01). The peak salbutamol level at 25 minutes after dose six was 0.25 (0.18) ng/ml, and this also was significantly lower than the matched control of 1.24 (0.36) ng/ml (p<0.01), see Figure 3-6 (b) and Table 3-3. An algorithm has been previously developed that identifies the acoustic properties of an inhalation and is capable of calculating the peak inspiratory flow rate (105,109). All participants who performed the low inspiratory flow error were shown to have generated a low flow with each inhalation.

3.4.4.3 Multiple Inhalations

Baseline levels after a period of no salbutamol doses was near zero in this group. Participants (n=5) took their first dose with more than one inhalation (see Figure 3-5 (e) and (f)) and 25 minutes later their mean (SD) salbutamol level was 0.44 (0.13) ng/ml. This was very similar to the control phase of 0.51 (0.08) ng/ml and the difference was not statistically significant, p-0.36. The trough level before dose six was 0.56 (0.21) ng/ml, again not significantly different from the control phase of 0.72 (0.12) ng/ml (p=0.16). The mean (SD) peak salbutamol level 25 minutes after dose six was 0.99 (0.27) ng/ml. This was not significantly different than the control phase of 1.15 (0.37) ng/ml (p=0.28), see Figure 3-6 (c) and Table 3-3.


(a)
Usage Technique
Used Correctly
Technique Error
Date
(b)
Exhalation
Inhalation
Priming
(c)
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Date
(d)
Inhalation
Priming
(e)
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Used Correctly
Technique Error
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(f)
Inhalation
Inhalation
Priming
(g)
Usage Technique
Used Correctly
Technique Error
Date
(h)
Inhalation
Exhalation
Priming

Figure 3-5: Examples of Different Inhaler Technique Errors:

Figures (a), (c), (e) and (g) are calendar plots of inhaler use over time with days on the x axis and time of day on the y axis. A green dot indicates good technique for that dose, while a yellow diamond indicates poor technique. Figures (b), (d), (f) and (h) are audio examples recorded on the INCA™ device from the adjacent calendar plot, providing a visual example of the circled inhaler technique error. Figure (a) and (b) are an example of participant who made the exhalation into the device after drug priming before inhalation error. Figure (c) and (d) is an example of a participant who performed the low inspiratory flow error, the inhalation profile is barely visible. Figure (e) and (f) is an example of a participant who performed the low breath hold error. Figure (g) and (h) is an example of a participant who performed the multiple inhalation error.

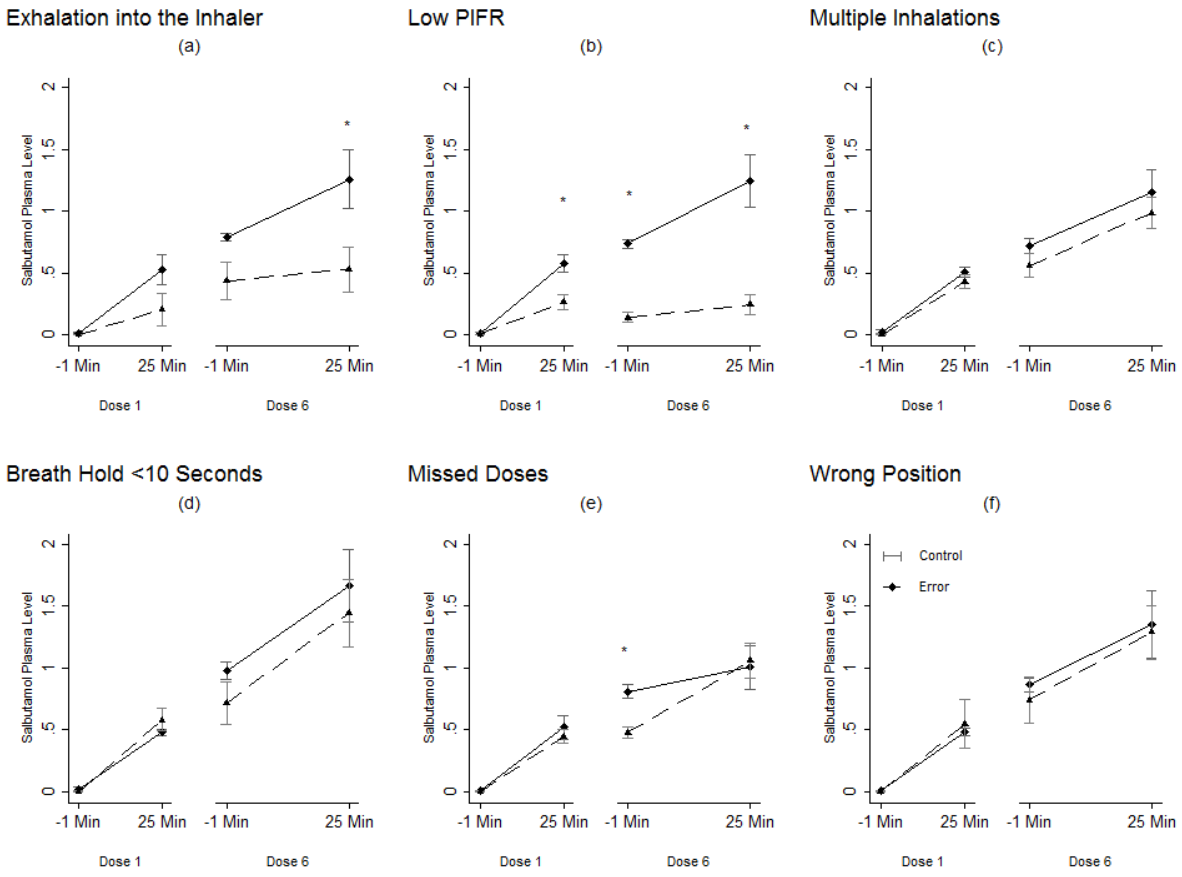

Figure 3-6: Comparing Salbutamol Levels for Each Inhaler Error:

Six inhaler errors were compared to matched controls. Significant differences in salbutamol levels were seen with the exhalation error (a), low peak inspiratory flow rate (PIFR), (b) and missed doses, (e). Low inspiratory flow was consistently lower than matched control. Exhalation error (a) became significantly lower than matched control by dose six and missed doses was significantly lower than matched control at trough levels after missing two doses.

3.4.4.4 Breath Holding less than 5 seconds

For this error participants (n=5) took their first dose correctly but only held their breath for four seconds or less before exhaling fully (see Figure 3-5 (g) and (h)). Twenty-five minutes later, the mean (SD) salbutamol level was 0.58 (0.20) ng/ml, this was not significantly different than the control phase, 0.48 (0.06) ng/ml (p=0.37). Continuing this error for the next 4 doses, before dose six the mean (SD) salbutamol level was 0.54 (0.29) ng/ml and not different to the control phase, 0.74 (0.11) ng/ml (p=0.42). Twenty-five minutes later, the mean (SD) peak salbutamol level was 1.10 (0.46) ng/ml, and not significantly different to the control phase, 1.25 (0.44) ng/ml (p=0.61), see Figure 3-6 (d) and Table 3-3.

3.4.4.5 Missing Doses

Participants (n=6) took their first dose correctly leading to an increase in salbutamol levels up to 0.45 (0.13) ng/ml. Participants then took their second and third doses six hours apart, but missed their fourth and fifth dose. The mean (SD) trough level after missing two doses of salbutamol was 0.48 (0.10) ng/ml. This was significantly lower than the control phase of 0.81 (0.13) ng/ml, p=0.02. Participants then took their sixth dose correctly and 25 minutes later their mean (SD) peak salbutamol level measured at 1.06 (0.36) ng/ml, this was not significantly different to the control phase of 1.01 (0.39) ng/ml (p=0.51), see Figure 3-6 (e) and Table 3-3.

3.4.4.6 Wrong Inhaler Position

The participants (n=4) in this error phase held the Diskus^{TM} inhaler vertically, as opposed to the recommended horizontal position, and took a normal dose. The mean (SD) peak level at 25 minutes was 0.55 (0.40) ng/ml, not significantly different to the control phase of 0.49 (0.06) ng/ml, p=0.77. Participants held the inhaler in this position for each subsequent dose. Before dose six, the mean (SD) trough salbutamol level was 0.74 (0.37) ng/ml and 25 minutes later it was 1.29 (0.43) ng/ml. Neither values were significantly different from the control phase, p=0.75 and p=0.39 respectively (see Figure 3-6 (f) and Table 3-3). See Table 3-3 and Figure 3-6 for a summary of the changes in salbutamol levels for each inhaler error.

Table 3-3: Salbutamol Levels at Different Time Intervals:

All values are presented as mean (SD) ng/ml salbutamol levels. Fourteen participants were recruited to this study in total; all completed the control phase of the study. 5 patients performed the exhalation error phase, 5 patients performed the low inspiratory flow error, 5 performed the multiple inhalation error, 5 performed the poor breath hold, 6 missed doses and 4 participants used their inhaler in the wrong position. All baseline levels, Dose 0 Time 0 were near to zero. Exhalation into the inhaler after drug priming and before inhalation lead to a low level of salbutamol over time, only significant at 25 minutes after dose 6. Low inspiratory flow error had a consistently low level of salbutamol throughout the study. Missed dosses error lead to a low trough level before dose 6 was taken. *$p<0.05$ comparing to matched control levels. ¯The difference in numbers between the matched control and errors in the exhalation error, missed doses error and wrong position error, is due to removing the two participants whose salbutamol level fell 25 minutes after dose 6.

	n	Dose 1 Time 25 min	Dose 6 Time 0	Dose 6 Time 25 min
ALL CONTROL PARTICIPANTS	14	0.50 (0.14)	0.82 (0.11)	0.82 (0.11)
EXHALATION ERROR				
Error	5	0.21 (0.29)	0.44 (0.35)	0.53 (0.40)*
Matched Control	4¯	0.53 (0.25)	0.77 (0.05)	1.45 (0.29)
Mean Difference Control – Error		0.37 (0.31)	0.26 (0.42)	0.89 (0.27)
LOW INSPIRATORY FLOW ERROR				
Error	5	0.27 (0.13)*	0.14 (0.09)*	0.25 (0.18)*
Matched Control	5	0.58 (0.12)	0.69 (0.16)	1.27 (0.28)
Mean Difference Control – Error		0.30 (0.08)	0.58 (0.16)	0.99 (0.48)
MULTIPLE INHALATION ERROR				
Error	5	0.44 (0.13)	0.56 (0.21)	0.99 (0.27)
Matched Control	5	0.51 (0.08)	0.72 (0.10)	1.21 (0.35)
Mean Difference Control – Error		0.11 (.03)	0.13 (0.27)	0.07 (0.52)
POOR BREATH HOLD ERROR				
Error	5	0.58 (0.20)	0.54 (0.29)	1.10 (0.46)
Matched Control	5	0.48 (.05)	0.66 (0.18)	1.23 (0.38)
Mean Difference Control – Error		-0.02 (0.16)	0.19 (0.30)	0.18 (0.29)
MISSED DOSES ERROR				
Error	6	0.45 (0.13)	0.48 (0.10)*	1.06 (0.36)
Matched Control	5¯	0.52 (0.21)	0.65(0.19)	1.21 (0.35)
Mean Difference Control – Error		0.11 (0.19)	0.22 (0.07)	0.01 (0.29)
WRONG POISITION ERROR				
Error	4	0.55 (0.40)	0.74 (0.37)	1.29 (0.43)
Matched Control	3¯	0.49 (0.06)	0.82 (0.11)	1.58 (0.35)
Mean Difference Control – Error		-0.06 (0.45)	0.08 (0.47)	0.36 (0.54)

3.5 DISCUSSION

Inhaled medications may become complicated by the introduction of a device required to deliver the medication. Unlike pill/oral-based medication, inhaled medication requires this 'device', such as the Diskus™, to deliver the medication, which introduces the potential for human error in using these devices. Currently there are over 10 difference inhaler devices in the market (42,178). Each comes with its own list of instructions and potential for human error. The aim of this study was to identify which of these errors directly affected drug delivery

In my previous work, Chapter 2, I identified and described the frequency of several common inhaler errors made by patients using a Diskus™ inhaler. These errors included exhaling into the inhaler after drug priming and before inhalation, poor inspiratory flow rate and multiple inhalations (which in theory combines the exhalation error and poor breath hold as patients exhale directly after inhaling and then inhale again without a break). Although technically not an error in technique, missed doses can be considered an error in inhaler handling, since it affects the pharmacokinetic profile of the medication. The mean missed dose per patient was 18 out of a potential 60 doses. Another possible error previously reported is the specific position of the inhaler. For the Diskus™ inhaler it is suggested that the inhaler be held horizontal when used (169).

In this pharmacokinetic study 14 healthy volunteers were recruited. Each participant was trained on the correct use of the Diskus™ inhaler device. To serve as a control, all participants took 6 doses correctly 6 hours apart and over 2 days. Participants were then taught how to perform all the specific inhaler errors identified in Chapter 2. Before and twenty-five minutes after the first and last doses blood samples were taken

Taking six consecutive doses of salbutamol, with correct technique and adequate interval between doses, led to a stable trough salbutamol level. After missing doses there was a significant reduction in the trough salbutamol levels. A persistently low inspiratory flow rate also resulted in a significant reduction in the trough salbutamol level. A low inspiratory flow

rate also led to a significant reduction in the peak salbutamol level. Exhalation after priming but before inhalation led to a significant reduction in peak salbutamol levels.

There were several novel findings in this study. As mentioned, of the technique errors, only low inspiratory flow rate and exhalation into the mouthpiece after priming but before inhalation significantly reduced plasma salbutamol levels. Missing doses only had a significant effect on trough levels. In contrast, multiple inhalations, low breath hold and wrong inhaler position had no significant impact on salbutamol levels.

Low inspiratory flow rate seemed to have the most significant effect on plasma salbutamol levels. At the end of each phase each participant returned his or her inhaler. It was noted that in those performing the low inspiratory flow rate error, the inhaler was returned with a dry powdered drug residue all over the inhaler, see Figure 3-7. Suggesting, that with the poor inspiratory flow, a proportion of the drug transferred to the mouthpiece with each blister, is left in the mouthpiece and with time this residue gets displaced around the inhaler. Therefore, with this inhaler error, there is a large amount of drug wasted leading to low levels of drug delivery. In a Cochrane review, the authors found that only 46-59% of patients had efficient inhalation technique (179). With such low levels of proper inspiratory effort, these patients are only getting a small proportion of medication into their airways, potentially leading to adverse effects such as poor disease control, increased exacerbations, higher mortality (180) and possibly oral candida and vocal cord issues, such as hoarseness.

Exhalation into the inhaler after drug priming appeared to have a cumulative effect. There was no immediate effect on salbutamol levels, but over time there was a significant reduction in salbutamol levels after dose 6. Multiple inhalations and low breath hold are common errors identified in a cohort of respiratory patients (Chapter 2). However, in this study neither of these errors had a significant effect on the salbutamol plasma levels.

Current methods of assessing inhaler technique utilize checklists. These checklists describe what are thought to be key steps in correctly taking an inhaler and only assess inhaler technique at one point in time (155). In a study by Murphy et al, the authors evaluated inhaler technique with a checklist based method and instructed those with poor technique

appropriately. At a 3 to 4 month follow up, the percentage of patients with poor technique reduced from 63% to 20%, with little clinical effect (181) Although technique was adequate at the follow up visit, there is no way to ensure that these patients had good technique in the 3 to 4-month interval.

With the introduction of electronic monitors, inhaler adherence can be monitored over time (113). However, none of the current electronic monitors are able to monitor inhaler technique. In this study, I have demonstrated that inhaler technique is both a crucial, and with some errors, critical component of measuring inhaler use. In a previously published randomized clinical trial looking at the effectiveness of an asthma education program that included education on inhaler technique, the authors found that the group randomized to the treatment arm had fewer exacerbations and greater increases in the Mini Asthma Quality of Life Questionnaire (182). Thus highlighting the potential importance of monitoring inhaler technique, in respiratory diseases, such as asthma, which are dependent on inhaler treatment. In another study examining the impact inhaler technique has on emergency department visits, the authors found poor inhaler device use was associated with poor asthma control and frequent emergency department visits (183), further strengthening the importance of inhaler technique.

Figure 3-7: Low Inspiratory Flow Error:

This is an image of a ÐÁÒÔÉÃÆÐÁÎÔ‰Ó inhaler mouthpiece after performing the low inspiratory flow error for 6 doses. In the image you can see the deposition of the dry powder inhaler all around the mouth piece, therefore leading to wasted drug and reduced drug delivery.

3.5.1 Limitations

This study has some limitations. Firstly, the Diskus™ inhaler device was the only inhaler device used. As mentioned previously there are over 10 inhaler devices in the market all with their own specific instructions. However, the errors found to be significant on drug delivery in this study, exhalation and low inspiratory flow, are still applicable to any dry powder based inhaler, such as the Turbohaler™ or the Elipta™ device.

For this study I used salbutamol as the inhaled drug. There are numerous other compounds prescribed to patients with airways disease, such as salmeterol, fluticasone and budesonide. All these different inhaled drugs have different mechanisms and pharmacokinetic studies with those medications may be somewhat different. Additionally, gastrointestinal absorption from inhaled medication may affect systemic drug level measurement. However, the principle message of this study, that poor inspiratory effort and exhalation after drug priming before inhalation lead to poor drug delivery still remains true for any inhaled medication studied.

There was no power calculation done for this study; participant numbers were low and were healthy volunteers. Without a prior power calculation there is the potential for a type II error, where a significant difference with some of the other errors (i.e breath hold) may have been missed. Unfortunately, two participants control phase samples showed a decrease in salbutamol dose after inhalation and had to be excluded when comparing to matched error phase, however including these patients in the analysis did not alter the findings. Additionally, it is not certain what impact these findings may have on patients with airways disease However, it is reasonable to assume the implications of inhaler errors will hold true.

3.6 CONCLUSION

After identifying which inhaler errors were common in a community-based population I tested if these errors had any impact on drug delivery, by measuring salbutamol plasma levels. In this study I have identified two technique errors that should be considered as critical technique errors; exhalation into the device after drug priming and before inhalation and low inspiratory flow rate. Not surprisingly, missing doses also leads to a reduction in drug delivery. Other common errors, multiple inhalations, poor breath hold and wrong inhaler position had no impact on drug delivery. In this study I have proven that inhaler technique is an important component of inhaler use and should be considered when measuring and discussing inhaler adherence. I also have identified an important component of some inhaler errors, that being the additive effective of a consistent error. With particular reference to the exhalation error, repeating this error over time led to a significant reduction in drug delivery by dose six.

Based on the findings of this study and my previous chapter, I have shown that quantifying adherence as the mean possession ratio from the dose counter has major limitations. This method does not account for inhaler errors and ignores the additive/cumulative effect of drug ingestion. As inhaler errors (both in regards to time of use and technique of use) have an additive effect in regards to drug accumulation and therefore drug delivery, a measure of adherence that is calculated as a function of drug accumulation is an appropriate method of calculating adherence as it would give health care providers and patients a better understanding how the components of adherence (time and technique of use) effect drug delivery. However, the clinical relevance of these technique errors and drug delivery are not clear from this study.

In the following chapter, Chapter 4, I will develop a new method of calculating adherence in relation to drug accumulation accounting for the technique errors identified as critical from this study and use this method to calculate adherence from then on. I will compare it to the current method of calculating adherence (mean possession ratio) and test its relationship with clinical outcomes, such as quality of life or possibly lung physiology.

Chapter 4 :

A METHOD OF QUANTIFYING ADHERENCE THAT INCORPORATES INHALER TECHNIQUE AND INHALER USE

4.1 INTRODUCTION

In Chapter 2 of this thesis several common inhaler technique errors were identified in a cohort of patients with respiratory disease. Following this, in Chapter 3, I demonstrated that some of these inhaler errors have a significant impact on drug delivery. Therefore, it would seem that inhaler technique should be included in the assessment and calculation of adherence. An individual may take their inhaler according to the dosing schedule, but incorrect technique may result in no medication being delivered. In this scenario the average use over time is meaningless unless data on the technique of use is also incorporated into the calculation of the adherence. Hence, in this Chapter I will describe a new method to quantify adherence that accounts for variations in dosing schedules alongside inhaler user technique.

4.2 BACKGROUND

Electronic monitors are now considered to be the gold standard for objectively quantifying adherence (82). For inhaled medication, in addition to electronic monitors, physicians can use the dose counter on inhaler devices to estimate medication average adherence (i.e. Doses used based on the dose counter divided by the number of doses prescribed for a certain time interval). Most studies using electronic recording devices have reported adherence as the average adherence (i.e. mean possession ratio) or, the Mean Daily Dose, over the study period (184) (185) (158). However, this method does not reflect variations in the way that patients use their treatments. For example, the mean adherence is the same whether an individual took the medication according to the prescribed schedule or took all the doses in the first half of a dosing period, leaving none in the second half. Another major flaw in this calculation relates to the time between doses. As this interval increases, there is an increase in the averaging of significant missed doses and overdoses (185). Therefore, over averaging is a significant pitfall in this method of calculating adherence. Furthermore, electronic recording devices usually do not assess if the inhaler was taken correctly (128,155,158,169,180,183,186-188).

As mentioned previously, the INhaler Compliance Assessment (INCA^{TM}) device assesses inhaler use over time by recording the audio associated with inhaler use (153). Analysis of this information provides a means to assess the time of use, the interval between doses and the proficiency of inhaler use can be assessed (153). Technique errors identified by this method include failing to prime the inhaler, dispersing the medication by exhalation into the inhaler after priming and other errors such as dose dumping (105-106). In addition, the acoustic features of inhalation are highly reflective of objectively measured peak inspiratory flow rate, meaning that the device can estimate the dose of medication delivered at each inhalation (109-108). With this device, the exact time and date of inhaler opening, drug priming and correct inhaler use can be accurately collected over an extended period of time. This specific information on time of use allows for the calculation of the interval between each dose, which aids in understanding drug exposure when the pharmacokinetic properties of the medication are considered.

"Pharmacokinetics is proposed to study the absorption, the distribution, the biotransformation's and the elimination of drugs in man and animals" (34). Area Under the Curve (AUC) is a commonly used method in assessing drug exposure. For example, in a previously published paper assessing the bronchodilator properties of once daily (24-hour interval) versus twice daily (12 hour interval) dosing in a cohort of asthma patients, the authors used $AUC_{(0\text{-}12h),ss}$ and $AUC_{(0\text{-}24h),ss}$ to compare the drug exposure of the two drug formulations. Additionally, it is common practice to use AUC in measuring drug impact on lung physiology. In this same paper, the authors used the trapezoidal rule to calculate the Forced Expiratory Volume in 1 second (FEV_1) $AUC_{(0\text{-}24h),}$ divided by the observation time (24 hours) (189).

I hypothesised that I could calculate adherence as an area under the curve (AUC) by combining information recorded to the INCA^{TM} device including the time of use, the interval between doses and adjusting for incorrectly taken doses. To test this hypothesis, I analysed data recorded to INCA^{TM} devices by 239 respiratory patients.

4.3 METHODS

4.3.1 Study Design

Patients for this study were prospectively recruited from five specialty asthma clinics in Ireland from January 2011 to December 2015. Participants in this analysis included all asthma patients studied to date, both those who participated in a pilot preliminary study (n=32) and also from a single blind prospective multicentre randomised controlled clinical trial (n=207) which followed (Chapter 7). The full protocol of the study has been published (190). All patients from both groups (active and control) of the randomised control trial were combined for this analysis.

On enrolment the patients were shown how to use the inhaler and errors were corrected using a 10 point checklist, providing an inhaler proficiency score (191-193). Over the following months (4, 8 and 12 weeks) the patients returned to the clinic, their inhaler technique was checked and improved if necessary, and adherence encouraged. The study was approved by local hospitals ethics committees and registered on Clinicaltrials.gov, NCT01529697.

4.3.2 Participants

Inclusion criteria were patients aged ≥18 already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (157,194) who, in addition, had at least one exacerbation treated with systemic glucocorticoids in the prior year. The dose of inhaled corticosteroid and long acting beta-agonist (LABA) was not changed during the study. Exclusion criteria included an unwillingness to participate in a clinical study or prior hypersensitivity to salmeterol/fluticasone. Asthma diagnosis was made using a clinician diagnosis supported by one or more of the following: obstructive spirometry with at least 12% reversibility, a positive bronchial provocation challenge or variability in the diurnal peak expiratory flow (PEFR) of more than 15%. All patients provided written informed consent.

4.3.3 Electronic adherence monitor

The development and validation of the INCA™ audio recording device is reported in Appendix A. The device is attached to an inhaler and records the audio associated with an individual using their inhaler. Participants in this analysis received an INCA™ enabled salmeterol/fluticasone Diskus™ inhaler each month.

4.3.4 Extraction of features of inhaler use and calculating adherence

Audio raters assessed each acoustic recording for evidence of critical errors, as previously described (105,106,153). Critical errors in inhaler use, such as low inspiratory flow and exhalation into the inhaler were classified as no dose. While non-critical errors, such as vertical position of the inhaler, were classified as a complete dose.

The interval between doses was calculated based on drug half-life and the measurement of doses taken was related to the drug interval (for this study, the pharmacokinetic profile and drug half-life of salmeterol was used). If an inhaler dose was taken within one half-life after the previous dose, this was counted as one dose. Where the interval between doses was greater than one half-life and less than two half-lives, this was considered as a 0.5 dose. Where the interval between doses was greater than two half-lives and less than three half-lives, this was considered as 0.25 dose. Where the interval between doses was greater than three half-lives and less than four half-lives, this was considered as 0.125 dose. Finally, in cases where the dose interval was greater than four half-lives, this was considered as no dose.

Information collected on the time, interval between doses and technique of inhaler use were combined to calculate an Area under the cure (AUC) metric, using the trapezoidal function. For this analysis, the AUC was divided into equal spaced areas (1 day) until the end of a selected time interval (N) leaving N trapezoids. The trapezoid equation is as follows:

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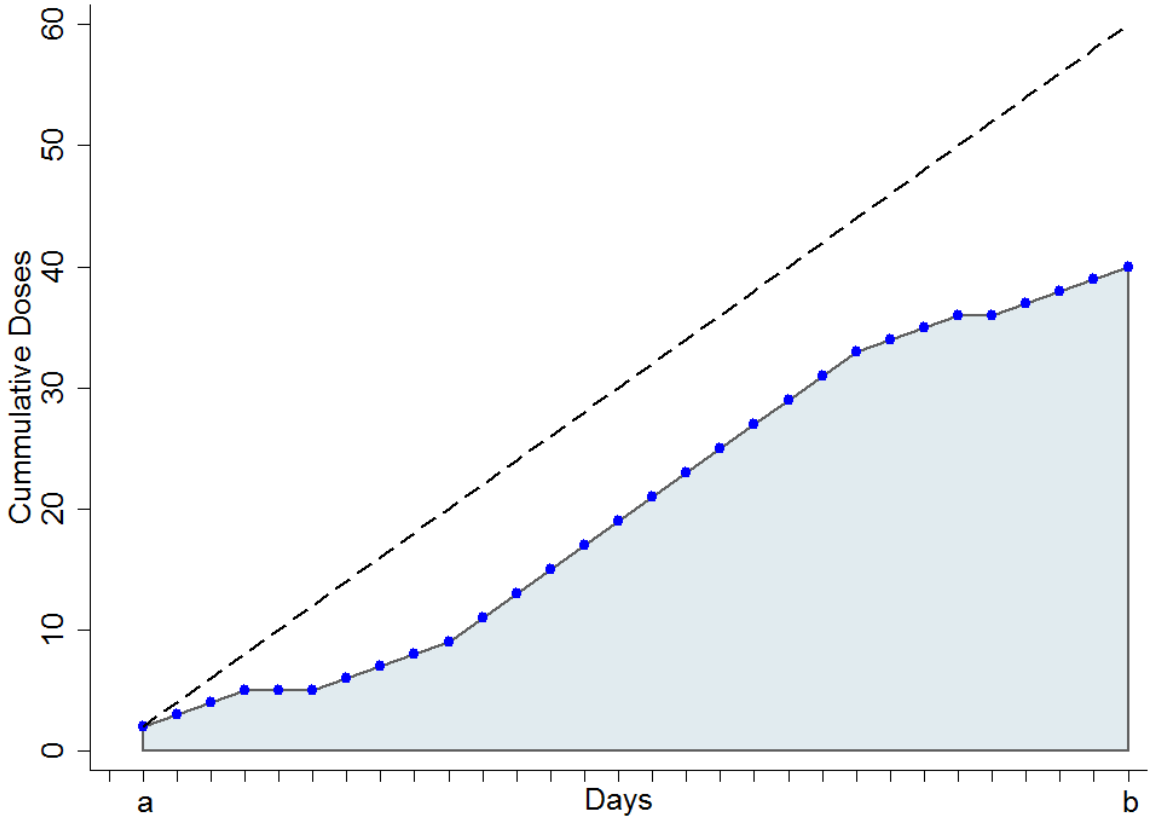

Figure 4-1: Example of Area Under the Curve for Cumulative Doses

Where ٱ ٵ is the length of the first wall of the trapezoid and ٱ ٶ is the length of the second wall of the trapezoid and ٶ ط ٵ is the width of the trapezoid.

In this analysis the width remains constant at 1; hence the daily AUC is as follows:

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The full equation sums the areas of all calculated AUCs over a selected time interval (N) which can be expressed as:

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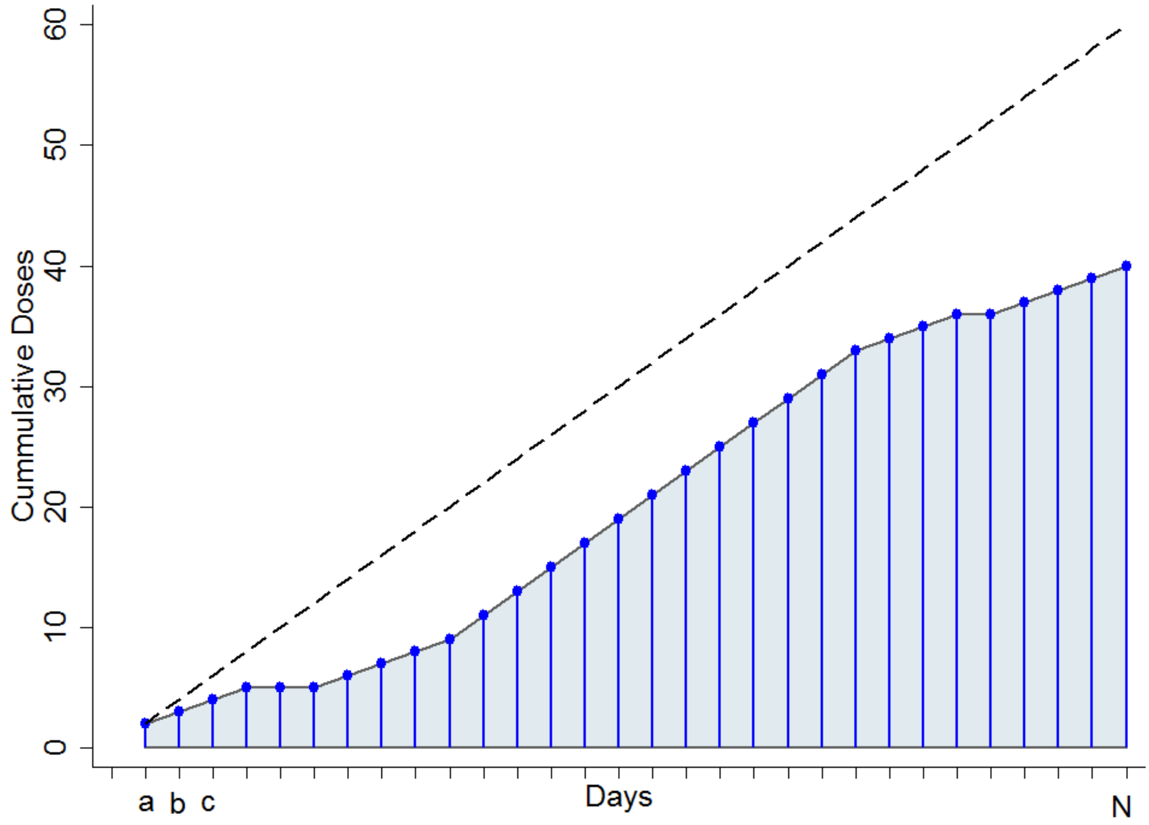

Figure 4-2: Trapezoid Function for Each Day of Measured Adherence

Initially, the AUC is calculated for the expected doses, denoted by ᷇Ὠ ᾼὩὼ . Following this the AUC is calculated for the participant's attempted dosing, denoted by ᷇Ὠ ὣὸ , Attempted dosing refers to the number of doses that patients attempt to take (i.e. evidence of drug priming in the acoustic analysis, these doses may be taken correctly or incorrectly) and used to calculate the Attempted Adherence, ᷇Ὠ ὃ᷆Ὗ .

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This value, relative to the expected doses, ᷇Ὠ ᾼὩὼ , gives information on overdosing, denoted by ᷇Ὠ έᾺὩ and missed doses, denoted by ᷇Ὠ άᾺὩ . By removing doses where a critical error has occurred, the actual doses, denoted by ᷇Ὠ ὣᾺὩ , may be deduced. Subtracting this value from ᷇Ὠ ὃ᷆Ὗ gives us the Technique Rate, denoted by ᷇Ὠ ὸᾺὩ .

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The Interval Adherence ʺΩ Ώ is calculated as a ratio of the attempted interval adherence ʺΩ Ώώ̋ὸ to the expected interval adherence ʺΩ ΏΏΩὼ .

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Furthermore, by removing the technique errors we can calculate the Actual Adherence ʺΩ ö̏ő .

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See Figure 4-3 for a graphical display of this process and Table 4-1 for a definition of terms.

4.3.5 Analysis of Peak Expiratory Flow Rate (PEFR)

A similar method to that described above was used to analyse PEFR data. Patients recorded PEFR readings twice daily (AM and PM) for up to one month. Expected PEFR was calculated based on age, sex and height. This was plotted for the study period (i.e. 30 days) and using the trapezoid function per day, the PEFR AUC was calculated. A ratio was then calculated comparing the recorded PEFR to the expected PEFR from AM and PM readings separately.

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ΰ̃ ΰ ΰ̃ΏΟʺΟΥ ö̏ʺΥő ʺΩ ΰ̃ ΰ سي ʺΩ ʹΥΏΩω̃έὶΏΩΏΩ ΰ̃ ΰ ΰ̃ΏΟʺΟΥ / ʺΩ ΏΟὼὴΏΩω̃ὸΏΩ ΰ̃ ΰ ΰ̃ΏΟʺΟΥ Þ

PEFR variability (195) was calculated as the difference between AM and PM PEFR AUC.

ö̏ ΰ ΰ̃ ΰ ώ̓ώ̋ὶΏώ̋ω̃ΏὰΏὸώ ʺΩ ö̏ ΰ ΰ̃ ΰ سي ʺΩ ö̏ ΰ طي ʺΩ ΰ̃ ΰ Þ

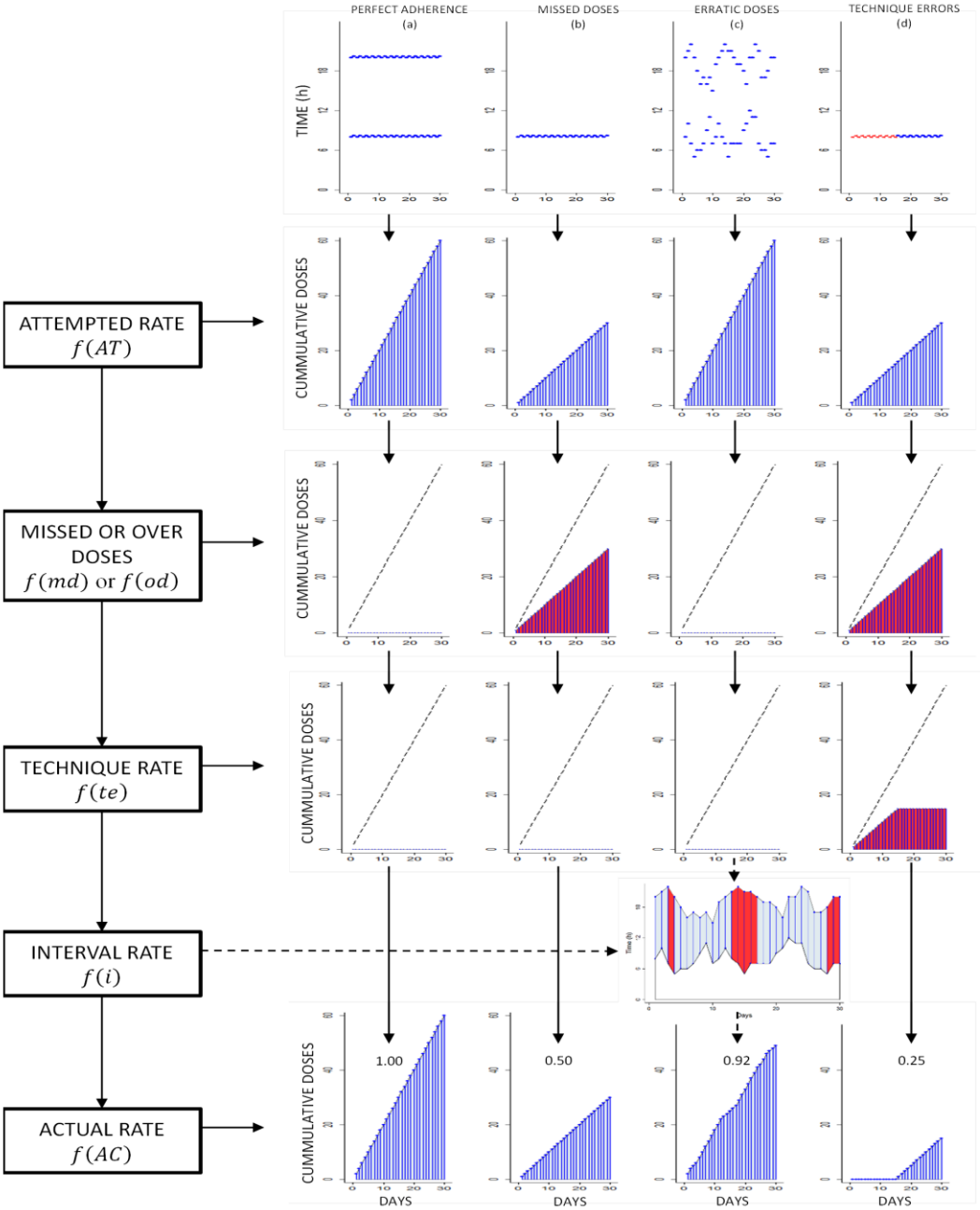
PERFECT ADHERENCE
(a)
MISSED DOSES
(b)
ERRATIC DOSES
(c)
TECHNIQUE ERRORS
(d)
TIME (h)
ATTEMPTED RATE
$f(AT)$
CUMMULATIVE DOSES
MISSED OR OVER DOSES
$f(md)$ or $f(od)$
TECHNIQUE RATE
$f(te)$
INTERVAL RATE
$f(i)$
ACTUAL RATE
$f(AC)$
1.00
0.50
0.92
0.25
DAYS

Figure 4-3: Calculation of Adherence Algorithm:

Examples of patients prescribed a medication twice daily for 30 days are shown. Column A is an example of a patient with perfect adherence over a 30-day period. Attempted Adherence, [redacted] is perfect with 60 doses taken over 30 days. There were no missed doses, no technique errors, and the interval between doses is within one half-life, the Actual Adherence rate, [redacted], is 1.00 (100%). Column B is an example where the medication was taken only once daily for 30 days. The Attempted Adherence, [redacted] is half that of column A and there were 30 missed doses over 30 days. In this example there were no technique errors. Due to missing doses every day the interval between doses was also poor and [redacted] is 0.50 (50%). Column C is an example of a patient who takes the medication (with no technique errors) every day, twice a day, but with erratic timing. There was perfect Attempted Adherence, with no missed doses and no technique errors. Due to the erratic time of use, some doses which have an interval beyond the half-life of the drug, [redacted], the [redacted] is reduced to 0.92 (92%). Finally, column D is an example of a patient who takes the medication only once daily and makes a technique error for the first 15 days of the 30 days. Therefore, the, [redacted] is half that of expected (50%) due to missing 30 doses. There were also 15 doses with technique errors, and due to missing doses every day the interval between doses was poor, therefore the [redacted] is 0.25 (25%).

Table 4-1: Definition of Different Adherence Terms:

The table below lists the terms used in this chapter for calculating adherence and their definitions. The final adherence outputs are ▉ ═╢ , Attempted Adherence, which is a calculation of adherence as an area under the curve based on the cumulative doses a patient attempted to take, that is that they at least primed the inhaler by blistering the drug; and ▉ ═╒ , Actual Adherence, which is a calculation of adherence as an area under the curve based on the cumulative doses a patient took correctly and with correct interval, based on the pharmacokinetic properties of the inhaled medication.

Measures	*Definition*	*Adherence Rate*
̈Ω ώ̆	Length of the first wall of the trapezoid	
̈Ω ώ̃	Length of the second wall of the trapezoid	
ώ̃ ط̇ ώ̆	Width of the trapezoid	
̈Ω ̈Ωὼ	AUC for the expected doses	
̈Ω ώ̆ὸ	AUC for attempted doses	
̈Ω ö″Ύ	Ratio of expected doses and attempted doses	*Attempted Adherence*
̈Ω ά̈Ω	AUC of missed doses	
̈Ω έ̈Ω	AUC of over doses	
̈Ω ώ̈Ω	AUC for actual doses	
̈Ω ̈Ωώ̆ὸ	AUC for attempted interval	
̈Ω ̈ΩΩὼ	AUC for expected interval	
̈Ω ̈Ω	Ratio of attempted interval adherence and expected interval adherence	
̈Ω ὸ̈Ω	Difference of Actual doses and attempted adherence	*Technique Rate*
̈Ω öő	Difference of Interval rate and technique errors	*Actual Adherence*

4.3.6 Outcome Measures

At the end of each month the INCA^{TM} device was collected from the participant. Audio data was downloaded from each device to provide information on inhaler use for the previous month. Additional information recorded at each visit included the Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Test (ACT), the patient's self-reported reliever medication use, PEFR and any recent exacerbations, see Appendix F for details on the study protocol and time points of data collection. Change in AQLQ (196,197) was divided into those who did (improvers) and did not (non-improvers) have an improvement of 0.5 points (the minimal clinically important difference in AQLQ). ACT ≥19 is considered well controlled. Using this cut off, patients were categorised into controlled and uncontrolled. Change in PEFR was also categorised into improvers and non-improvers based on a 10% cut off (157,194)

4.3.7 Clinician assessment of clinically meaningful thresholds of adherence

Separate acoustic data, from 30 patients from 3 different cohort studies (severe asthmatic patients from a tertiary centre clinic, chronic obstructive pulmonary disease inpatients from a tertiary care centre and respiratory patients from general practice clinics) who had used the INCA^{TM} device for at least one month, were analysed by two independent physicians (physician classification). Both physicians were independently shown visual representations of each patients adherence (measured by the INCA device), first in regards to timing and then secondly with respect to inhaler technique. The physicians were asked to rate each component of adherence (timing and technique) as either "poor" or "good". Examples of good and poor timing and technique are shown in the Appendix C. As there is no current gold standard for calculating adherence, this classification (a physicians interpretation of adherence) was used to calculate the sensitivity of the actual adherence rate as well as the attempted rate, mean daily dose and average adherence (from the dose counter).

4.3.8 Statistical Analysis

Descriptive statistics were used to present basic patient details for those included in this analysis. Means and standard deviations (SD) are presented for continuous variables and frequencies and percentages for categorical variables. For each patient and each month of data, the following adherence measures were calculated: dose counter (Average Adherence), Mean Daily Dose, ‟Ω ά'Ω , ‟Ω έ'Ω , ‟Ω ö"Y , ‟Ω ò'Ω , and ‟Ω öő . Baseline adherence measures at month 1 were initially examined. T-tests were used to compare the means of these different adherence rates. Proportions were compared employing a χ^2 analysis. Over the three months' differences in adherence measures and associations with clinical outcomes were examined using an ordinary least squares (OLS) regression. Each adherence measure regression coefficient was compared to ‟Ω öő for improvers and non-improvers separately. To compare these coefficients a test of linear hypothesis after estimation was used, testing if the linear expressions are equal. As there is no gold standard for calculating adherence a sensitivity analysis was done by categorising adherence into either good or poor based on an 80% cut off for each adherence measure. With this categorisation, each adherence measure's sensitivity and specificity at identifying improvers and non-improvers (AQLQ and PEFR) and controlled and uncontrolled (ACT) is reported. All statistical analysis was conducted using Stata Release 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

4.4 RESULTS

4.4.1 Participants

The clinical characteristics of the 239 participants included in this analysis can be seen in Table 4-2 (a more detailed description of this patient cohort is presented in Chapter 7). The patient cohort was primarily female (62%) with a mean (SD) age of 49 (16.1) years. A large proportion of patients in this cohort were poorly controlled with a mean AQLQ of 3.9, ACT of 12.2 and 145 (61%) patients used a short acting beta-agonist on a daily basis. I will now describe the different adherence measures for this patient population, including the new method of calculating inhaler adherence.

Table 4-2: Baseline Population Characteristics:

The baseline characteristics of the study population reported is shown. [1]Unless otherwise stated. [2]Forced Expiratory Volume in 1 second, [3]Asthma Control Test at visit 1,[4]Asthma Quality of Life Questionnaire at visit 1.

	Mean (SD)[1]
NUMBER OF PATIENTS	239
AGE (YEARS)	49 (16.1)
NUMBER OF MALES (%)	91 (38%)
FEV_1[2] L/SECOND	2.2 (0.88)
FEV_1 (%) PREDICTED	74.1 (22.9)
NUMBER OF EXACERBATIONS IN THE PREVIOUS YEAR	4.3 (3.5)
ACT V1[3]	12.2 (4.5)
AQLQ V1[4]	3.9 (1.3)
NUMBER OF PATIENTS RELIEVER USE (%)	
NEVER	49 (21%)
<1/WEEK	15 (6%)
1/WEEK	8 (3%)
2-5/WEEK	22 (9%)
EVERY DAY	145 (61%)

4.4.2 Baseline adherence to inhaled therapy

In the first month there were 11 (<6%) device failures, 5 (<3%) devices were lost and a further 6 (<3%) patients had missing dose counter information. The total number of audio files, for the first month, with evidence of drug priming was 7973, compared to a total of 8169 doses on the dose counter (correlation coefficient = 0.981). The reason for the differences between the two measures is due to episodes of multiple priming of the inhaler without inhalation (as described previously); this is recorded by the dose counter as doses taken. The mean (SD) number of audio files per patient from the 60 dose Diskus™ inhaler was 48 (10.8), while from the dose counter the mean (SD) number of doses recorded was 49 (18.4).

Analysis of the time stamped audio data recorded to the INCA™ device showed errors in inhaler handling, errors in overdosing and errors in missed doses. The most common errors in inhaler use included 308 events (3.1% of all attempted doses) of low peak inspiratory flow rate (PIFR) and 283 events (2.8% of all attempted doses) of exhalation into the device, the two errors identified as 'critical' in Chapter 3. Other errors included multiple inhalations with no breath hold and multiple priming of the inhaler without inhalation. The mean (SD) technique error rate, ‟Ω ὸΩ ἦ was 14.2% (21.5).

Overdosing was infrequent in this population and the mean (SD) overdosing rate, ‟Ω ἐΩ , was 6.6% (9.2). However, missing doses was much more common and the mean (SD) missed doses rate, ‟Ω ἀΩ , was 20.7% (18.7). Using the AUC method described above accounting only for evidence of priming of the inhaler, the mean (SD) Attempted Adherence, ‟Ω ὅ″Ύ , was 79.4% (20.7). Combined with the technique error rate this meant that the mean (SD) Actual Adherence, ‟Ω ὅὅ , at one month was 61.8% (28.5), significantly different from ‟Ω ὅ″Ύ ἦ p<0.01, see Table 4-3 and Figure 4-4.

4.4.2.1 INCA and Dose Counter Data

Data for both the dose counter and the INCA™ device was available for 217 (91%) of the 239 patients. For these patients the average (SD) dose counter adherence was 84.4% (19.1) and the Mean Daily Dose was 85.0% (21.3).

Using an 80% cut off to indicate good adherence, 67 (30%) patients had good ῍Ω öő over the first month of inhaler use. This number was much lower than that calculated using other adherence measures, see Table 4-4. As a result the Average Adherence, using the dose counter, had 37.1% sensitivity and 93.0% specificity, with a 90.2% positive and 46.2% negative predictive value to Actual Adherence, ῍Ω öő .

Table 4-3 Summary of All Adherence Measures:

The mean adherence for all patients as calculated using different adherence measures. The Actual Adherence (▌═ꟻ) was significantly lower than the Average Adherence, Mean Daily Dose and the Attempted Adherence (▌═╢). *The difference in the Average Adherence by dose counter and Attempted Adherence is due to multiple blisters and some unrecorded dose counters.

Adherence Measure	*Mean (SD)*
Actual Adherence ῍Ω öő	61.8 (28.5)
*Average Adherence from Dose Counter**	84.4 (19.1)
Mean Daily Dose	85.0 (21.3)
*Attempted Adherence** ῍Ω ö῎ϒ	79.4 (20.7)
Missed Dose Rate ῍Ω ά῾Ω	20.7 (18.7)
Over Dose Rate ῍Ω έ῾Ω	6.6 (9.2)
Technique Error Rate ῍Ω ὸ῾Ω	14.2 (21.5)

Table 4-4: Sensitivity and Specificity Analysis of Adherence Measures:

This table displays the number of patients considered adherent for various measures of adherence, using 80% as a cut-off for good and poor adherence. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the dose counter, Mean Daily Dose and Attempted Adherence in correctly classifying good and poor adherence relative to the Actual Adherence (using the traditional 80% cut-off for good adherence) is presented in the second component of this table. The currently used method of calculating adherence, average adherence, has extremely low sensitivity relative to the Actual Adherence ( ).

ADHERENCE MEASURE	**n**	**> 80% Mean (SD)**	**n**	**≤ 80% Mean (SD)**
Actual Adherence	67	90.9% (4.5)	156	49.3% (25.1)
Average Adherence from Dose Counter	153	93.4% (12.0)	64	62.9% (15.6)
Mean Daily Dose	161	94.2% (14.0)	62	61.1% (18.3)
Attempted Adherence	140	91.4% (5.4)	83	59.0% (21.2)
ADHERENCE MEASURES COMPARED TO ACTUAL ADHERENCE				
	Sensitivity	**Specificity**	**PPV**	**NPV**
Average Adherence from Dose Counter	37.1%	93.0%	90.2%	46.2%
Mean Daily Dose	52.8%	96.6%	96.4%	54.1%
Attempted Adherence	43.0%	97.0%	96.2%	49.2%

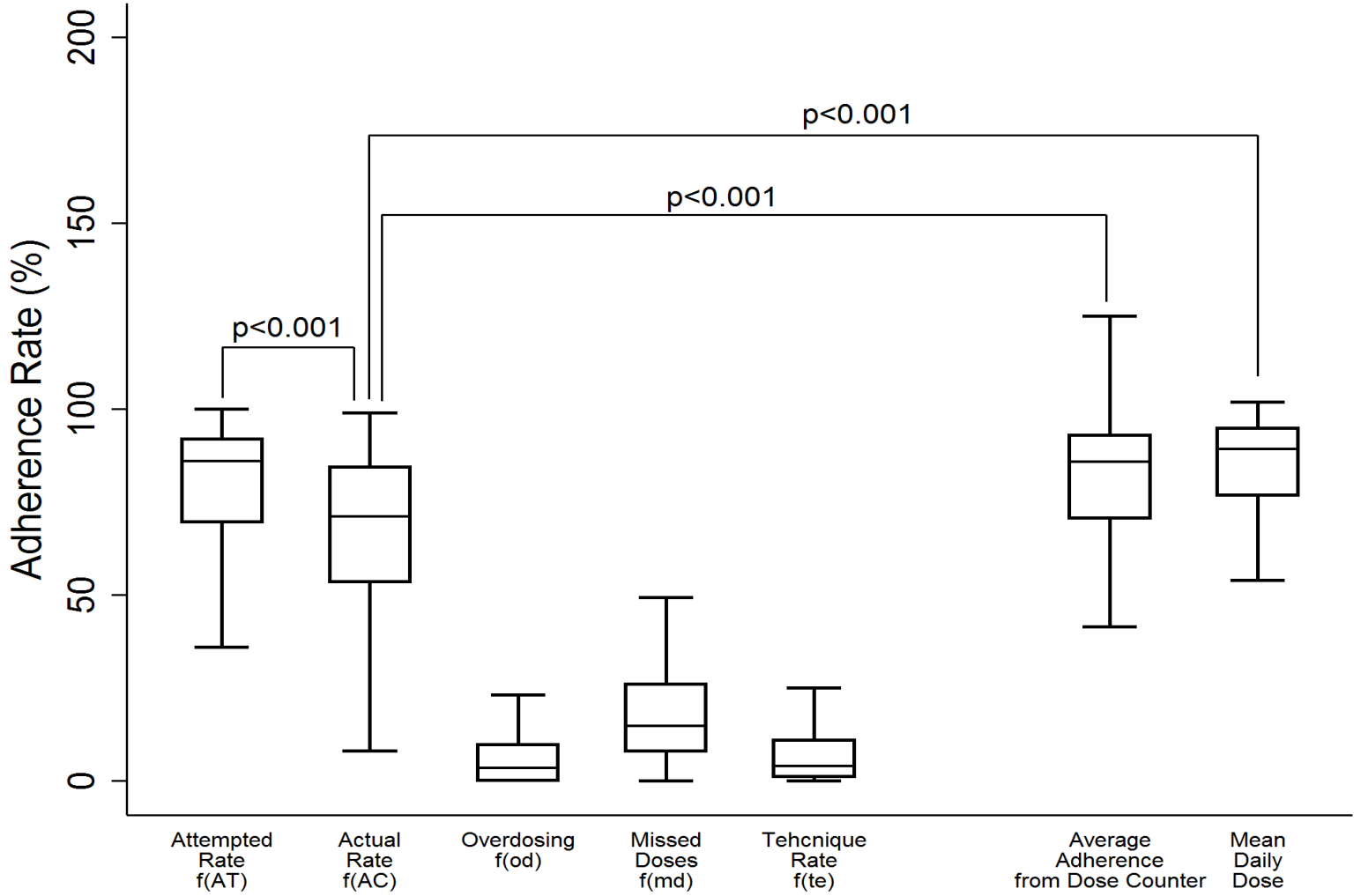
Adherence Rate (%)
0
50
100
150
200
p<0.001
p<0.001
p<0.001
Attempted Rate f(AT)
Actual Rate f(AC)
Overdosing f(od)
Missed Doses f(md)
Tehcnique Rate f(te)
Average Adherence from Dose Counter
Mean Daily Dose

Figure 4-4: Comparison of Different Adherence Measures:

This is a graphical representation of adherence calculated using various methods. The ÄÁÔÁ ÕÓÅÄ ÆÏÒ ÔÈÉÓ ÇÒÁÐÈ ÉÓ ÔÈÅ ÆÉÒÓÔ Í Ï ÎÔÈ ÍÏ É ÈÁÌÅ ÕÓÅÆÒ Í Á cohort of 217 (of 239) asthma patients enrolled in a prospective adherence intervention clinical study who were asked to use a dry powder inhaler twice daily (see Chapter 7). This cohort of patients missed several doses in their first month of observation and made several inhaler technique errors. The combination of these errors and poor interval between doses allowed for the calculation of the Actual Adherence rate. Compared to the other methods of calculating adherence, the Actual Adherence rate, *f(AC)*, is significantly different e.g. Average Adherence from the dose counter and the Mean Daily Dose, and the attempted rate, *f(AT)* (the electronic time of use measure), $p<0.001$.

4.4.3 Associations between adherence measures and clinical outcomes

I will now highlight the associations between several clinical outcomes in this cohort of asthma patients and the previously mentioned adherence calculations.

4.4.3.1 Quality of Life

Patient reported AQLQ change from the start of the monitoring period to the end of the study was analysed and patients were categorised into improvers and non-improvers as detailed in the methods above. A regression model with the change in AQLQ and each adherence measure for improvers and non-improvers was then created. The coefficient of the regression model for the ‴Ω öő was 1.1 for improvers and 2.2 in non-improvers, which were significantly different from ‴Ω ö‴Ƴ ($p \leq 0.01$ & $r^2=0.2$ for non-improvers), Mean Daily Dose ($p \leq 0.03$ & $r^2=0.7$ for improvers, $p<0.02$ & $r^2=0.2$ for non-improvers), and the Average Adherence ($p<0.03$ & $r^2=0.7$ for improvers, $p \leq 0.02$ & $r^2=0.2$ for non-improvers), see Figure 4-5.

For the purpose of this analysis, an AQLQ ≥5 was considered to be indicative of a good quality of life score (196,197). At month three, both good quality of life score (AQLQ ≥5) and good adherence (≥80%) were seen in only 17% of patients when adherence was calculated by the ‴Ω öő method compared to 36% when adherence was calculated using the dose counter. In contrast, among those with an AQLQ <5, therefore a poorer quality of life, 35% had an ‴Ω öő <80% and only 16% had an average dose counter adherence <80% ($p<0.01$, χ^2 test). The sensitivity and specificity of the various measures of adherence in identifying patients with an improvement in AQLQ is shown in Table 4-5.

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4.4.3.2 Asthma Control

At month three, 20% of patients had an ACT ≥19 with an ‴Ω öő ≥80%, and 31% had an ACT <19 with an ‴Ω öő <80%. In contrast, 27% of patients had an ACT ≥19 with an average adherence ≥80% and only 19% had an average adherence <80% with an ACT<19 ($p<0.01$, χ^2 test), see Figure 4-6.

Patient reported ACT change from the start of the monitoring period to the end was divided into those who did and did not have an improvement of 3 points (the minimally clinically important difference in ACT). The mean and standard deviation ‴Ω öő over the three months was 68.9% (23.7) for those who had an improvement in ACT. For those with an ACT score that did not improve or even reduced, the mean and standard deviation ‴Ω öő over the 3 months was 71.2% (30.9), see Table 4-5. A regression model with ACT and the different measures of adherence for improvers and non-improvers was performed. The slope of the regression line for the ‴Ω öő was -0.0003 for improvers and -0.0007 in non-improvers, which were not different from ‴Ω ö‴Ύ (-0.003 for improvers, 0.01 for non-improvers), mean daily dose (0.001 for improvers, 0.01 for non-improvers), and the average adherence (-0.006 for improvers, 0.003 for non-improvers).

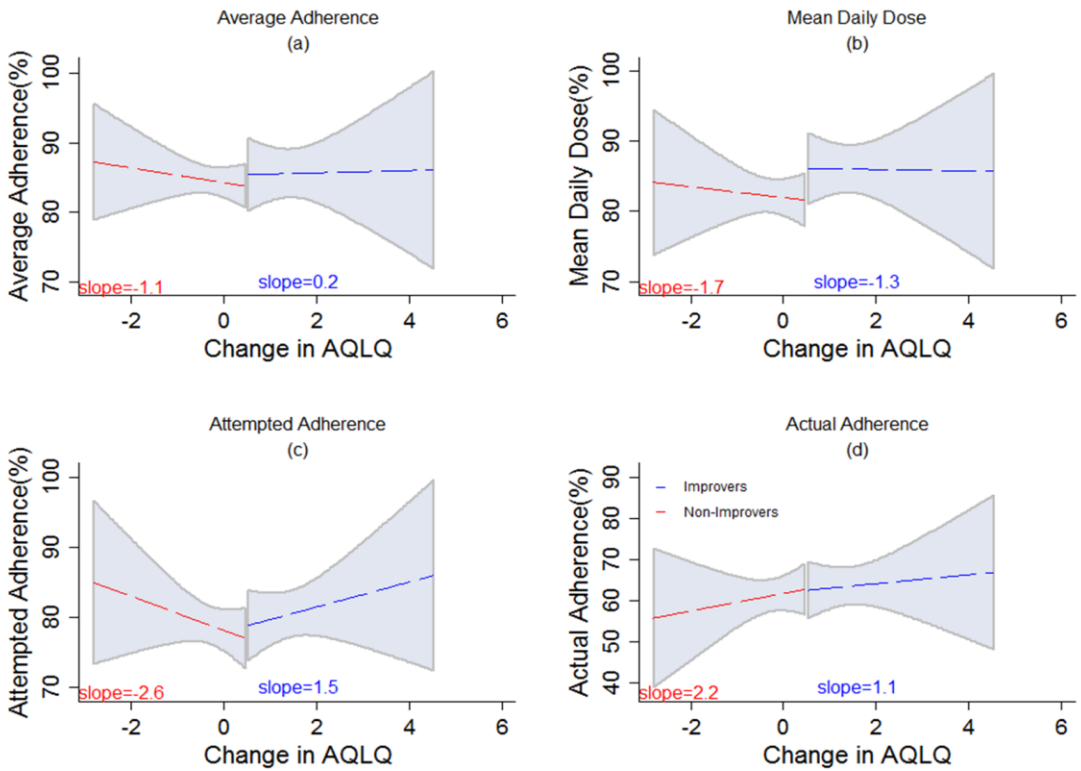

Average Adherence
(a)
Average Adherence(%)
70
80
90
100
slope=-1.1
slope=0.2
-2
0
2
4
6
Change in AQLQ
Mean Daily Dose
(b)
Mean Daily Dose(%)
70
80
90
100
slope=-1.7
slope=-1.3
-2
0
2
4
6
Change in AQLQ
Attempted Adherence
(c)
Attempted Adherence(%)
70
80
90
100
slope=-2.6
slope=1.5
-2
0
2
4
6
Change in AQLQ
Actual Adherence
(d)
Improvers
Non-Improvers
Actual Adherence(%)
40
50
60
70
80
90
slope=2.2
slope=1.1
-2
0
2
4
6
Change in AQLQ

Figure 4-5: Asthma Quality of Life and Adherence:

Asthma Quality of Life (AQLQ) value was recorded on a monthly basis, the minimal clinically important improvement in AQLQ is a 0.5 increase. Patients ×ÅÒÅ ÄÉÖÉÄÅÄ ÉÎÔÏ ÔÈÏÓÅ ×ÈÏ ÈÁÄ Á ÃÈÁÎÇÅ ÉÎ !1,1 Iπ‰υ ÏÖÅÒ ÔÈÒÅÅ Í ÏÎÔÈÓ (improvers) and those with a change <0.5 (non-improvers). In (a) the relationship between the changes in AQLQ and Average Adherence calculated from the Diskus™ dose counter is shown. Using this method of calculation of adherence, paradoxically, non-improvers had a higher level of adherence than those who improved. In (b) the relationship between the changes in AQLQ and Mean Daily Dose is shown. Non-improvers similarly showed no relationship between adherence and change in AQLQ. In (c) the relationship between the changes in AQLQ and Attempted Adherence is shown. Non-improvers had a higher adherence rate for a bigger drop in AQLQ, similar to Mean Daily Dose; however improvers had a better adherence rate as the improvement in AQLQ increased. In (d) the relationship between the changes in AQLQ and Actual Adherence is shown. Non-improvers had low adherence rates, which increased as the fall in AQLQ decreased and improvers had higher adherence rates, which improved as the change in AQLQ increased. There was a significant difference comparing Average Adherence (dose counter) with Actual Adherence and Average Adherence with Attempted Adherence, $p<0.01$ and $p<0.03$ respectively.

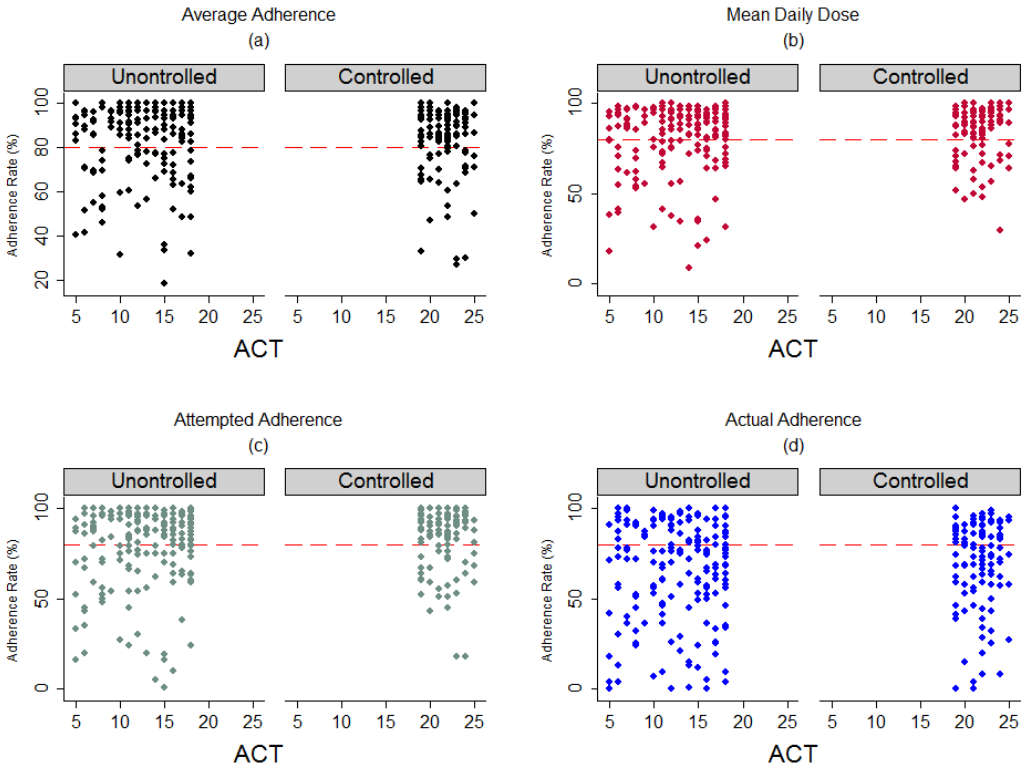


Figure 4-6: Asthma Control and Adherence:

Patients were divided into controlled and uncontrolled based on an Asthma Control Test (ACT) >19 indicating controlled. Each adherence measure was compared for controlled and uncontrolled based on ACT. In this comparison there was no significant difference between any of the calculated adherence rates. However, the proportion of uncontrolled patients with a poor adherence rate (<80%) was higher when the Actual Adherence (d) was used to calculate adherence (n=107)in comparison to the Average Adherence (n=57), Mean Daily Dose (n=57) and Attempted Adherence (n=67).

Table 4-5: Asthma Quality of Life and Asthma Control and Different Adherence Measures:

Adherence rates at month 3 and their relationship with changes in Asthma 1ÕÁÌÉÔÙ ÏÆ ,ÉÆÅ ¡ ! 1 , 1Ç ÁÎÄ !ÓÔÈ Í Á #Ï ÎÔÒÏÌ ¡ !#4Ç ɕI0.5-point improvement in ! 1 , 1 ÆÒÏ Í - Ï ÎÔÈ ρ ÔÏ - Ï ÎÔÈ σ 2ÅÃÅÉÖÅÒ Ι ɕσ É Í ÐÒÏÖÅ Í ÅÎÔÉÎ !#4 ÆÒÏ Í Month 1 to Month 3. Non-Improvers in AQLQ had lower adherence rates for all measures at months 3, but not statistically significant. However, with ACT, non-improvers had higher level of adherence with all calculated measures of adherence, again not significantly different from improvers. Receiver Operator Curve (ROC) analysis demonstrates the sensitivity and specificity of each adherence measure in correlation to improvements in AQLQ and ACT. Actual Adherence had the highest sensitivity of all the calculated measures of adherence for both ACT and AQLQ.

	AQLQ		ACT	
ADHERENCE MEASURE	**Improver***	**Non-Improver**	**Improver****	**Non-Improver**
Actual Adherence	66.4% (28.4)	64.4% (27.3)	68.9% (23.7)	71.5% (30.8)
Average Adherence from Dose Counter	87.2% (13.8)	88.6% (15.3)	84.8% (15.4)	90.6% (14.0)
Mean Daily Dose	83.3% (15.2)	83.6% (16.5)	82.6% (15.7)	83.2% (19.6)
Attempted Adherence	82.1% (16.5)	80.7% (20.2)	81.4% (17.7)	80.5% (23.8)
	Sensitivity	**Sensitivity**	**Sensitivity**	**Specificity**
Actual Adherence	66.7%	44.6%	45.5%	41.4%
Average Adherence from Dose Counter	19.2%	73.7%	15.6%	75.4%
Mean Daily Dose	25.0%	73.3%	31.4%	71.2%
Attempted Adherence	37.5%	66.0%	36.4%	64.4%

4.4.3.3 Lung Function

The mean (range) variability between morning and evening PEFR (AM to PM variability) was 4.9% (1-90) in month 1, 5.6% (1-85) in month 2 and 5.0% (1-80) in month 3. Compared to the other measures of adherence, ‴ ööő demonstrated the greatest correlation to AM PM PEFR variability, ($p \leq 0.03$ & $r^2=0.3$), see Figure 4-7 . The sensitivity and specificity of the various measures of adherence in identifying patients with a ≥10% improvement in AM PEFR are shown in Table 4-6.

4.4.3.4 Beta-Agonist Use

Patients that used their SABA every day, had a mean (SD) ‴ ööő of 59.0% (30.2), Average Adherence of 83.9% (16.1), a Mean Daily Dose of 84.7% (19.4) and a mean Attempted Adherence of 79.7% (19.5), $p<0.01$ when all rates are compared to ‴ ööő . Categorising patients into those who use their beta-agonist once or more in a week and those who use it less than once a week, there was only a significant difference in comparing Actual Adherence. Patients who used their beta-agonist once or more in a week had a mean (SD) Actual Adherence of 63.2 % (28.3) which was significantly lower than those patients who used their beta-agonist less than once a week, 73.0% (23.1), $p<0.01$. See Figure 4-8.

4.4.3.5 Exacerbations

Over the three-month period, there were only 35 documented severe asthma exacerbations. Patients that had an exacerbation had a mean (SD) Average Adherence of 87.5 % (17.9), a Mean Daily Dose of 86.7% (29.8), an Attempted Adherence of 76.5% (21.7) and an Actual Adherence of 69.1% (27.4). There was no significant relationship seen in terms of exacerbation and the different calculations of adherence, see Figure 4-9.

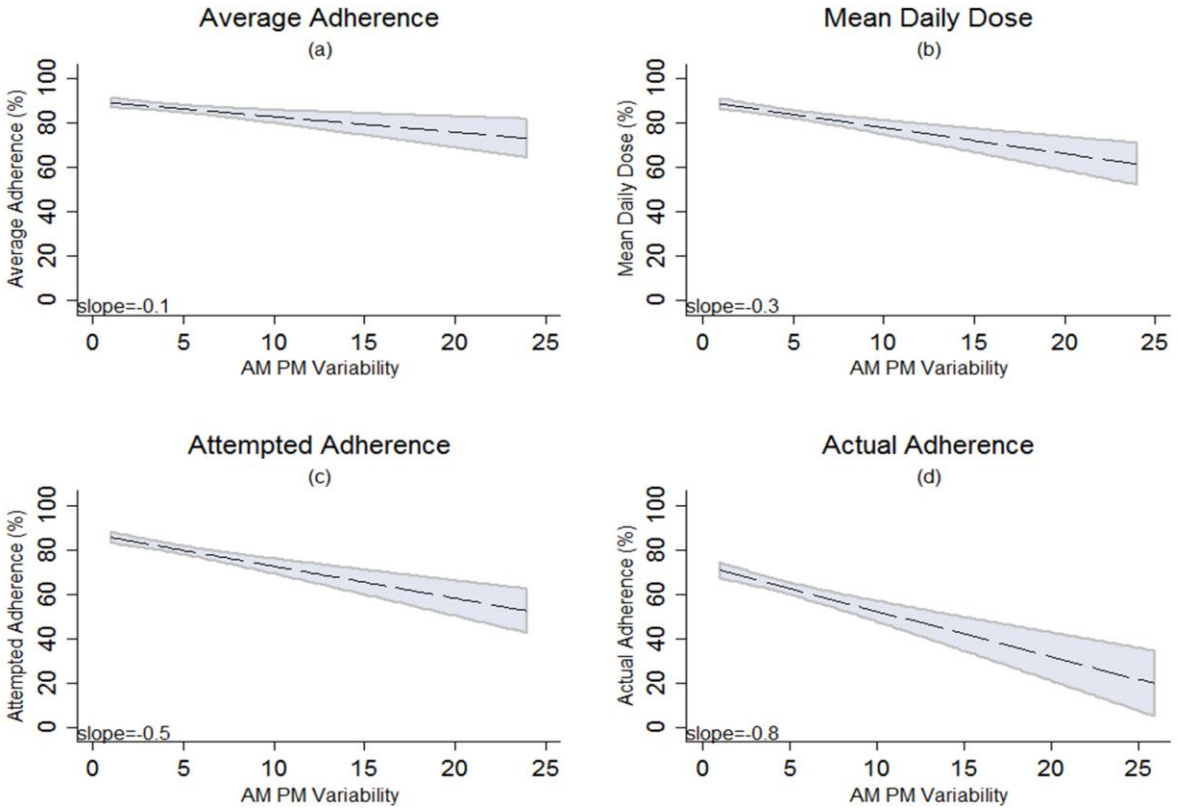

Average Adherence
(a)
Average Adherence (%)
0 20 40 60 80 100
slope=-0.1
0 5 10 15 20 25
AM PM Variability
Mean Daily Dose
(b)
Mean Daily Dose (%)
0 20 40 60 80 100
slope=-0.3
0 5 10 15 20 25
AM PM Variability
Attempted Adherence
(c)
Attempted Adherence (%)
0 20 40 60 80 100
slope=-0.5
0 5 10 15 20 25
AM PM Variability
Actual Adherence
(d)
Actual Adherence (%)
0 20 40 60 80 100
slope=-0.8
0 5 10 15 20 25
AM PM Variability

Figure 4-7: Peak Expiratory Flow Rate and Adherence:

Twice daily Peak Flow Rate (PEFR) was divided into Morning (AM) and Evening (PM) readings. The mean variability between the AM and PM readings was calculated for each month for each patient. Figures (a)-(d) shows the change in AM-PM PEFR Variability for the four measures of adherence, (a) Average Adherence calculated from the Dose Counter, (b) the Mean Daily Dose, (c) Attempted Adherence (■ ═╢) and (d) Actual Adherence (■ ═). Actual Adherence (■ ═) showed the most negative relationship with AM-PM PEFR Variability (slope of -0.8). There was a significant differences between Average Adherence with both ■ ═ and ■ ═╢ p=0.01 and p=0.03 respectively.

Table 4-6: Peak Expiratory Flow Rate and Different Adherence Measures:

Adherence rates at month 3 and their relationship with changes in morning (AM) ÁÎÄ ÅÖÅÎÉÎÇ ¡0 - ¶ 0ÅÁË %ØÐÉÒÁÔÏÒÙ &ÌÏ × 2ÁÔÅ ¡0%&2¶ ɛ ı ρ π Þ É Í ÐÒÏÖÅ Í ÅÎÔÉÎ AM/PM PEFR readings; Improvers with both AM and PM PEFR from month 1 to Month 3 had higher adherence rates for all calculated measures when compared to non-improvers. None of these comparisons were statistically significant, however with Actual Adherence, improvers had a near significantly better adherence rate when compared to the non-improvers, p=0.09. Receiver Operator Curve (ROC) analysis demonstrates the sensitivity and specificity of each adherence measure in correlation to improvements in PEFR. Actual Adherence had the highest sensitivity in correctly categorising patients into improvers and non-improvers with regards to change in lung physiology (PEFR).

	AM PEFR		**PM PEFR**	
ADHERENCE MEASURE	**Improver***	**Non-Improver**	**Improver***	**Non-Improver**
Actual Adherence	68.5% (28.4)	65.7% (27.6)	86.7% (10.1)	67.7% (26.9)
Average Adherence from Dose Counter	87.2% (13.0)	89.4% (14.5)	91.7% (4.7)	87.9% (15.1)
Mean Daily Dose	84.4% (13.7)	84.0% (16.3)	92.1% (6.3)	82.6% (17.2)
Attempted Adherence	81.8% (16.6)	82.4% (18.5)	92.3% (9.2)	80.6% (19.1)
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Actual Adherence	59.8%	46.9%	55.0%	66.7%
Average Adherence from Dose Counter	19.5%	71.9%	21.5%	13.1%
Mean Daily Dose	27.1%	69.7%	32.1%	100%
Attempted Adherence	32.5%	63.6%	37.8%	83.3%

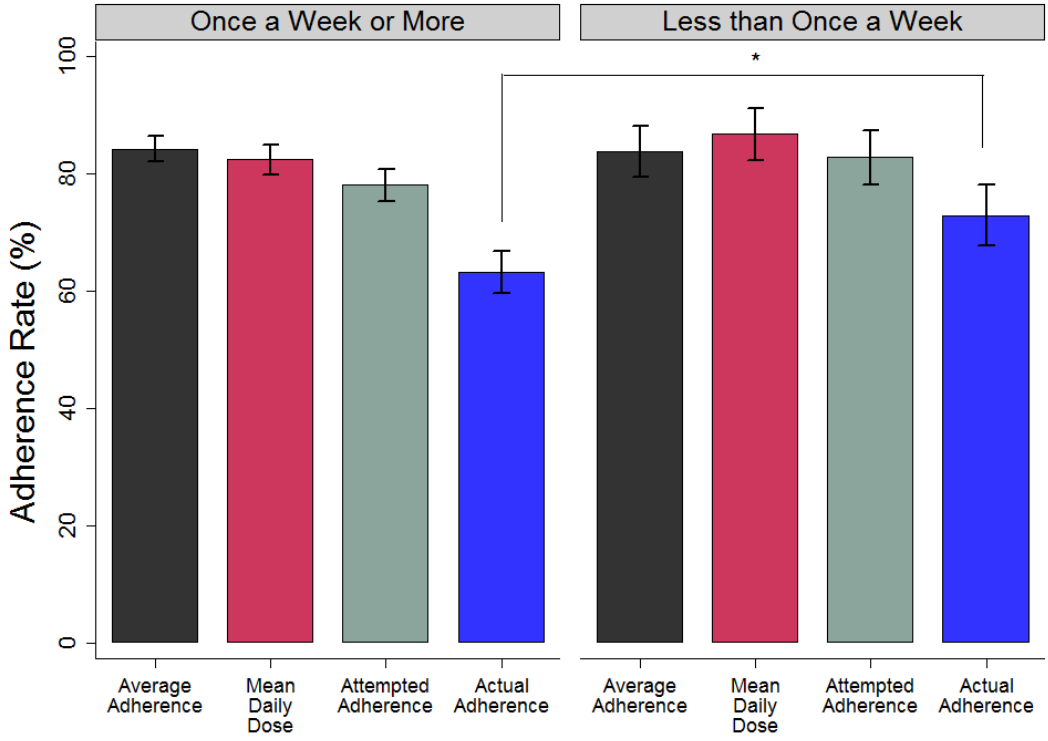


Figure 4-8: Reliever Use and Adherence:

For this analysis patients were categorised into those that used their reliever inhaler frequently (1 or more inhalation in a week) and those that rarely used their reliever inhaler (less than once a week). Each adherence measure was calculated in each category and compared with an unpaired t-test. Patients who used their reliever inhaler frequently had an average adherence of 84.3%, a Mean Daily Dose rate of 82.4%, an Attempted Adherence of 78.1% and an Actual Adherence of 63.2%. Actual Adherence was significantly different from all the other measures of adherence, $p<0.001$. Patients who rarely used their reliever inhaler had an Average Adherence of 83.9%, a Mean Daily Dose rate of 86.9%, an Attempted Adherence of 82.9% and an Actual Adherence 73.0%. In comparing adherence measures between categories, only Actual Adherence was significantly lower in those patients that used their reliever once a week or more, $p<0.01$.

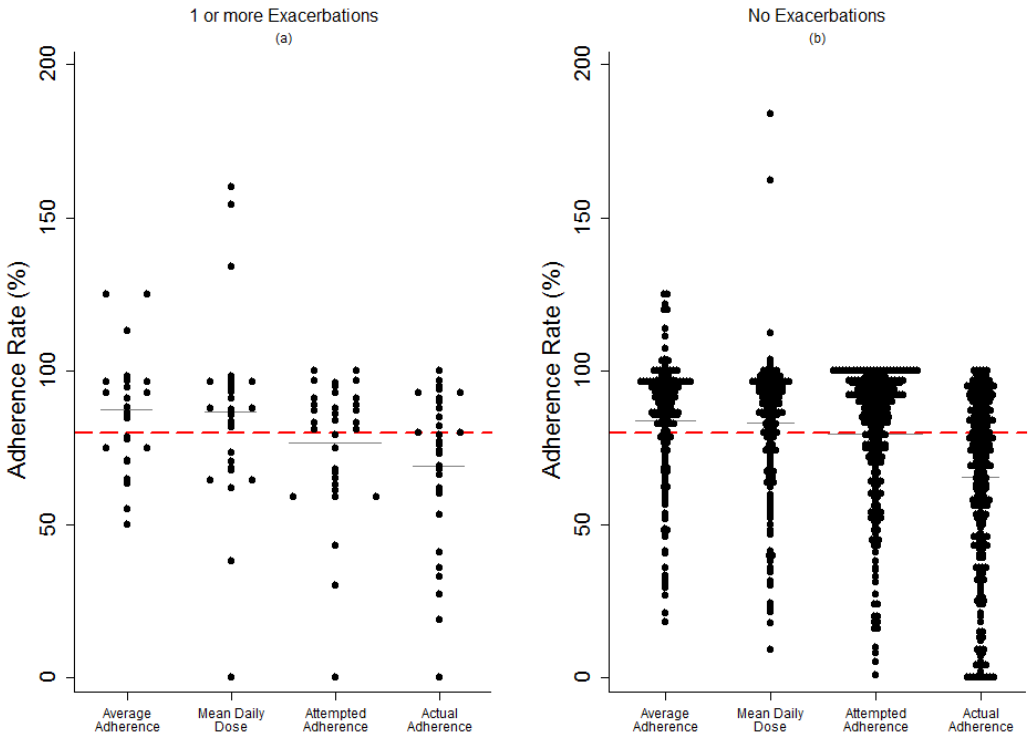


Figure 4-9: Exacerbations and Adherence:

There were only 35 severe exacerbations of asthma during this 3 month study. Figure (a) illustrates the different adherence measures for patients with 1 or more exacerbation, while Figure (b) is all the patients who had no exacerbation during the study period. In both figures the Actual Adherence is significantly lower than the other measures of adherence. However, there is no significant difference in any of the adherence measures between those that did and did not have an exacerbation.

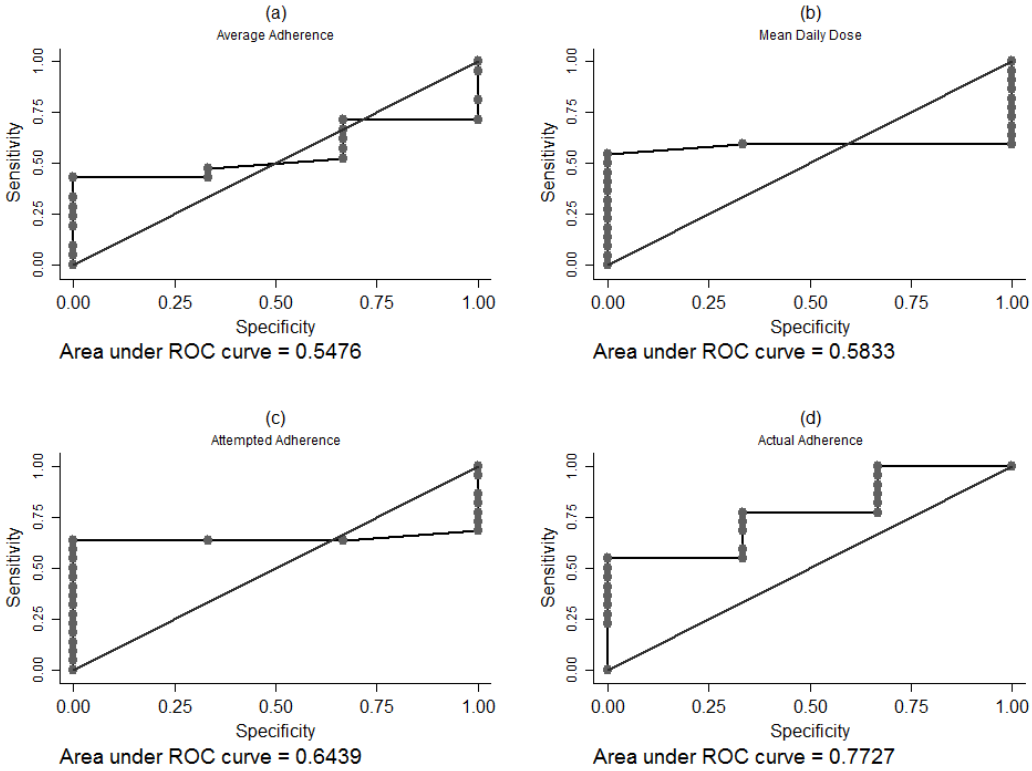
4.4.4 Clinician assessment of clinically meaningful thresholds of adherence.

To identify what is good and what is poor adherence for this new method of calculating adherence, a sensitivity analysis was performed based on clinicians' opinion (as there is no gold standard for adherence) of INCA™ recorded adherence in 30 patients. The characteristics of the 30 patients used for this analysis are shown in Table 4-7. Receiver operator characteristic curves (ROC) and sensitivity/ specificity analysis of ‵Ω öő , Average Adherence, Mean Daily Dose, and ‵Ω ö″Ύ from these assessments are shown in Figure 4-10. All calculated adherence measures had poor sensitivity, but good specificity in identifying poor adherence (as judged by physicians). Actual Adherence ‵Ω öő had the highest sensitivity at 66.67%, with a cut-off of <45% to identify poor adherence.

Table 4-7: Baseline Patient Demographics:

This table describes the baseline characteristics of the patients used in developing thresholds for adherence. Ten patients were from a tertiary severe asthma clinic, 10 patients were from an in hospital COPD population and 10 patients were from a community care cohort of respiratory patients on a salmeterol/fluticasone Diskus™ inhaler. *FEV_1 Forced Expiratory Volume in 1 Second, **CAT, COPD Assessment Test, ***AQLQ, Asthma Quality of Life Questionnaire

	N	Mean	Min	Max
Age (years)	30	55.49	27.24	88.00
Sex (%)	30	33% Male 67% Female		
Smoking (%) History	24	47% Never Smoker 25% Current 29% Ex-Smoker		
FEV_1 (L/min)*	20	1.84	0.72	4.07
FEV_1 (% predicted)	20	38.32	0.18	114.00
Diagnosis	30	50% Asthma 47% COPD 3% Other		
CAT**	10	18.80	11.00	28.00
AQLQ***	10	4.69	2.00	6.60



	Cut Off (%)	Sensitivity (%)	Specificity (%)	% Correctly Classified
Average Adherence	<83.34	42.86	100.00	50.00
Mean Daily Dose	<80.56	54.55	100.00	60.00
Attempted Adherence	<79.00	63.64	100.00	68.00
Actual Adherence	<45.00	66.67	100.00	73.33
Technique Rate	>9.00	72.74	100.00	76.00

Figure 4-10: Receiver Operating Curve and Sensitivity/Specificity Analysis:

This Figure and table displays a sensitivity/specificity analysis of each calculated ÁÄÈÅÒÅÎÃÅ Í ÅÁÓÕÒÅ 4ÈÉÒÛ ÐÁÔÉÅÎÔ ÁÄÈÅÒÅÎÃÅ ÁÔ ÏÎÅ Í ÏÎÔÈ ×ÅÒÅ ÖÉÓÕÁÌÉÓÅÄ and interpreted by two independent physicians as being good or poor (binary outcome). A receiver operating curve analysis was then performed to test the sensitivity and specificity of each adherence measure. Actual Adherence Ω öő had the largest ROC Area Under the Curve at 0.7727 and had the highest sensitivity of 66.67% with a cut-off of 45% to suggest poor adherence. Using this cut-off 73% of patients were correctly classified as good and poor adherence. In comparison, using the 83% cut-off for the Average Adherence from the dose counter, only 50% of patients were correctly classified. Technique rate was also sensitive at defining good and poor adherence. Using 9% as a cut off for technique rate lead to a sensitivity near 73% in defining good adherence (i.e. <9% technique rate).

4.5 DISCUSSION

Both electronic recording devices and manual dose counters are commonly used to assess adherence in clinical trials. Traditionally, adherence is judged to be good, when the Average Adherence is >80% of expected use. However, there is no scientific basis for assessing adherence as an average value or that 80% adherence is a valid method of demonstrating good adherence. The purpose of this study was to review some common methods of assessing adherence and to compare these with a proposed new method. The term, adherence, refers to the way in which a patient follows the physician's prescription, based on the pharmacokinetic principles of the medication. I reasoned that by using the information recorded to the INCA^{TM} device, which records the time of use and the time between doses I could describe adherence in a way that was more clinically meaningful. From my previous chapter I identified that inhaler errors have an effect on drug delivery, in both an immediate sense, as seen with low peak inspiratory flow rate and as a cumulative effect, seen with the exhalation into the inhaler error. Therefore, adjusting for the modifying effect on the dose administered caused by incorrect user technique should be an added component in calculating adherence. To put all this information together, I used the principles learnt from Chapter 3 with regards to measuring the pharmacokinetic effect of a medication and I calculated medication use as an AUC metric, a measure commonly used to reflect plasma drug concentration. I then compared the relationship of this method of calculating adherence and other established methods in a cohort of asthma patients (190,198).

Despite inhaler training, adherence education, knowingly using an electronic recording device and participating in a clinical trial focused on promoting adherence, episodes of missed doses, over use, dose dumping and critical errors in inhaler use were all recorded. As a result, adherence calculated in the proposed manner was significantly lower than that quantified by other commonly used methods, such as mean adherence (1,25,28,199) or the Mean Daily Dose (103,184).
Over a three-month period in which adherence and clinical outcomes such as AQLQ, ACT, PEFR and inhaled beta agonist use were quantified, only Actual Adherence

(ℚ ÖŐ) reflected the changes in patient outcomes. In contrast, Average Adherence calculated from the dose counter, the Mean Daily Dose and the Attempted Adherence (ℚ Ö″Ɣ) all failed to distinguish between those who did and did not have clinically meaningful improvements in several related clinical measures. For example, an inverse relationship was found, for non-improvers, between the currently used measures of adherence and changes in AQLQ. Additionally, PEFR correlated only with ℚ ÖŐ , with less morning to evening variability in PEFR associated with higher levels of ℚ ÖŐ . Likewise, significantly higher beta agonist reliever use was associated with lower ℚ ÖŐ . With asthma control, a large proportion of uncontrolled patients had an Actual Adherence ℚ ÖŐ less than 80%. These relationships were not seen with other measures of adherence. These results demonstrate the importance of variation in time of use and errors in inhaler handling, and emphasize the need to incorporate this information into the calculation of adherence. These findings also enforce the idea that adherence which accounts for time of use, interval between doses and technique of use is strongly related to drug delivery. This in turn relates to clinical outcomes, as Actual Adherence ℚ ÖŐ , is the only calculated measure of adherence which combines all of these components together in a measure of drug delivery.

4.5.1 Limitations

There are several limitations in this study. Firstly, the pharmacokinetic profile of the medication used, in this case salmeterol/fluticasone, is more complex than the simple assumptions made in this calculation. In particular, salmeterol for which the exact pharmacokinetics are not fully known and inhaled corticosteroids for which there is also likely to be a complex and patient specific relationship. However, in my previous chapter, I have shown a relationship between the pharmacokinetic profile of salbutamol and acoustically assessed adherence which can be utilised as a model for any inhaled medication. Additionally, the patients studied were already prescribed inhaled salmeterol/fluticasone prior to recruitment for this study. Hence, it is not too surprising that there were relatively small changes in lung function and quality of life. Patients with severe asthma who are new to a long acting beta-agonist/inhaled corticosteroid combination inhaler are expected to have large

improvements in quality of life and physiological measurements (200-203). Furthermore, the duration of follow up (3 months) was relatively short and possibly not of sufficient duration to see more significant correlations with clinical parameters and the study population was also relatively small (204). Nonetheless, the novel measurement of adherence that is described demonstrates significant associations with several measures of asthma, demonstrating its appropriateness. Future experimental tests of the approach described here will involve testing in larger populations and for longer periods of time.

There is currently no gold standard for calculating adherence. To test the sensitivity and specificity of this new method of calculating adherence I used two physicians assessment of adherence, from INCA data, as a gold standard. This is a significant limitation to the analysis, as the gold standard in this case used data that is also used to calculate Actual Adherence. Nonetheless, it would appear that a physicians understanding of adherence is better aligned to Actual Adherence, than adherence calculated from the dose counter.

I have previously described the significant effect of both low PIFR and that of exhalation into the inhaler have on drug delivery. For the purpose of calculating the impact of inhaler technique errors on adherence I used a binary response (present/not present) but different degrees of user errors will have different effects on drug delivery and this will need to be further evaluated and incorporated into a weighted method of calculating adherence. In this study, the two errors in inhaler user technique most commonly presented were that of poor inspiratory flow rate insufficient to disperse the medication appropriately and exhalation into the inhaler after drug priming. While there may be subtle differences in the impact of these errors, these are the errors most critical for effective drug delivery.

Adherence and non-adherence to an intervention has serious and obvious implications for a clinical trial. Variations in adherence influence the statistical power of a study, impacts the effect size of different therapies and has serious implications for estimates of the incidence of adverse events in a study. Additionally, knowing the

adherence of a therapy in a clinical trial can provide insight into patient acceptability of a new treatment or new inhaler device. The results of this study highlight the limited sensitivity of the currently used method of describing adherence as a mean value.

The approach for calculation of Actual Adherence (ℚ ÖŐ) described here would be useful for clinical trials involving a diverse range of respiratory conditions, including inhaled antibiotics or other agents, where either errors in timing and user technique may directly affect drug accumulation. This may also be important in Phase 2 studies where adjustment for patients achieving per protocol adherence may help avoid type 2 errors in data analysis.

4.6 CONCLUSION

After identifying common inhaler errors in a primary/pharmacy care based cohort I then examined each of these errors effect on drug delivery. Based on these findings I then developed a method for calculating inhaler adherence modelled on the concepts of drug pharmacokinetics incorporating both the time and the technique of inhaler use. To further my results from Chapter 3, I then tested this method of calculating adherence relationship with clinical outcomes, to capture the clinical effects inhaler technique errors have. This method of calculating adherence not only identifies which component of adherence is deficient but is also more reflective of the clinical changes expected from a medication than current methods used to assess adherence. The findings from this and previous chapters direct me into further research and analysis.

In my second chapter I looked at some potential determinants of inhaler adherence, however this was with low patient numbers and few baseline variables were observed. In the next few chapters I will be analysing data from a larger group of patients with a large number of baseline variables and some clinical outcomes. With this larger dataset I examine further into the determinants of inhaler use and technique of use.

For this study, patients had a diagnosis of asthma and attended a tertiary out-patient. A few patients in Chapter 2 had a diagnosis of Chronic Obstructive Pulmonary disease (COPD), however most also had asthma. In the next chapter I will look at adherence rates in a cohort of COPD patients admitted to hospital. I will examine what inhaler errors are common in this population and see how incorporating technique errors, timing of use and interval of doses affects the calculation of adherence. I will also look at the relationship of this method of calculating inhaler adherence and clinical outcomes in this very different group of patients.

Lastly, in this study physicians classified patient adherence by looking at inhaler time of use and inhaler technique of use. This categorisation of inhaler use creates 4 possible patterns of inhaler use: good timing with good technique, good timing with poor technique, poor timing with good technique and bad timing with poor technique. In the next few chapters I will be analysing a larger group of patients. I will therefore investigate further for any potential patterns of inhaler use with an unbiased cluster analysis and look for determinants in these patterns.

Chapter 5 :

AN OBJECTIVE ASSESSMENT OF INHALER ADHERENCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

5.1 INTRODUCTION

As I have shown in Chapters 2, 3 and 4, inhaler adherence is not a simple binary issue of whether an individual has or has not taken their medication. In contrast, it is a much more complex issue related to each phase of medication use (112), and, for medications that involve a medical device, technique of use must be considered. In Chapter 4 I developed a new method of calculating inhaler adherence that includes time of use, interval between doses and technique of use. Hence, I needed to test this new method in different populations of patients. In this Chapter and Chapter 6 I will use this new method in a cohort of Chronic Obstructive Pulmonary Disease (COPD) patients and in Chapter 7 I will use this method to evaluate inhaler adherence in a cohort of asthma patients over 3 months. I chose COPD patients because they are easy to access from an inpatient setting of a tertiary hospital, assessment of the implementation phase of adherence has not been done in this cohort and the focus was high cost patients.

5.2 BACKGROUND

COPD is a common chronic condition characterised by airflow limitation, which is frequently treated with inhaled corticosteroids (ICS) (40). The clinical course of COPD may be interrupted by periodic exacerbations. Randomised clinical trials have shown that regular use of inhaled bronchodilator therapy reduces the rates of exacerbations. A report by the Organisation for Economic Co-operation and Development (OECD) indicates that in the developed world COPD is one of the most common causes of hospital admission (205). Aside from the health-care cost implications, COPD exacerbations impact both the quality of life and life expectancy of patients (68,206,207). Following an exacerbation 30% of patients are re-admitted within 90 days (208-210). Reducing re-admissions has therefore become a main focus for the care of COPD patients both as a means of reducing healthcare cost and as a surrogate measure of quality of care. One of the key strategies in reducing re-admission has focused on medication use and in particular, on inhaler technique and adherence. It has been recognised that inhaler technique is poor among patients

with COPD, which means that even when the medication is taken a clinical response may not be achieved (211-213).

There are a number of techniques currently used for monitoring adherence including patient self-report and pharmacy refill records. As mentioned previously, neither of these methods provides information on whether the individual has actually taken the medication. However, electronic monitors can objectively assess inhaler adherence (97,151,158,214). Most electronic monitors used on inhalers report when the inhaler has been used and do not identify how well the inhaler has been taken (which may be considered as un-intentional non-adherence). As previously mentioned, the INCA™ (153) device assesses inhaler use over time by recording the audio associated with inhaler use. As I have shown in my previous chapters, with this device it is easy to identify critical technique errors (68,105,106,206). Hence, INCA™ technology allows the identification and characterisation of an individual's inhaler use and technique over time. To my knowledge there have been no studies on inhaler adherence in COPD, assessed by electronic recording devices.

The objectives of this study were to firstly describe inhaler adherence in patients with COPD and secondly to identify common inhaler technique errors using a commonly used preventer inhaler, salmeterol/fluticasone Diskus ™ inhaler.

5.3 METHODS

5.3.1 Study design and Setting

This was a prospective observational study exploring adherence to a regularly prescribed combination long acting beta-agonist/inhaled corticosteroid inhaler by patients with COPD following discharge from hospital. The study was performed in a single centre in the Republic of Ireland and was approved by the Beaumont Hospital Ethical (Medical Research) Committee, Dublin, Ireland. The study period was from February 2012 to February 2016. Due to a lack of funding there was a gap in recruitment from June 2012 to January 2014.

5.3.2 Participants

Consecutive patients admitted to hospital, for any reason, were screened. Eligibility criteria included: a known diagnosis of COPD (based on obstructive spirometry, $FEV_1/FVC<70\%$ or $FEV_1<80\%$), aged over 40 years, a smoking history and already prescribed a salmeterol/fluticasone Diskus™ inhaler. In an attempt to reduce selection bias, all eligible patients, regardless of disease severity or reason for admission, were approached and those who agreed to participate provided written informed consent. The goal was to recruit over 200 patients and have at least 200 months of measured adherence after drop outs or device failures.

5.3.3 Variables Collected

At recruitment, data was collected on patient age, sex, body mass index (BMI), smoking history, salmeterol/fluticasone dose and reason for admission.

5.3.3.1 Reason for admission

For this study, reason for admission was divided into two categories: 1. Hospital admission for a COPD exacerbation and 2. Hospital admission not related to COPD. They were dichotomised in this way as patients admitted due to a COPD exacerbation disease would be considered, rationally, to have more motivation to use an inhaler on discharge. A COPD exacerbation was defined as a worsening of symptoms (shortness of breath, cough, wheeze) requiring steroids and antibiotics

prescribed by the admitting medical service. Patients categorised as "Hospital Admission not related to COPD" included those with a previous diagnosis of COPD on salmeterol/fluticasone Diskus™ inhaler who were admitted to hospital for an unrelated cause (i.e. surgical admission).

5.3.3.2 Disease Severity

To evaluate COPD severity, data on the number of COPD admissions in the previous year and pulmonary function (FEV_1 (L) and % predicted) was collected and Cough Peak Expiratory Flow Rate (cough PEFR L/min, Mini-Wright Clement Clarke International LTD) was measured. Patients were asked to complete the COPD Assessment Test (CAT) as a measure of disease-specific quality of life (215). The CAT is an eight-item questionnaire. Each question has a grading from 0 to 5 with regards to impairment (0 suggesting no impairment to 5 indicating severe impairment). The total score indicates the level of impairment: very high (>30), high (>20), medium (10-20), low (<10) and the upper limit of normal in healthy non-smokers (5).

To score their dyspnoea, a measure of symptom impairment, patients were asked to use the Medical Research Council (MRC) Dyspnoea Scale (1 to 5, 1 not limited and 5 unable to leave the home due to breathlessness) (216). With this information, patients were classified into GOLD defined grades A, B, C or D (207,217). Within this GOLD classification, any patient admitted to hospital with an exacerbation is automatically either a grade C or D.

5.3.3.3 Personal Factors

Co-morbid medical history (measured with the Charlson Co-Morbidity Score (116)) and the number of regular medications currently prescribed were recorded. The Charlson Co-Morbidity Score is an ordinal value, the higher the value the greater co-morbidity associated.

Information on cognitive function (using the Montreal Cognitive Assessment, MoCA (218)) and psychological status (with the Hospital Anxiety Depression Score, HADS (219) was recorded. The MoCA is a questionnaire with a maximum score of 30 and

divides patient cognition into 3 severities based on the total final score: Normal cognitive impairment, above 26; Moderate cognitive impairment, 19 to 26 and severe cognitive impairment is a score less than 19. The test can also be divided into specific cognitive domains: Visuo-spatial/Executive function, Naming, Memory, Attention, Language, Abstraction, Delayed Recall and Orientation. The HADS is a 14-item questionnaire, with 7 questions regarding anxiety and 7 questions regarding depression. Each question has a score range from 0 to 3. Anxiety and depression distress are scored separately and a score of 8-10 suggests mild impairment, 11 to 14 moderate impairment and a score of 15 or greater suggests severe impairment in that domain. A higher overall score indicates more emotional distress.

Health literacy was assessed using the European Health Literacy Survey (EHLS) Cure and Care Section only (220). This is a 16-item questionnaire, and patients are given 5 response options for each question: 1. Very Easy (1 point), 2. Fairly Easy (2 points), 3. Fairly Difficult (3 points) 4. Very Difficult (4 points) and 5. Don't Know (5 points). Therefore, the higher the overall score, the poorer the health literacy. The mean score of the 16 questions can also be categorised as follows: 1. Likely Sufficient Health Literacy (score 1-2), 2. Likely Problematic Health Literacy (score 2- 3) and 3. Likely Inadequate Health Literacy (score 3-5).

Patients' beliefs in medicine were assessed by the Beliefs in Medication Questionnaire (BMQ). The BMQ is divided into a general section (8 questions) which assess general beliefs about medicine and a specific section (10 questions), which assess beliefs about drugs prescribed specifically for the patient's personal use. The BMQ general is subdivided into questions regarding medication harm, and medication overuse. The BMQ specific is subdivided in to questions regarding medication necessity and medication concern. Each question has 5 grades of response from Strongly Agree to Strongly Disagree. A total score of >50 indicates negative beliefs in medicine (144). The individual scores for each section (harm, overuse, benefit, necessity, concern) of the questionnaire offers some understanding as to why a patient has negative or positive beliefs about medicine.

Patients were also asked to report on their medication adherence with the Morisky Medicate Adherence Scale (MMAS-8) (221). The MMAS-8 is an 8-item questionnaire regarding self-reported adherence. Questions 1 to 7 are yes or no questions, and question 8 is a graded question with 5 possible options. A total score is calculated and a score greater than 2 is regarded as low adherence, 1 to 2 is medium adherence and 0 indicates high adherence. The BMQ and MMAS-8 were added late into the study protocol therefore not all patients have this information.
See Appendix D for copies of these questionnaires.

5.3.3.4 Socio-Economic Factors

Data on the patient's level of social support were collected. This included data pertaining to levels of governmental support for healthcare cost, social isolation (i.e. who lives at home, does the patient have a carer) and frailty (i.e. does the patient have a chairlift, a bedroom downstairs, meals delivered or need a carer). A categorical variable, "isolation", was created as follows: 1 = Not Alone + Has a Carer, 2 = Not Alone + No Carer, 3 = Alone + Has a Carer, 4= Alone + No Carer; A categorical variable, "frailty" was created as follows: 1= Need a Chair lift, 2 = Bedroom Downstairs, 3 = Bedroom Downstairs/Need a Chair Lift + Meals delivered to the Home, and 4 = Bedroom Downstairs/Need a Chair Lift + Need of a Carer +/- Meals delivered home.

5.3.4 Objective measurement of inhaler adherence and technique using the INCA™ device

An INCA™ audio recording device was attached to a salmeterol/fluticasone Diskus™ inhaler to objectively assess both time of use and technique of inhaler use. As previously described, each time a patient opens their inhaler a digital audio recording is made. These recordings are used to calculate the time of use, the interval between doses and the proficiency of inhaler use.

In hospital, patients were repeatedly shown how to use the inhaler by the ward staff, each time the medication was dispensed, as per written Hospital Policy. Inhaler proficiency was also assessed using a 10-point checklist on inhaler use, the

Inhaler Proficiency Score (193). This was an ordinal score, in that the lower the score the poorer the patient's proficiency. At recruitment patients were given a new 60-dose salmeterol/fluticasone Diskus™ inhaler with an attached INCA™ device, for one month of use. On discharge, they were asked to continue using their inhaler as they had been shown, twice per day and that they would be contacted between 26 and 30 days later for a courier to collect their inhaler.

5.3.4.1 Calculation of adherence

Two independent raters assessed the acoustic recordings for evidence of critical errors, as previously described (105,106,153). The inter-rater agreement was 88.4%. Information on the time, interval between doses and technique of inhaler use were combined to calculate an area under the curve (AUC) metric, using a trapezoidal function. This method of calculating adherence has been described in Chapter 4. Initially, the AUC is calculated for the expected doses. Following this, the AUC is calculated for the participant's Attempted Adherence (audio files where there was evidence of drug priming), where non-attempted adherence demonstrates intentional non-adherence. Removing doses where a critical technique error (i.e. failing to prime the inhaler, exhalation into the inhaler after priming and before inhalation, or generating a low inspiratory flow) allows for calculation of the Actual Adherence, a combination of intentional and un-intentional non-adherence.

5.3.5 Statistical Analysis

All categorical variables were summarized using the number of observations and percentage of patients. Continuous variables were summarised using mean (SD) and ordinal data with median (IQR). In cases where data was not normally distributed a log transformation was performed to achieve normality. These data were analysed on a log scale and all results back transformed. Between-group comparisons, for those admitted for a COPD exacerbation and those COPD patients admitted for another reason, were conducted using an unpaired t-test, ANOVA, Chi-squared test and Mann-Whitney test, where appropriate.

5.4 RESULTS

5.4.1 Participants

Over the study period, 265 patients consented to participate with complete data on both baseline variables and electronically recorded adherence data were available for 204 patients over an average of 29.2 days, see flow diagram, Figure 5-1.

5.4.1.1 Disease Severity

The characteristics of the patients are shown in Table 5-1. The participants were elderly, mean (SD) age 71 (9.8) years with a mean FEV_1 of 1.3L, 52% predicted. Cough PEFR was low in these patients, mean (SD) measurement of 159.6 (99.2) suggesting an element of hyperinflation and possibly muscle weakness. The CAT score ranged from 0 to 38 but had a mean (SD) of 20.5 (7.9) suggesting high impairment. The median MRC was 4, which on the scale is defined as "Stops for breath after walking about 100 yards or after a few minutes on level ground." Most patients had experienced a COPD exacerbation in the previous year (mean=1.3). Based on this information, the majority of the patients, 76% (n=199), were GOLD grade D, the highest risk group.

5.4.1.2 Personal Factors

In addition to their COPD, these patients had a significant amount of other medical diseases (mean Charlson co-morbidity score of 6) and were currently prescribed a median of 12 medications. Forty-seven percent of the patients had evidence of moderate cognitive impairment, MoCA score (19-24) and a further 33% had severe cognitive impairment, with a MoCA score less than 19.

The mean (SD) HADS score for this cohort was 12.9 (7.5). Thirty-eight percent (n=101) of patients scored greater than 7 for anxiety, while 26% (n=69) scored greater than 7 for depression. The mean (SD) health literacy score for each of the 16 questions was 2.1 (0.67) suggesting problematic health literacy. The overall BMQ for this cohort of COPD patients was 52.0 (SD=10.7) indicating negative beliefs in medication. There was a slightly higher score seen in the BMQ general portion of

the questionnaire (25.1 vs. 26.7, p=0.06). The highest score was seen in the 'harm' questions, indicating that as a group, the negative beliefs in medication may be related to thoughts of harm related to medications. The mean (SD) MMAS-8 score, for the patients that filled this questionnaire, was 1.2 (1.3), this translates to medium self-reported adherence.

5.4.1.3 Socio-Economic Factors

The majority of the patients recruited to this study had government sponsored Health Insurance (n=260). One fourth were socially isolated (Isolation score> 2) with 28% of patients living alone. Over a third had indices of frailty (Frailty score >2), 50% of patients had a bathroom downstairs.

Other than features regarding the severity of COPD and indices of isolation/frailty, there were no significant differences in the characteristics of the patients admitted with an exacerbation of COPD and those admitted with another cause.

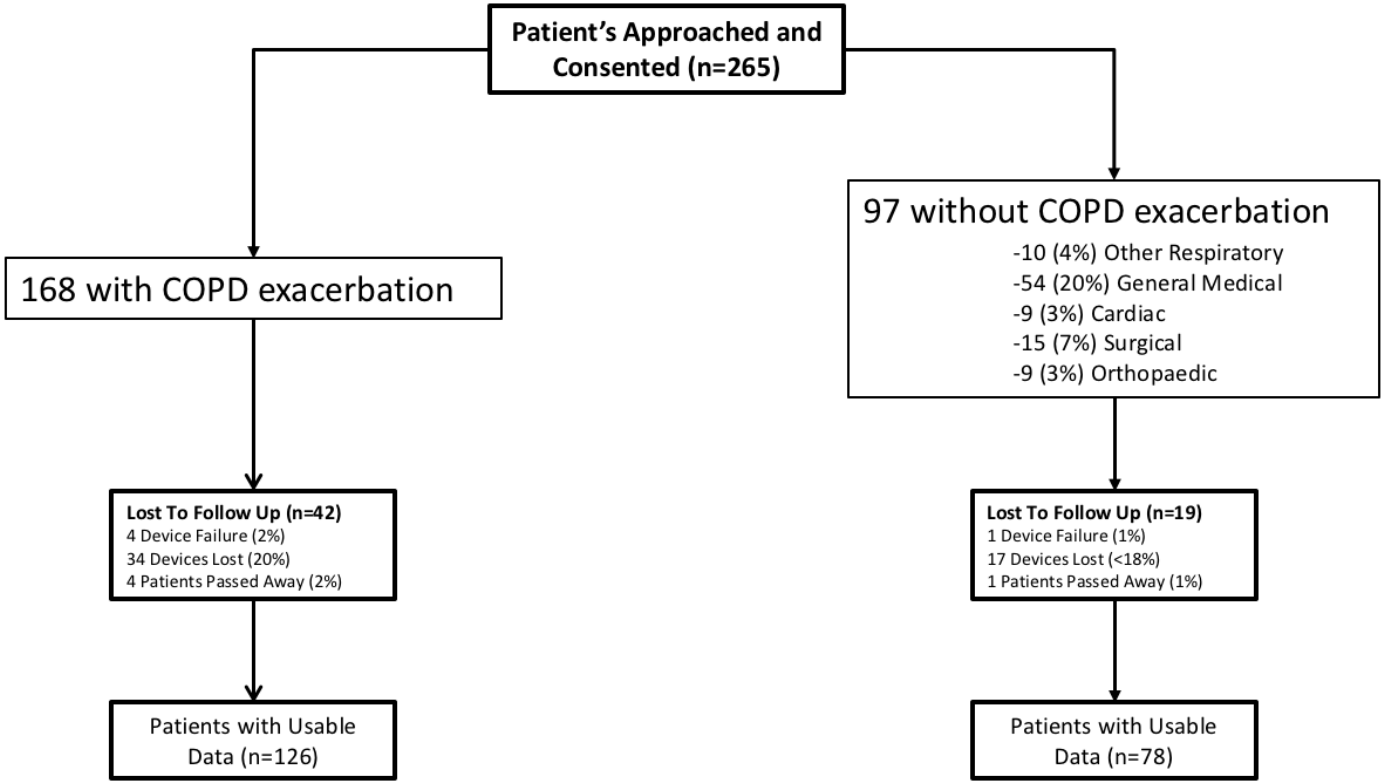


Figure 5-1: Study Flow:

During the study period, 265 patients with COPD were recruited. Due to lost devices, device failures and patients passing away, there was adherence data on 204 patients.

Table 5-1: Baseline Patient Characteristics based on Reason for Admission:

The clinical features of the cohort include the demographics, COPD features, personal and socio-economic factors. Data for all patients in the cohort, as well as patients who were admitted to hospital with an exacerbation of COPD and those who had COPD but were admitted for other reasons are shown. All values are presented as mean (SD) except where indicated. BMI, body mass index; FEV_1, forced expiratory volume; Cough PEFR, cough peak expiratory flow rate; CAT score, COPD assessment test; MoCA, Montréal cognitive assessment; *Isolation Score and ^frailty scores were calculated as described in the methods section.

	All Patients	COPD Exacerbation	Not COPD Exacerbation	p value
DEMOGRAPHICS	(n=265)	(n=168)	(n=97)	
Mean Age	70.6 (9.8)	70.2 (10.1)	71.2(9.2)	0.41
Sex (% Female)	53%	57%	47%	0.15
BMI	27.5 (6.6)	26.7 (6.5)	29.0 (6.6)	0.05
Median Pack Years smoked (IQR)	47.0 (47.1)	47.0 (43.5)	47.0 (50.0)	0.99
Currently smoking (%)	22%	25%	18%	0.22
Salmeterol/fluticasone Dose (% 1000mcg/day)	75%	77%	71%	0.28
Inhaler Proficiency Score (range 0-10)	7.6 (1.6)	7.5 (1.5)	7.6 (1.7)	0.69
DISEASE SEVERITY				
FEV_1 (L)	1.3 (0.6)	1.2 (0.6)	1.5 (0.6)	<0.01
FEV_1 (%)	51.7 (21.3)	49.0 (20.3)	57.7 (22.3)	<0.01
Cough PEFR (L/min)	159.6 (99.2)	150.60 (87.7)	173.1 (112.3)	0.09
CAT score (range 0-30)	20.5 (7.9)	21.2 (7.7)	19.3 (8.1)	0.06
Number of COPD admissions in previous year	1.3 (1.7)	1.8 (1.8)	0.7 (1.2)	<0.01
Median MRC dyspnoea score (IQR)	4 (1)	4 (1)	3.5 (1)	0.27
Number in GOLD Grade (%)				
A	4 (1)	0 (0)	4 (4)	0.02
B	56 (21)	0 (0)	56 (58)	<0.01
C	6 (2)	5 (3)	1 (1)	0.47
D	199 (76)	163 (97)	36 (37)	<0.01
PERSONAL FACTORS				
Charlson Co-Morbidity	5.9 (1.8)	5.7 (1.7)	6.2 (2.0)	0.06
Median No. of Regular Medications (IQR)	12 (7)	11 (8)	12 (7)	0.11
Median No. of Nebulisers used (IQR)	1 (1.5)	1 (1)	1 (1)	<0.01
MoCA score (range 0-30)	20.2 (6.2)	19.9 (6.2)	20.7 (6.2)	0.36
HADS Total score (range 0-42)	12.9 (7.5)	12.8 (7.5)	13.0 (7.5)	0.81

	All Patients	COPD Exacerbation	Not COPD Exacerbation	p value
Anxiety component of HADS (range 0-7)	6.9 (4.6)	6.7 (4.4)	7.2 (4.9)	0.44
Depression component of HADS (range 0-7)	5.6 (4.1)	5.5 (4.2)	5.8 (3.9)	0.51
Total European Health Literacy Score (range 16-80)	33.7 (10.7)	33.7 (10.1)	33.8 (11.6)	0.94
Mean European Health Literacy Score per Question (range 1-5)	2.1 (0.67)	2.1 (0.63)	2.1 (0.72)	0.91
Beliefs in Medicine Questionnaire (range 18-90)	52.0 (10.7)	52.2 (11.3)	51.9 (10.2)	0.89
MMAS-8 (range 0-2)	1.2 (1.3)	1.2 (1.5)	1.2 (1.2)	0.89
SOCIO-ECONOMIC DETAILS				
Patients Living Alone (%)	28%	21%	37%	<0.01
Patients with a Carer (%)	21%	20%	22%	0.72
Number of Floors in Home	1.8 (0.5)	1.8 (0.5)	1.9 (0.5)	0.41
Patients with a Stair Lift (%)	18%	17%	19%	0.77
Patients with Downstairs Bathroom (%)	50%	50%	51%	0.23
Patients with Downstairs Bedroom (%)	29%	31%	26%	0.44
Patients who get Meals Delivered (%)	4%	3%	5%	0.24
Median Isolation Score (IQR)*	2 (1)	2 (0)	2 (2)	<0.01
Patients Isolation Score* >2 (%)	28%	20%	38%	0.01
Patients with Government Sponsored Health Insurance (%)	98%	98%	99%	0.56
Median Frailty Score (IQR)^	2 (2)	2 (2)	2 (2.5)	0.47
Patients Frailty Score >2 (%)	33%	30%	38%	0.64

5.4.2 Adherence to a twice-daily preventer inhaler

I will now describe different adherence calculations for this patient population.

5.4.2.1 Inhaler Time of Use Errors (Attempted Adherence)

Analysis of the time of inhaler use indicated that, in contrast to the instruction that the inhaler was to be used twice per day and twelve hours apart, most patients used the inhaler irregularly during the month following discharge. There were both periods of excessive dosing (≥3 doses in 24 hours) and periods of missed doses (<2 doses in 24 hours), see Table 5-2 and Figure 5-2 (b), (d), (f) and (g). There were 4568 total missed doses in one month of follow up, with a median of 17 missed doses per patient. Only 10 patients (5%) never attempted to use their inhaler and 29 patients (14%) used their inhaler less than 20% of the time (i.e. 2 to 3 times a week). See Figure 5-3 for a distribution of Missed Dose Rate in this cohort and Figure 5-6 for a summary of all adherence measures calculated. The overall mean (SD) Attempted Adherence for this population of patients was 59.4% (29.7), see Table 5-3

5.4.2.2 Inhaler Technique Errors

Analysis of the digital audio data indicated that most patients intermittently or frequently made errors in inhaler handling in the month after hospital discharge, despite reasonably good inhaler technique on discharge with a mean inhaler checklist score (IPS) of 8 out of a possible 10. The most common error made was low inhalation flow, (PIFR <35L/min), see Figure 5-2 (d) and (e). Of the total 8133 audio files recorded to the INCA^{TM} device, this error occurred in 1941 (24%) inhalations. A further 984 (12%) made repeated short inhalations, termed multiple inhalations. Exhalation into the inhaler after priming the dose and before inhalation occurred in 277 events (3.4%), see Figure 2(a) and (c). In Chapter 3, low PIFR rate and exhalation into the inhaler affected drug delivery, while multiple inhalations did not. In Chapter 2, 2 patients were shown to dose dump whereas in this COPD cohort there were 30 audio files (0.03%) with evidence of more than 1 drug blister, again suggestive of dose wasting. See Figure 5-3 & Figure 5-4 for a distribution of inhaler technique errors among this cohort.

Table 5-2: Frequency of Inhaler Errors in Timing and Technique:

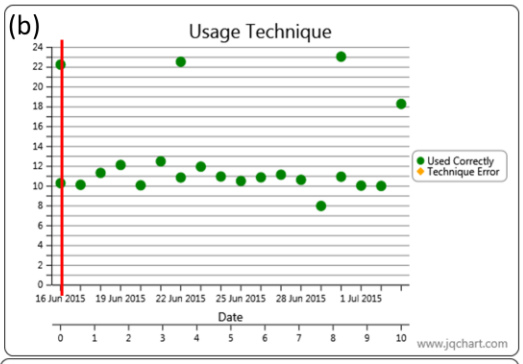
&ÒÅÑÕÅÎÃÙ ÏÆ ÄÉÆÆÅÒÅÎÔ ÔÙÐÅÓ ÏÆ ÅÒÒÏÒÓ ÂÁÓÅÄ ÏÎ ÁÎÁÌÙÓÉÓ ÏÆ ÔÈÅ ÒÅÃÏÒÄÉÎÇÓ ÍÁÄÅ ÔÏ ÔÈÅ).#!4- ÄÅÖÉÃÅ ÏÖÅÒ ÏÎÅ Í ÏÎÔÈ ÏÆ ÕÓÅ8 4ÈÅ ÄÁÔÁ ÓÈÏ× Î ÒÅÆÌÅÃÔÓ ÔÈÅ ÖÁÒÉÏÕÓ ×ÁÙÓ ÔÈÁÔ ÐÁÔÉÅÎÔÓ Í ÁÙ Í ÉÓÕÓÅ ÁÎ É ÎÈÁÌÅÒ3ÐÅÃÉÆÉÃÁÌÌÙ ÁÔÔÅ Í ÐÔÅÄ ÄÏÓÅÓ ÒÅÐÒÅÓÅÎÔ ÁÕÄÉÏ ×ÈÅÒÅ ÔÈÅ ÐÁÔÉÅÎÔ ÁÔÔÅ Í ÐÔÅÄ ÔÏ ÔÁËÅ ÔÈÉÒ Í ÅÄÉÃÁÔÉÏ Î ¡É8Å8 ÅÖÉÄÅÎÃÅ ÏÆ ÄÒÕÇ ÐÒÉ Í É Î ÇÇ8 4ÅÃÈÎÉÑÕÅ ÅÒÒÏÒÓ É ÎÃÌÕÄÄ ÔÈÅ ÆÏÌÌ ×É Î Ç ÃÒÉÔÉÃÁÌ ÅÒÒÏÒÓ É Î É Î ÈÁÌÅÒ ÈÁ Î ÄÌÉ Î Ç¢ ÂÌÉÓÔÅÒÉ Î Ç ÂÕ Î Ï É Î ÈÁÌÁÔÉ Î ℎ É Î ÈÁÌÁÔÉ Ï Î ÆÌÏ × ÌÅÓÓ ÔÈÁ Î συ,ƬÓÅÃℎ Í ÕÌÔÉÐÌÅ ÓÈÏÔÔ É Î ÈÁÌÁÔÉ Ï Î Ó Á Î Ä ÅØÈÁÌÁÔÉ Ï Î É Î Ô Ï ÔÈÅ É Î ÈÁÌÅÒ ÁÆÔÅÒ ÐÒÉ Í É Î Ç8 %ØÔÒÁ ÄÏÓÉÎÇℎ ÉÓ ÄÅÆÉÎÅÄ ÁÓ σ ÏÒ Í ÏÒÅ ÄÏÓÅÓ É Î Á ς τ-ÈÏÕÒ ÐÅÒÉÏÄℎ Í ÉÓÓÅÄ ÄÏÓÅÓ ÁÓ Ґς ÄÏÓÅÓ É Î Á ς τ-ÈÏÕÒ ÐÅÒÉÏÄ8 4ÈÅ ÔÏÔÁÌ Î Õ Í ÂÅÒ ÏÆ ÅÒÒÏÒÓ Á Î Ä ÔÈÅ Í ÅÄÉÁÎ Á Î Ä Í ÅÁÎ ÒÁÔÅÓ ÁÒÅ ÓÈÏ× Î ÂÅÌÏ×8

	Attempted Doses	Technique Errors	Extra Doses	Missed Doses
Total Number	8133	4103	778	4568
Median per person (IQR)	46 (32)	15 (27)	3 (4)	17 (27)
Median Rate (IQR)	62.5 (49.5)	12.0 (34.0)	6.7 (13.3)	33.1 (40.7)
Mean Rate% (SD)	59.4 (30.0)	24.3 (27.5)	10.7 (12.4)	38.6 (26.7)
Number of people (%) with >20% & <50% Mean Rate	69 (34)	50 (24)	30 (15)	68 (33)

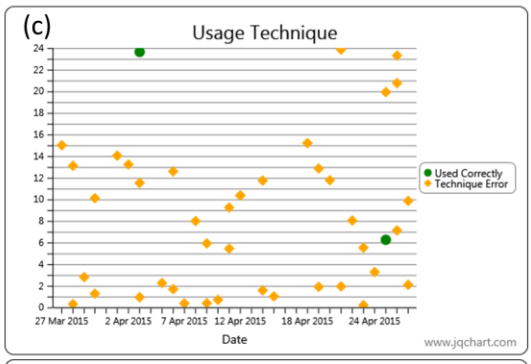
(a)

IN HOSPITAL AT HOME

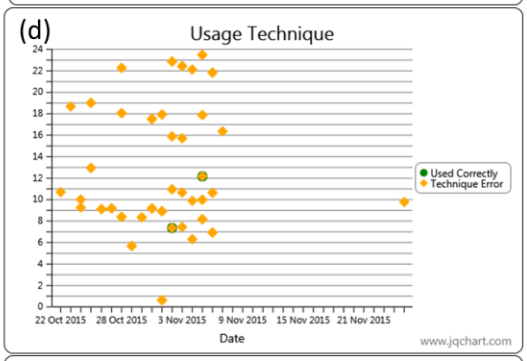
(b)



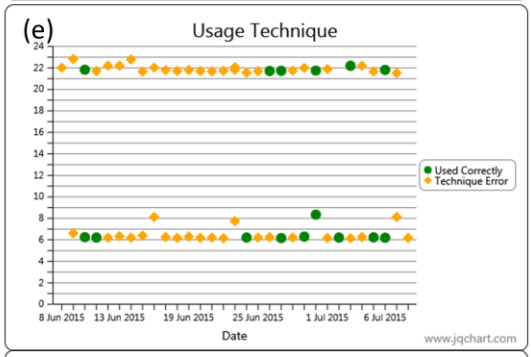
(c)



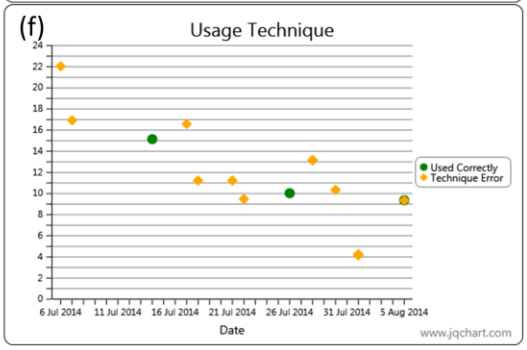
(d)



(e)



(f)



(g)

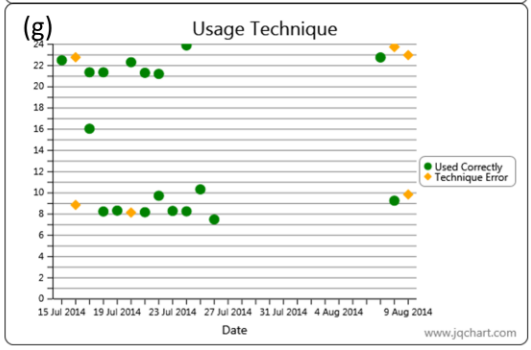


Figure 5-2: Examples of Different Inhaler Use:

Figure (a) is an example of an inhaler returned from a patient who persistently exhaled into the device before inhaling, introducing moisture into the mouthpiece. The image clearly shows clumped drug deposition in the mouth piece, i.e. wasted medication. Figures (b) to (g) are graphical representations of adherence data collected from the INCA™ device over time (hours of the day on the y-axis and date on the x-axis). Each mark on the graph indicates a dose taken; a green dot indicates good technique while an orange diamond indicates poor inhaler technique. Figure (b) is a patient who was given the adapted inhaler the day before discharge. Following their discharge home this patient, for the most part, only took their medication once daily. Figure (c) is the adherence data for a patient who made the persistent error of exhaling into the inhaler after drug priming and before inhalation leading to drug clumping (a). Figure (d) is an example of a patient who was overusing their inhaler, although with poor technique (low inspiratory flow) and then subsequently stopped using their inhaler for several weeks. Figure (e) is a patient who took their inhaler with good interval between doses but with a persistent technique error, low PIFR. Figure (f) is an example of a patient who rarely took their medication, and when using their inhaler, it was with poor inspiratory flow. Figure (g) is an example of a patient who took their inhaler regularly and correctly for several days and then just stopped taking their medication for 2 weeks.

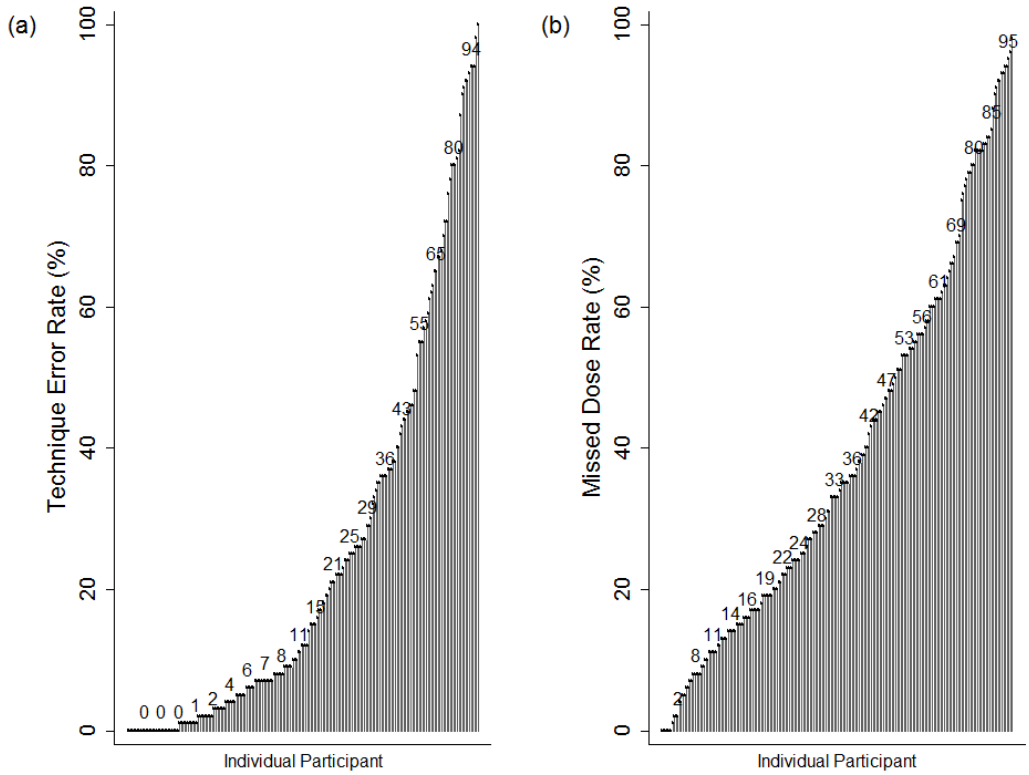
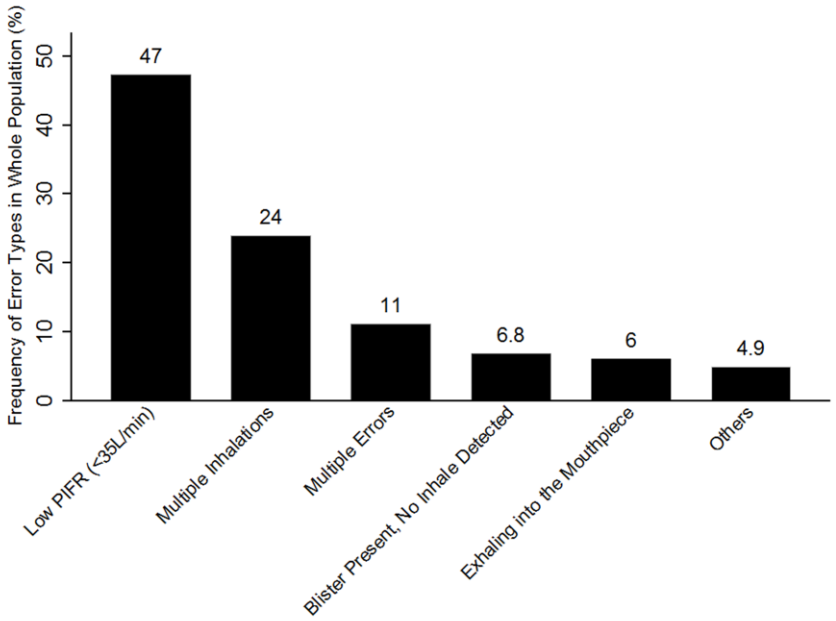


Figure 5-3: Distribution of Technique Error and Missed Doses Rates:

These figures show the wide variation in inhaler technique error (a) and missed doses (b). There were patients that made no inhaler errors and patients that made a consistent inhaler error with each inhaler dose attempted. Similarly, with missed doses, very few patients missed zero doses but there was a patient ×ÈÏ ÄÉÄÎ‰Ô ÔÁËÅ ÔÈÅÉÒ ÉÎÈÁÌÅÒ ÏÎÃÅ ÄÕÒÉÎÇ ÔÈÅ ÏÎÅ Í ÏÎÔÈ ÏÆÆÏÌÌÏ× ÕÐ‡ 4ÈÉÓ highlights the wide variation in inhaler use within this cohort of patients, some patients miss doses, some make technique errors and some do both.



Error Type	Number	Mean per patient (SD)	Range
Low PIFR <35L/min	1941	9.6 (14)	0-60
Multiple Inhalations	984	4.5(11)	0-58
Multiple Errors	454	2.2 (7)	0-56
Blister Present, No Inhale Detected	279	1.4 (5)	0-47
Exhaling into the mouthpiece	246	1.2 (3.5)	0-34
Others	199	1.0 (2.9)	0-28
TOTAL ERRORS	**4103**	**20.2 (18)**	**0-60**

Figure 5-4: Inhaler Technique Errors:

The most common technique error in this cohort of COPD patients was low PIFR followed by multiple inhalations and multiple errors (i.e. more than one error in an audio file).

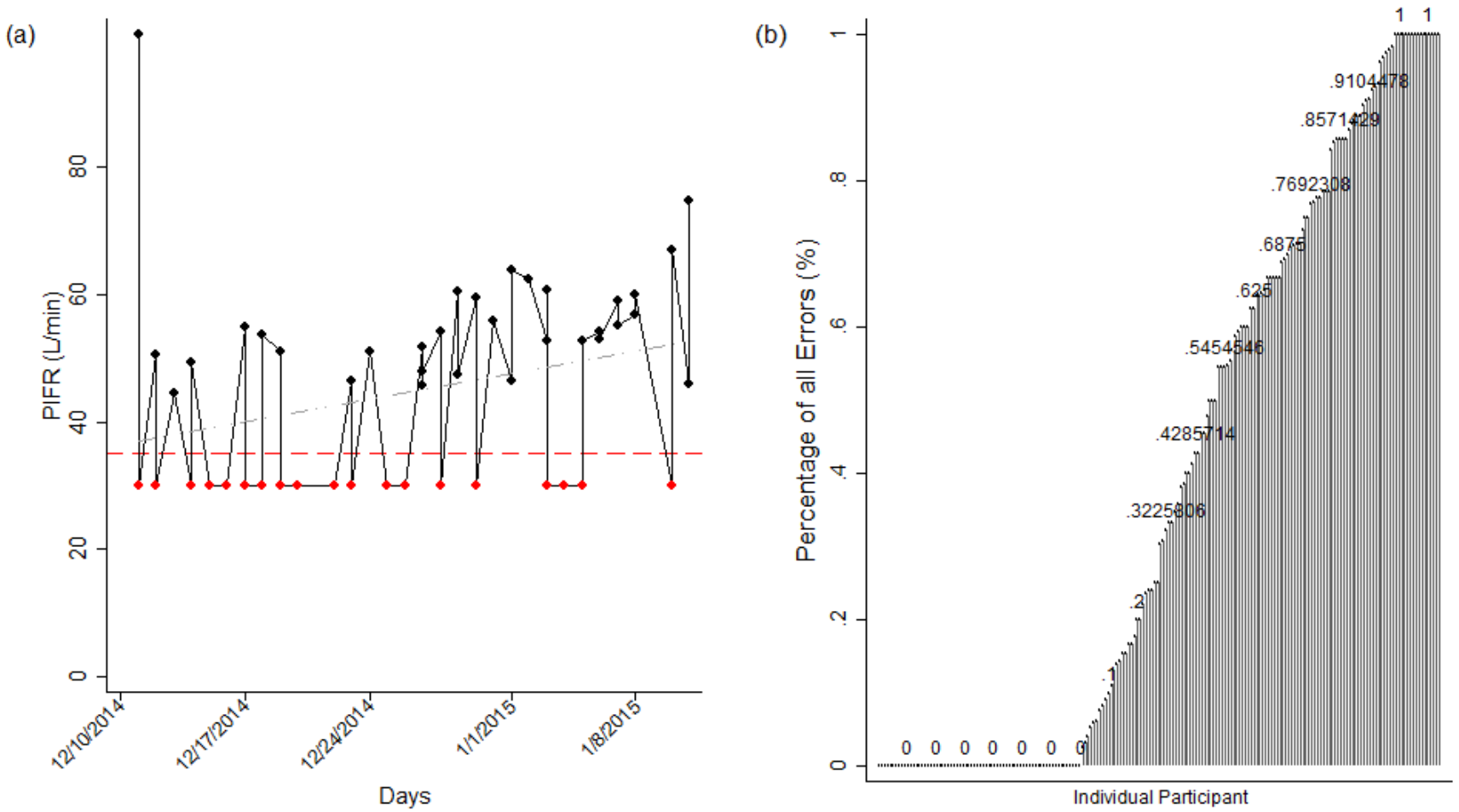

(a)
PIFR (L/min)
0
20
40
60
80
12/10/2014
12/17/2014
12/24/2014
1/1/2015
1/8/2015
Days
(b)
Percentage of all Errors (%)
0
.2
.4
.6
.8
1
0 0 0 0 0 0 0
.1
.2
.3225806
.4285714
.5454546
.625
.6875
.7692308
.8571429
.9104478
1 1
Individual Participant

Figure 5-5: Low Peak Inspiratory Flow, the Most Common Inhaler Error:

In this cohort of COPD patients, the most common inhaler technique error was low PIFR. Audio analysis of inhalation profiles recorded from the INCA™ can estimate the PIFR for each inhalation. From my previous work in Chapter 3, it is clear that this error leads to extremely low levels of drug delivery. Figure (a) is an example of a COPD patient admitted with a COPD exacerbation followed over one month. This patient had very variable levels of PIFR (all red marks indicate flow below 35L/min). However, over time the frequency of low PIFR events reduced, as seen with the fitted grey dash-line, suggesting that during an exacerbation low PIFR may be due to bronchoconstriction and possibly hyperinflation. As the exacerbation is treated with systemic steroids and bronchodilators, the PIFR increases. Figure (b) shows the distribution of this specific inhaler error as a proportion of all errors. This again represents the variability in this population, where some patients did not make this error at all, and some patients only made this error during their one month follow up.

5.4.2.3 Overall Adherence (Actual Adherence)

Using the AUC method (described in Chapter 4) to calculate adherence, the median (IQR) and mean (SD) Actual Adherence over the study period was 6% (42.0) and 22.9% (29.1) of what would be expected if all the doses had been taken correctly and on time. Only 7% of the study population had an Actual Adherence over 80%. There was no difference in the Actual Adherence between those who were discharged following an exacerbation of COPD, median (IQR) 6% (47.0), mean (SD) 23.6% (29.6) and those COPD patients who had another reason for admission, median (IQR) 6% (32.0) and mean (SD) 21.8% (28.9), p=0.64, see Table 5-3 for a summary of adherence measures by reason for admission.

Table 5-3: Adherence Measures by Reason for Admission:

Overall this population of COPD patients had a low Attempted Adherence and high Technique Error Rate, resulting in a low Actual Adherence, 22.9%. Patients were categorized into those that were recruited during an admission for a COPD exacerbation and those recruited during an admission for another cause (i.e. surgical admission). There was no significant difference comparing adherence measures between these two groups.

	ALL PATIENTS	COPD EXACERBATION	NOT COPD EXACERBATION	p value
ADHERENCE		(n=127)	(n=77)	
Actual Adherence (%)	22.9 (29.1)	23.6 (29.6)	21.8 (28.9)	0.68
Average Adherence (%)	73.1 (25.7)	75.8 (23.9)	69.0 (27.8)	0.07
Attempted Adherence (%)	59.4 (29.7)	61.9 (29.6)	55.3 (28.6)	0.12
Technique Error Rate (%)	24.3 (27.5)	26.5 (27.5)	20.6 (27.4)	0.14

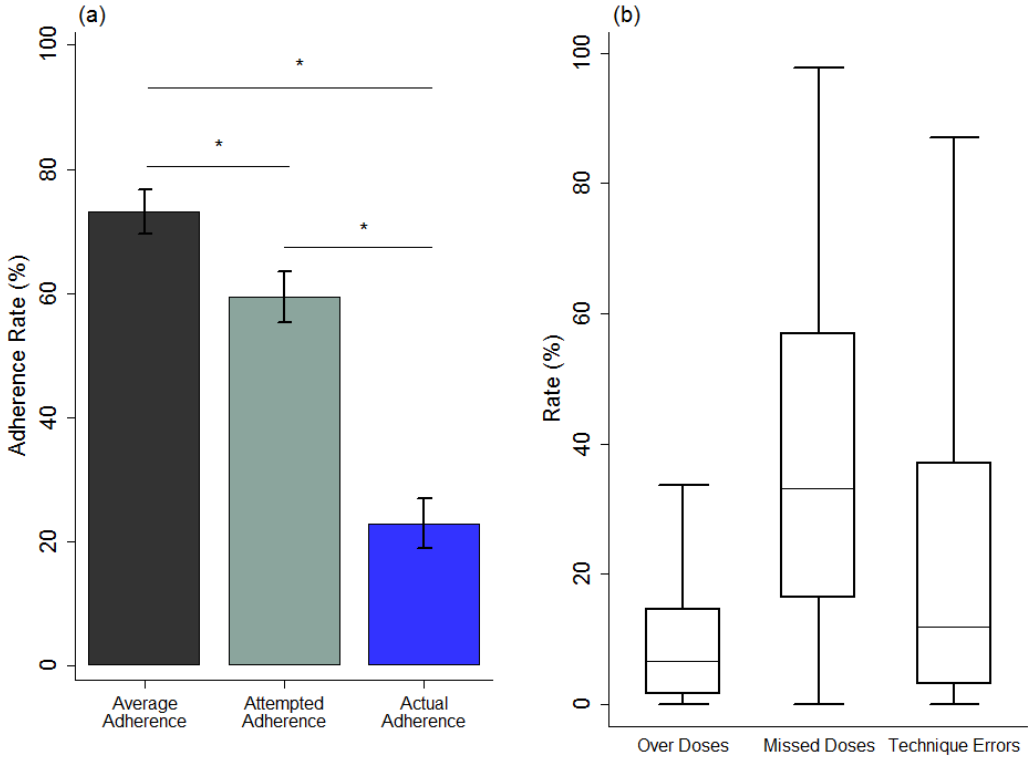


Figure 5-6: Different Adherence Measures Calculated:

Figure (a) displays the difference in adherence calculated from the dose counter (Average Adherence) and the measures from the INCA™ device, the Attempted Adherence (how frequently the patient tried to take their inhaler) and the Actual Adherence (accounting for time of use, interval between doses and technique of use). There was a significant difference between the Average Adherence and the Actual Adherence, $p<0.01$. There was a significant difference between the Average Adherence and the Attempted Adherence, $p<0.01$, due to patients performing multiple blisters in one dose and dose dumping. Figure (b) displays the high levels of over doses, missed doses and technique errors in this cohort of COPD patients. (*$p<0.01$)

5.4.2.4 Inhaler Adherence in Hospital and at Home

Patients were initially recruited while in hospital, and were discharged home within 7.1 (0-30) days. While in hospital patients were instructed on proper inhaler technique by nursing staff. Overall Attempted Adherence in hospital was 48.1% (SD=31.2) and was 52.7% (SD=33.2) at home, p=0.71. Incorporating time of use, interval between doses and technique of use, mean (SD) Actual Adherence was 19.9% (26.0) in hospital and 28.1% (32.7) at home, p=0.33. There were no significant differences comparing patients admitted with a COPD exacerbation and those admitted for another cause. Therefore, even with inhaler instruction, this cohort of patients had poor inhaler technique while in hospital which continued following discharge.

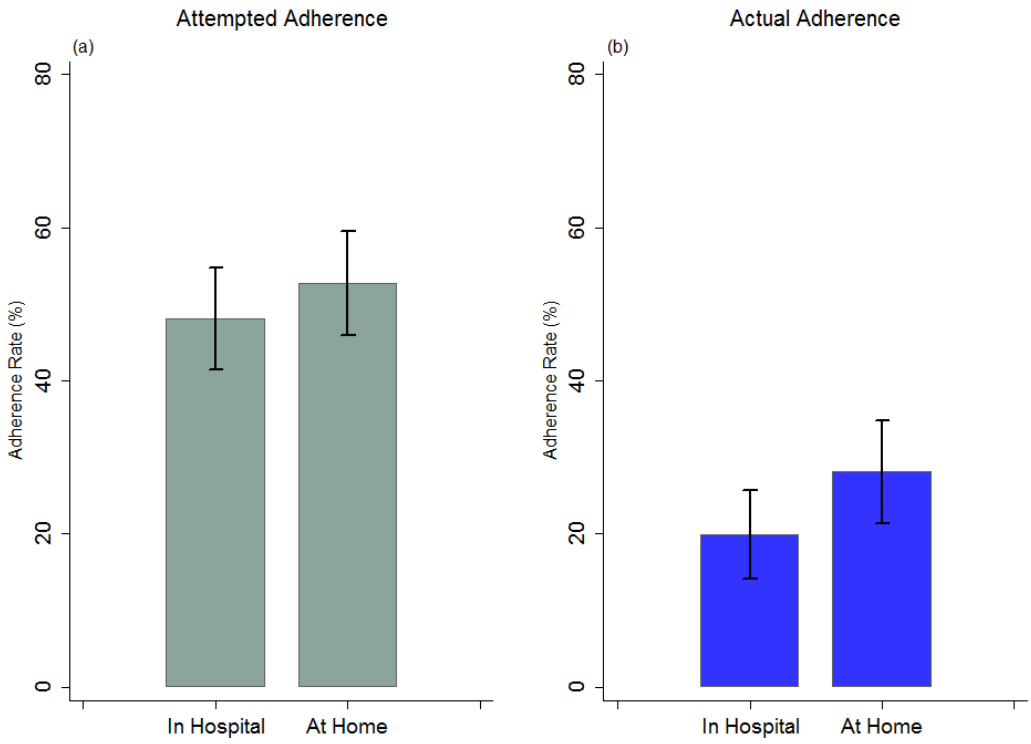


Figure 5-7: Inhaler Adherence in Hospital and then at Home:

Figure (a) represents the calculated Attempted Adherence for patients in hospital and then at home. Figure (b) represents the calculated Actual Adherence for patients in hospital and then in home. For both adherence calculations there was no significant difference between in hospital and at home.

5.5 DISCUSSION

In the month following discharge from hospital, only 7% of patients with COPD used their preventer inhaler therapy regularly and with correct technique more than 80% of the time. Interestingly, adherence while patients were in hospital was no different to adherence while at home, suggesting that current inhaler training in hospital is not sufficient to encourage good inhaler behaviour in this patient cohort. Re-admission following an exacerbation of COPD has become a measure of quality of care (222) in the hospital system. Interestingly, Vestbo and colleagues, found that hospital readmission with a COPD exacerbation was lower amongst those patients with better adherence (68). It is essential, therefore, that strategies to reduce re-admission include emphasis on good adherence to maintenance inhaled medications and correct inhaler use. Currently, there is little information on inhaler adherence among COPD patients in this setting (following a hospital admission). Hence, I chose to study adherence in COPD patients being discharged from hospital.

Analysis of the information recorded to the INCA^{TM} device identified that most patients made errors in both inhaler use and technique. The most common technique error identified in this study was low PIFR, which occurred in 24% of all inhalations. The high frequency of this inhaler error was also found in a cohort of community care patients, described in Chapter 2. I have identified, in Chapter 3, that this particular inhaler error causes a significant reduction in drug delivery. For dry powder inhalers, the user is required to generate a sufficient inspiratory flow to de-agglomerate the particles for the inhaler to be effective. For many patients, particularly those experiencing increased hyperinflation during and after an exacerbation of COPD, it may not be possible to generate sufficient airflow for effective inhalation, leading to ineffective drug delivery.

The commonly used method of calculating adherence, the average adherence based on the dose counter, does not account for any technique errors. In this chapter I used a new method of calculating adherence to measure inhaler adherence in a cohort of COPD patients admitted to a tertiary hospital. The Average Adherence,

from the dose counter, for this population was 73.2%. However, as mentioned previously, this cohort made several critical technique errors that reduce drug delivery. With this in mind the Actual Adherence for this population was low at 22.9%, significantly lower than the average adherence ($p<0.01$).

5.5.1 Limitations

There are several limitations to this study. This was a single centre observational study and the findings of the study should be interpreted with this in mind, with respect to potential bias and lack of generalizability. Additionally, the majority (98%) of patients enrolled in this study held government sponsored health insurance, which is reflective of this cohort's age group and, in some cases, a lower socio-economic group. While some of the baseline patient characteristics in this cohort are quite different to those studied in randomised control trials of stable outpatient COPD (223), they are similar to those in recent observational cohort studies of hospital recruited COPD patients in the UK and USA (133,180,224-226). Therefore, it is likely that these results are representative of similar patients with COPD in other health areas. In addition, with regards to poor inspiratory flow, I am unable to say if this was due to impaired lung function or poor effort. However, this was not the aim of this study and future qualitative studies looking at factors related to adherence and intervention studies will address this issue. Over the study period <5% of eligible patients refused consent. This may be a form of selection bias, as the adherence of these un-recruited patients may not be represented in the current data set. However, with such a low level of recorded inhaler adherence and only a few patients refusing to participate, it is unlikely to have made a significant difference to this studies results.

As this study only analysed adherence over a one-month period, it is not known if adherence influences re-admission or if inhaler use changes over time. A further limitation was that only one pharmacological medication delivered by one device was studied. When the INCA™ device was first developed it was used with the Diskus™ device, as at the time this was the most commonly used treatment for patients with COPD. However, given that I am studying a behaviour that would likely

be repeated by this patient group with other inhalers, I believe that the results can be generalised, although future research will examine this. In my study I provided the adapted inhaler with the INCA^{TM} device attached and hence, deliberately concentrated on the implementation phase of adherence (112) and did not look at the initiation or persistence phases of adherence. The technology is also limited by the fact that the patient has to return the inhaler and device and the audio files have to be manually reviewed for the adherence to be calculated. However, an automated algorithm that can analyse these audio files has been validated in a cohort of asthma patients (227,228) and will have to be validated in a COPD cohort. Additionally, patients were aware that their adherence was being monitored for the month of the study. However, adherence remained poor and suggests that adherence in a real world population may even be worse.

There are several novel aspects to this study, including: the time period of the study, that is, immediately following discharge from hospital, the identification of the common inhaler errors in this patient cohort using a novel electronic adherence monitor and the use of a new method of calculating adherence as the AUC. These findings also have practical implications for possible adherence interventions in this patient population. This study was performed in a 'real world' population. However, this technology and methodology can also be utilised in a clinical trial setting and has potential use as an education tool to improve inhaler use and technique in clinical practice.

There has been a proliferation of devices delivering inhaled medications in the last few years which has challenged clinicians to train patients how to use these devices correctly. Pharmaceutical companies developing these devices should be mindful of creating easy to use fail-proof devices, and not overburden patients and clinicians with the responsibility of learning the nuances of correct technique.

5.6 CONCLUSION

Inhaler adherence, when accounting for time of use, interval between doses and technique of use is low in a cohort of COPD patients admitted to hospital. On discharge home, the inhaler adherence does not improve. In my second Chapter, I looked at inhaler adherence in a mixed group of respiratory patients in a primary/pharmacy care setting. The adherence, when accounting for technique errors (Actual MPR) in the cohort was 56.7% and common inhaler technique errors included low PIFR and exhalation into the inhaler after drug priming. I then developed a new method of calculating adherence in a cohort of asthma patients. The Actual Adherence at one month for this group of asthma patients was 61.8%.

In this Chapter, using this new method of calculating adherence, Actual Adherence was 22.9% in a group of COPD patients, much lower than that measured in the primary/pharmacy care cohort, lower than the asthma patients studied in Chapter 4 and lower than the average adherence (dose counter). Similar to the other studied cohorts, patients made errors in both timing and technique. The most common inhaler error in this group was similar to the other studied cohorts, that of low PIFR.

The design of successful adherence interventions requires a detailed understanding of the determinants of adherence in the population being targeted. In this study I have collected a large amount of patient information in relation to baseline demographics, disease severity, personal factors, and socioeconomic factors. In the following Chapter I will use this dataset to examine possible determinants of poor adherence and try to identify different patterns of inhaler use based on time of use and technique of use. Figure 5-2 displays several possible patterns of inhaler use based on time of use and technique of use; those who use their inhaler regularly but make consistent errors (c), those who use their inhaler infrequently but when they do use it they use it correctly (b) and those patients that use it infrequently and with poor technique (d). I will also look at the relationship of adherence measures, including my new method and measured clinical outcomes in this cohort of COPD patients.

Having shown that inhaler technique is poor in several different groups of patients and that certain inhaler errors impact on drug delivery, I will also look at how a multi-centre intervention geared at correcting technique errors can improve adherence over time (Chapter 7).

Chapter 6 :

DETERMINANTS AND PATTERNS OF INHALER ADHERENCE IN A COPD POPULATION

6.1 INTRODUCTION

This body of work began after identifying several common inhaler technique errors that are critical to drug delivery. With a new method of calculating adherence I was able to show that this method is more reflective of clinical outcomes than the Average Adherence and that adherence is much lower with this method, compared to the average adherence from the dose counter, in a cohort of COPD patients. Having identified such a low level of inhaler adherence in this patient population I sought to identify determinants of poor adherence in this same patient population.

6.2 BACKGROUND

Inhaler adherence in patients with COPD is extremely poor, in part due to poor inhaler technique (see Chapter 5). However, the use of inhaled medication in COPD and asthma remains integral to disease management (138,178,229) and understanding why patients don't take their prescribed treatment is equally important. In an attempt to understand inhaler adherence and possible causes for poor inhaler adherence Plaza et al (230) used a new questionnaire, the Test of Adherence Inhalers (TAI), to assess patient adherence (231). This questionnaire is a 12-item questionnaire. The first 10 questions are answered by the patient (patient domain) and each question is scored from 1 to 5 (with 1 being the worst possible score and 5 being the best possible score). The creators of this questionnaire devised the first five questions to identify patients with erratic non-adherence behaviour; these are the patients that forget to take their medication. The next 5 questions (items 6 to 10) were designed specifically to identify patients with intentionally non-adherent behaviour; this refers to patients who deliberately decide not to take their medication. The final two questions (items 11 and 12) are answered by the clinician and are scored 1 (bad) or 2 (good). These two questions were created to identify patients with unwitting non-adherent behaviour; this is patients who may not understand their medication use, dosage or, in the case of inhalers, technique of use. In this study 910 patients were included (500 asthmatic

and 410 with a diagnosis of COPD). Interestingly, patients with asthma were significantly less adherent than patients with COPD, contrary to my findings in Chapter 4 and Chapter 5. Erratic non-adherence behaviour was the most common adherence behaviour in both patient groups, followed by deliberate and unwitting behaviours. However, unwitting behaviour was more common in COPD patients when compared to asthmatics (31.2% vs. 22.8%, $p<0.001$). Further analysis identified factors that predicted non-adherence in each patient cohort. For patients with asthma, younger age and active working status were associated with non-adherence. In the COPD patient cohort, active working status and better pulmonary function was associated with non-adherence. As a whole population, only age less than 50 years and active working status were associated with non-adherence. The authors also noted that non-adherence was neither associated with asthma control (Asthma Control Test) nor symptom impact with COPD (COPD Assessment Test). These are at variance with data in the prior chapter and suggest that there is a need to understand further the drivers of adherence in this patient population.

Despite evidence that poor adherence among patients with COPD can impact clinical outcomes; there is relatively little information on the causes of suboptimal adherence in this patient group. In a landmark study, Vestbo and colleagues found that the least adherent patients in a clinical trial of patients with COPD randomised to receive salmeterol/fluticasone or placebo medication, had higher mortality and hospital readmission rates (68). This association was independent of the study intervention and suggests that poor adherence is associated with critically important, yet unidentified factors, other than simply not taking the medication. Hence it is important to understand the determinants of adherence among this cohort of patients.

The objective of this study was to test the hypothesis that Actual Adherence is more reflective of clinical outcomes than the commonly used Average Adherence, in a cohort of patients with COPD. I will also describe patterns and determinants of adherence to a commonly used preventer inhaler, salmeterol/fluticasone Diskus ™ inhaler.

6.3 METHODS

6.3.1 Study design and Setting

The analysis for this chapter was performed on data collected from the prospective observational study of patients with COPD discharged from hospital, described in Chapter 5.

6.3.2 Participants

As mentioned in the previous chapter (see Section 5.3.2), these were patients with a known diagnosis of COPD already on a salmeterol/fluticasone Diskus™ inhaler and admitted to hospital with either a COPD exacerbation or other cause (i.e. surgical admission).

6.3.3 Variables Collected

More extensively described in Chapter 5 (see section 5.3.3), a large amount of information was collected for each patient at recruitment. Data were collected on patient demographics, disease severity (including GOLD grade), personal factors and socio-economic factors.

At recruitment patients were given a new 60-dose salmeterol/fluticasone Diskus™ inhaler with an INCA™ device attached, to monitor adherence for the next 26 to 30 days.

6.3.3.1 Follow-Up and Clinical Outcomes

Twenty-six to 30 days after recruitment patients were contacted. During this phone interview information on any exacerbations or admissions for COPD requiring systemic steroids +/- antibiotics was recorded. Over the phone patients also completed questions for the COPD Assessment Test (CAT), Medical Research Council (MRC) Dyspnoea Scale, Hospital Anxiety and Depression Score (HADS), Beliefs in Medicine Questionnaire (BMQ) and the Morisky Medication Adherence Scale (MMAS-8). As the BMQ and the MMAS-8 were added late to the study protocol not all patients have this information collected.

6.3.3.2 Adherence Calculations

This information was based on the calculations done for Chapter 5 (see section 5.4.2), using the method developed in Chapter 4. Inhaler adherence for the month of follow up was calculated using the standard method, the average adherence (from the dose counter) and the new methods described in Chapter 4, the Attempted Adherence, Technique Error Rate and the Actual Adherence.

6.3.4 Statistical Analysis

All categorical variables were summarized using the number observed and proportion of patients. Continuous variables were summarised using mean (SD) and ordinal data with median (IQR). In cases where data was not normally distributed a log transformation was performed to achieve normality. This data was analysed on a log scale and all results back transformed. Between-group and in group comparisons were performed with an unpaired/paired t-test, ANOVA, Chi-squared test, Mann-Whitney test and Wilcoxon matched-pairs signed ranks test where appropriate. Between group comparisons included: MoCA category, MRC grade, CAT impairment, between GOLD classification, exacerbation and no exacerbation within the one moth follow-up, social isolation and socio-economic class. To identify potential factors that may predict Average Adherence, Attempted Adherence and Actual Adherence, a multivariate ordinary least squares (OLS) regression was performed for each measure. Response variables included in the regression models were: Age, Sex, Pack Years, current smoking status, Inhaler Proficiency Score, Cough PEFR, FEV_1, MoCA, CAT, MRC, Anxiety scores, Depression scores, Health literacy, Charlson Co-Morbidity score, and reason for admission.

Clustering was performed using an agglomerative hierarchical method, employing the wards-linkage function with squared Euclidian distance (232). This method was chosen over single-linkage clustering as being more robust to noise in the data. Qualitatively similar results were also obtained using average-linkage clustering. The number of clusters was chosen from inspection of the cluster dendrogram. Before clustering, variables were rescaled to have equal variance. This is required for algorithms employing a distance-based metric. Clustering was based on Attempted

Adherence and Technique Errors, with 4 potential clusters: 1. Poor Attempted Adherence and Poor Technique, 2. Good Attempted and Poor Technique, 3. Poor Attempted and Good Technique, 4. Good Attempted and Good Technique. A multinomial logistic regression was used to compare the different cluster groups in an attempt to predict cluster membership.

6.4 RESULTS

6.4.1 Participants

Between February 2012 and February 2016, 265 patients with COPD consented to participate in this study. The baseline characteristics of these patients are described in Chapter 5. I will now outline some of the results after one-month of adherence monitoring.

6.4.2 Follow-Up

Over the course of one month there were 61 patients (23%) where data was not available, 51 (19%) because INCA^{TM} devices were lost, 5 (<2%) due to device failures and 5 (<2%) patients passed away during the follow up period, see Chapter 5; Thus leaving 204 patients in total for analysis.

6.4.2.1 Phone-Based Questionnaires

At follow up, patients had a significant improvement in their disease-specific quality of life (CAT) and symptoms (MRC), $p<0.02$ and $p<0.01$ respectively. Although there was a slight decrease in anxiety and depression (HADS) this was not statistically significant ($p=0.26$).

Only 77 patients had BMQ measured at recruitment and at follow up however there was an increase in the BMQ after one month, suggesting even more negative beliefs in medication. Similar to recruitment, the highest scores were seen with the 'harm' and 'concerns' questions. Only 91 patients had the MMAS-8 measured at recruitment and again at the end of one month and there was no significant change as patients continued to report medium adherence at one month. See Table 6-1.

6.4.2.2 Exacerbations

During the month following recruitment there were a total of 77 exacerbations requiring systemic steroids and antibiotics. Seven patients had more than one exacerbation within the 4 weeks. Forty-three of those exacerbations (56%) lead to a hospital admission. Two further patients had a lower-respiratory tract infection

requiring antibiotics but did not need steroids. Patients who, when recruited, were admitted with a COPD exacerbation had a significantly higher incidence of re-exacerbation in the following month ($p<0.01$). Naturally, these patients also used more antibiotics ($p=0.02$) and steroids ($p=0.01$) in the month follow-up. Patients initially admitted with a COPD exacerbation also tended have more re-admissions to the hospital compared to those initially admitted for other reasons ($p=0.09$).

6.4.2.3 Inhaler Adherence

A more detailed description of inhaler adherence for this cohort of patients is presented in Chapter 5. At one month, the mean (SD) Average Adherence from the dose counter was 73.1% (25.7). Using information from the INCA^{TM} and using the method of calculating adherence described in Chapter 4, the mean (SD) Attempted Adherence was 59.4% (29.7) and Actual Adherence was 22.9% (29.1), both significantly different from the Average Adherence ($p<0.01$). This cohort of patients made many inhaler technique errors with a mean (SD) Technique Error Rate of 24.3% (27.5). There was no significant difference between those admitted for a COPD exacerbation and those admitted for alternative reasons.

Table 6-1: Clinical Questionnaires measured at Recruitment and One Month Later:

At one month following recruitment, patients were asked questions regarding the COPD Assessment Test (CAT), Medical Research Council Dyspnoea Scale (MRC), Hospital Anxiety Depression Score, (HADS), Beliefs in Medicine Questionnaire (BMQ) and Morisky Medication Adherence Scale (MMAS-8). There was a significant drop in quality of life (CAT) and symptoms (MRC). At one month patients had a slightly more negative belief in medications. *p value is comparing each clinical measure for all patients between baseline and end of month 1.

	AT BASELINE			END OF MONTH 1			
CLINICAL MEASURE	**ALL**	**COPD EXAC**	**NOT COPD EXAC**	**ALL**	**COPD EXAC**	**NOT COPD EXAC**	**p value***
CAT	20.5 (7.9)	21.2 (7.7)	19.3 (8.1)	19.0 (8.4)	19.8 (9.0)	17.8 (7.2)	<0.02
Median MRC (IQR)	4 (1)	4 (1)	3.5 (1)	3 (2)	4 (2)	(2)	<0.01
HADS	12.9 (7.5)	12.8 (7.5)	13.0 (7.5)	11.8 (8.3)	12.0 (8.4)	11.4 (8.1)	0.26
Anxiety	6.9 (4.6)	6.7 (4.4)	7.2 (4.9)	4.8 (4.3)	5.0 (4.5)	4.4 (3.9)	<0.01
Depression	5.6 (4.1)	5.5 (4.2)	5.8 (3.9)	6.0 (4.5)	6.2 (4.7)	5.8 (4.2)	<0.02
BMQ	52.0 (10.7)	52.2 (11.3)	51.9 (10.2)	55.4 (9.6)	56.2 (9.7)	54.8 (9.6)	<0.04
MMAS-8	1.2 (1.3)	1.2 (1.5)	1.2 (1.2)	1.2 (1.3)	1.2 (1.1)	1.3 (1.5)	0.96

6.4.3 Associations between Inhaler Adherence and Personal Factors

In the following section I will describe relationships between adherence measures and several patient related factors such as cognition, anxiety, depression, and beliefs in medications.

There was a high proportion of cognitive impairment in this patient cohort with 80% of patients classified with mild to severe cognitive impairment (based on the MoCA). Patients with this level of cognitive impairment had a significantly lower Attempted Adherence (57.0%, p=0.01) and Actual Adherence (20.7%, p=0.02). This relationship with cognition was not seen with the Average Adherence, see Figure 6-1.

There was no significant difference in adherence measures related to the presence or absence of anxiety symptoms based on the HADS. However, those patients with symptoms suggestive of depression tended to have a lower Attempted Adherence compared to those patients without depression (50.7% vs 60.2%, respectively p=0.07). This trend was not seen with the Average Adherence or the Actual Adherence.

Beliefs in Medicine scores were divided into those with negative beliefs and those with positive beliefs. There was no significant relationship seen with this patient grouping and the different calculations of adherence. Patients with inadequate health literacy had a lower Average Adherence (67%), Attempted Adherence (50%) and Actual Adherence (14%). However, none of these were significantly different than those with sufficient health literacy.

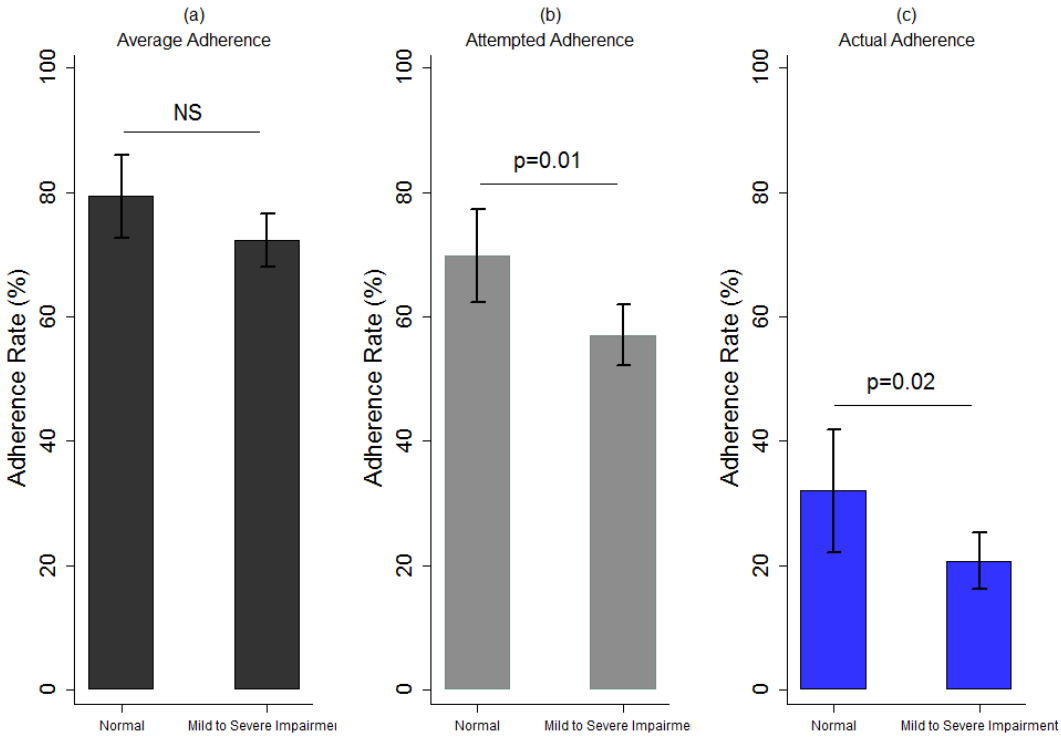


Figure 6-1: Inhaler Adherence and Cognition:

OÁÔÉÅÎÔßÓ ÃÏÇÎÉÔÉÏÎ ×ÁÓ assessed using the Montreal Cognitive Assessment (MoCA) and divided into normal or mild to severe impairment. With Attempted Adherence and Actual Adherence, patients with mild to severe cognitive impairment had significantly lower adherence, p=0.01 and p=0.02 respectively. This relationship was not seen when the Average Adherence was used to calculate inhaler adherence.

6.4.4 Associations between adherence measures disease severity & clinical outcomes

In the following section I will describe relationships between adherence measures and several disease related factors such as quality of life, symptoms, disease severity, lung physiology and exacerbations.

6.4.4.1 Quality of Life and Symptoms

CAT scores were grouped into high (>20), medium (10-20) and low impairment (<20). At the one-month follow up, patients with low impairment had a mean (SD) Average Adherence of 74.1% (30.2) and Actual Adherence of 34.4% (36.2), whereas those with high impairment had a mean (SD) Average Adherence of 69.2% (27.0) and an Actual Adherence of 22.9% (29.3). Those with high impairment had 5% lower Average Adherence (p=0.48) but a near 12% lower Actual Adherence (p=0.13).

The MRC is a scale from 1 to 5, with 5 being very symptomatic and 1 not at all. All categories of MRC were compared to each other with regards to the different adherence measures. At one month those patients with MRC scale 1 had an Average Adherence of 75.0% (27.1) and an Actual Adherence of 38.4% (34.6). Those patients at MRC scale 5 had a mean (SD) Average Adherence of 66.7% (27.7) and an Actual Adherence of 28.7% (25.8). That is an 8% difference in Average Adherence (p=0.35) and a statistically significant 10% difference in Actual Adherence, p=0.03. There were no other notable significant differences between the MRC categories.
See Table 6-2 and Figure 6-2.

Table 6-2: Inhaler Adherence, Quality of Life and Symptoms in COPD patients:

At one month following recruitment, patients were asked to answer question from the COPD Assessment Test (CAT) and to rank their breathlessness on the Medical Research Council (MRC) Dyspnoea Scale. Patients with high impairment had low Average Adherence (from the dose counter) and low Actual Adherence. Very symptomatic patients had a low Average Adherence and a very low Actual Adherence. *p value is from a paired t-test comparing all patients Average Adherence and Actual Adherence for each category of CAT and MRC.

	AVERAGE ADHERENCE			ACTUAL ADHERENCE			
CLINICAL MEASURE	**ALL**	**COPD EXAC**	**NOT COPD EXAC**	**ALL**	**COPD EXAC**	**NOT COPD EXAC**	**p* value**
CAT Impairment							
High	69.2 (27.0)	69.8 (22.7)	68.1 (27.9)	22.9 (29.3)	22.7 (29.7)	23.0 (28.8)	<0.01
Medium	73.8 (23.7)	78.1 (21.0)	68.7 (25.9)	21.0 (29.5)	20.9 (30.4)	21.1 (29.0)	<0.01
Low	74.1 (30.2)	81.7 (17.1)	60.0 (44.1)	34.4 (35.7)	34.4 (36.2)	34.4 (29.6)	<0.01
Low to High	*4.9*	*11.9*	*-8.1*	*11.5*	*11.7*	*11.4*	
MRC							
1	75.0 (27.1)	65.9 (38.5)	80.1 (19.3)	38.4 (34.6)	41.8 (37.9)	36.4 (34.9)	<0.01
2	79.6 (17.8)	76.9 (19.8)	85.4 (11.0)	22.8 (29.0)	19.6 (28.1)	30.4 (31.3)	<0.01
3	72.1 (24.7)	76.8 (21.9)	65.3 (27.5)	20.1 (28.1)	23.5 (30.7)	15.2 (23.7)	<0.01
4	68.9 (29.3)	74.2 (26.0)	59.5 (33.1)	25.4 (33.8)	25.8 (32.6)	24.6 (36.7)	<0.01
5	66.7 (27.7)	70.8 (25.0)	59.2 (31.9)	18.7 (25.8)	19.7 (30.0)	16.5 (14.1)	<0.01
MRC 5 to 1	**8.3**	**-4.9**	**20.9**	**19.7**	**22.1**	**19.9**	

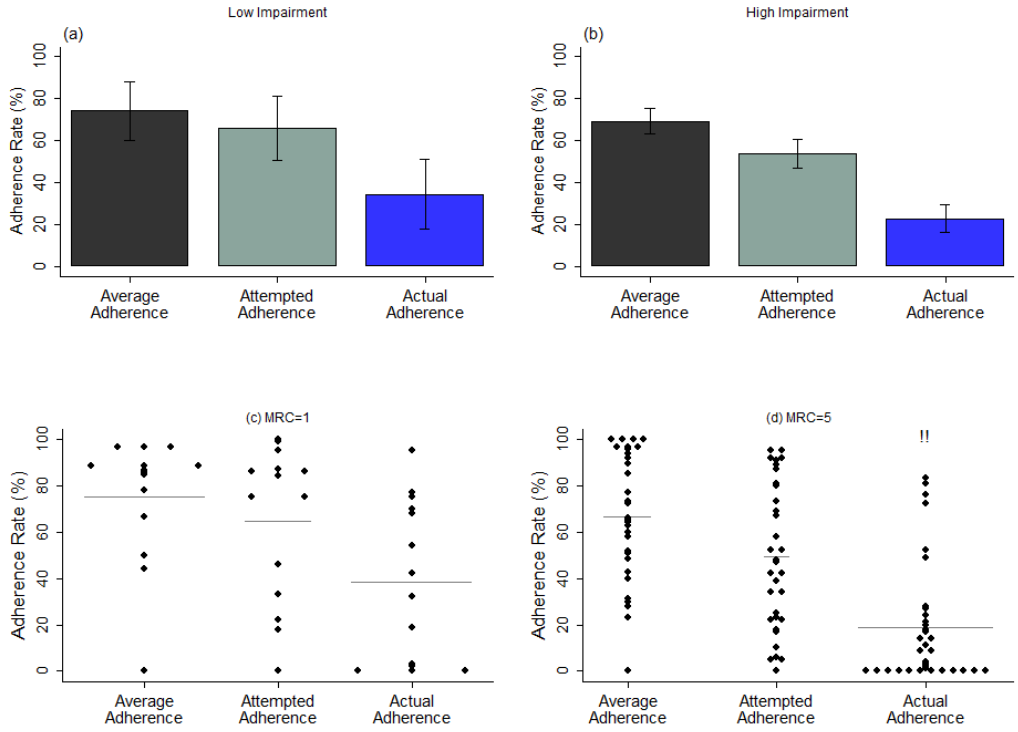


Figure 6-2: Inhaler Adherence, CAT and MRC:

Figures (a) and (b) relate to the CAT. Patients with low impairment (a) based on the CAT tended to have a higher Average Adherence, Attempted Adherence and Actual Adherence. However, none of these were significantly higher than those with High Impairment (b).

OÁÔÉÅÎÔÓ ×ÈÏ ÓÃÏÒÅÄ - 2# ∪ ¡ÄÇ ×ÅÒÅ Ô4ÏÏ ÂÒÅÁÔÈÌÅÓÓ ÔÏ ÌÅÁÖÅ ÔÈÅ ÈÏÕÓÅ ÏÒ ÂÒÅÁÔÈÌÅÓÓ ×ÈÅÎ ÕÎÄÅÓÓÉÎÇ ÈÁÄ Á ÓÉÇÎÉŁŁÃÁÎÔÌÙ ÌÏ×ÅÒ !ÃÔÕÁÌ !ÄÈÒÅÎÃÅ ÔÈÁÔ those who scored MRC 1 (c), Ô . ÏÔ ÔÒÏÕÂÌÄ ÂÙ ÂÒÅÁÔÈÌÉÓÎÅÓÓ ÅØÃÅÐÔ ÏÎ ÓÔÒÅÎÕÓ ÅØÉÓÅÓ 4ÈÉÓ ÄŁŁÅÒÅÎÃÅ ×ÁÓ ÎÏÔ ÓÅÅÎ ×ŁÔÈ ÔÈÅ !ÔÔÅÍÐÔÅÄ !ÄÈÒÅÎÃÅ or Average Adherence. !! p<0.05 comparing adherence rates between MRC 1 and MRC 5.

6.4.4.2 Disease Severity

Lung physiology was recorded as the most recent FEV_1 measured in a pulmonary function lab. In addition, patients had their Cough Peak Expiratory Flow Rate (Cough PEFR) measured at recruitment. Mean FEV_1 % predicted for this population was 52% and Cough PEFR was strikingly low at 160 L/min (normal is >500 L/min, (233)). There was no clear relationship with either FEV_1 ($p=0.54$) or Cough PEFR ($p=0.42$) and the Average Adherence. With the Attempted Adherence, there was no significant relationship with FEV_1 ($p=0.65$) but a linear relationship with Cough PEFR ($p=0.03$) was identified. Actual Adherence had the strongest relationship with Cough PEFR ($p<0.01$) but as well had no significant relationship with FEV_1 ($p=0.39$). See Figure 6-3.

Based on recruitment data collected patients were categorised into GOLD grade (combination of symptoms, exacerbation history and quality of life) and GOLD staging (based on FEV_1) (234). Using the current GOLD grading system, there was no significant difference between grades for any of the adherence measures calculated. However, with the older GOLD classification, based on lung physiology, a difference in adherence was seen only with Actual Adherence and not with the Average Adherence or Attempted Adherence. Patients with GOLD I severity had a mean (SD) Actual Adherence of 39.2% (37.9) while those with GOLD IV severity had an Actual Adherence of 19.32% (28.3), $p=0.05$, see Figure 6-4. There were no other significant differences between COPD severity and inhaler adherence.

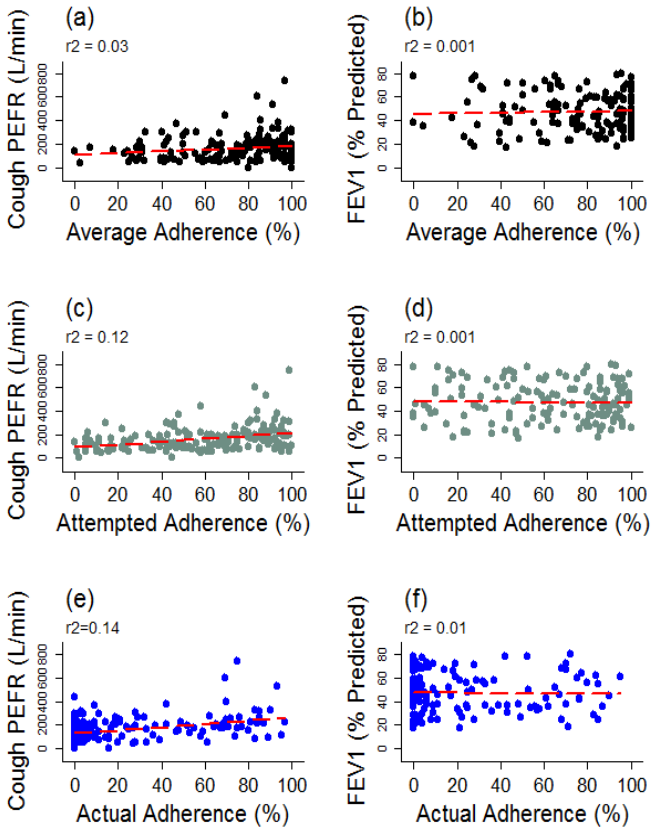


Figure 6-3: Inhaler Adherence and Lung Physiology:

Lung physiology was recorded as the most recently measured Forced Expiratory Volume in 1 second (FEV_1) and Cough Peak Expiratory Flow Rate (Cough PEFR) measured at recruitment. Each calculated adherence measure was tested for a correlation with these physiological measures. Figures (a), (c) and (e) represent relationships for Cough PEFR with Average Adherence Attempted Adherence and Actual Adherence respectively. Figures (b), (d) and (f) represent relationships with FEV_1. The strongest relationship was with Cough PEFR and Actual Adherence (e). Patients with higher Cough PEFR had a higher Actual Adherence (r^2=0.14).

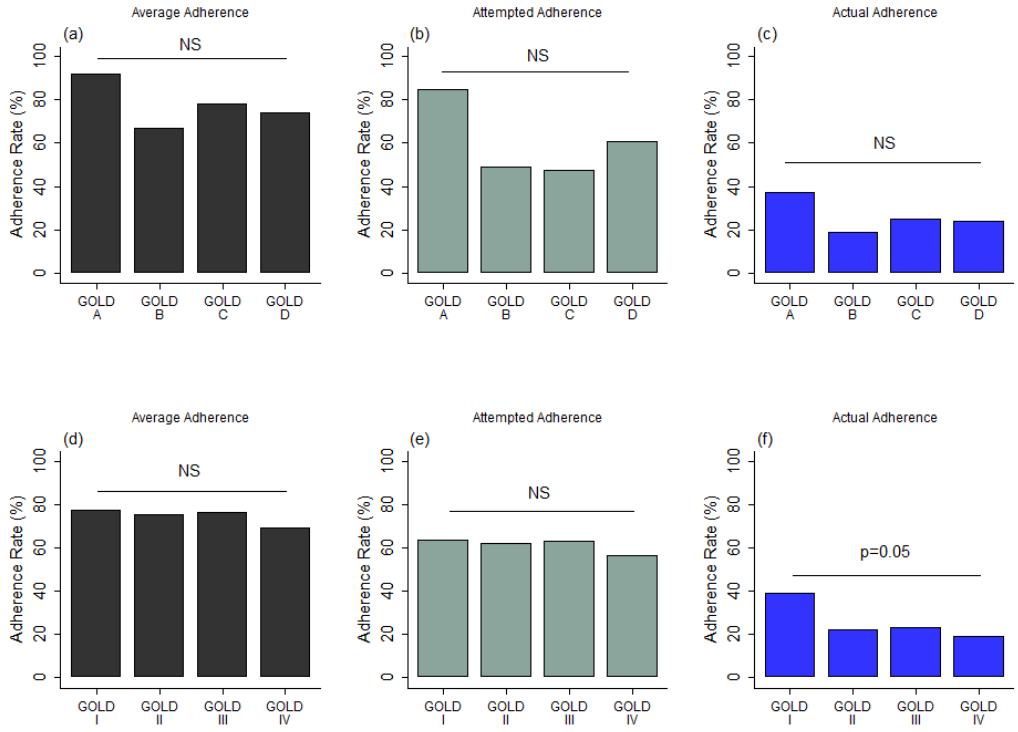


Figure 6-4: Inhaler Adherence and COPD Severity:

Figures (a) to (c) are based on the current GOLD grading system of A, B, C, D. With this classification system there were no significant differences between groups for any of the three adherence calculations.

Figures (d) to (f) are based on the old GOLD severity classification of I, II, III, IV, this was based purely on the patients FEV_1 % predicted. Of the three adherence calculations, only Actual Adherence showed a significant difference between GOLD I and GOLD IV patients, in such that GOLD IV patients had significantly lower Actual Adherence p=0.05.

6.4.4.3 Exacerbations

When comparing patients who had an exacerbation in the first month and required steroids +/- antibiotics (but not requiring a hospital admission) and those that did not; the mean (SD) Average Adherence was 65.7% (28.1) and 73.1% (25.6), respectively, p=0.41. The mean (SD) Attempted Adherence was 53.9% (31.8) versus 58.2% (30.0), p=0.48, while the mean (SD) Actual adherence was 11.7% (21.7) and 26.7% (31.3), respectively, p=0.01. The Technique Error Rate was also higher for patients that had an exacerbation in the month following recruitment, 31.6% (32.8) versus 19.7% (24.3), p=0.02.

Examining adherence rates for patients that required a hospital admission for their COPD compared to those that did not, the mean (SD) Average Adherence was 65.8% (29.7) and 74.8% (24.4) respectively, p=0.10. The mean (SD) Attempted Adherence was 54.1% (34.2) and 60.8% (28.9), p=0.29. While the mean (SD) Actual Adherence was 23.1% (29.3) and 24.2% (29.7) respectively, p=0.86.

See Figure 6-5.

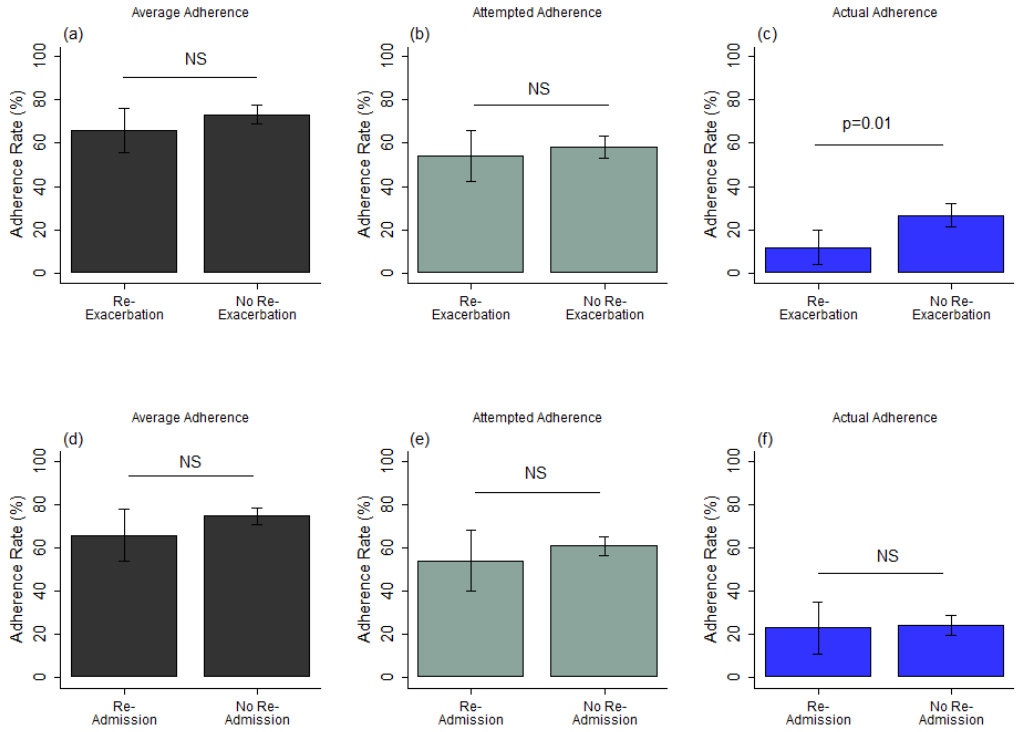


Figure 6-5: Inhaler Adherence and COPD Exacerbations/Admissions:

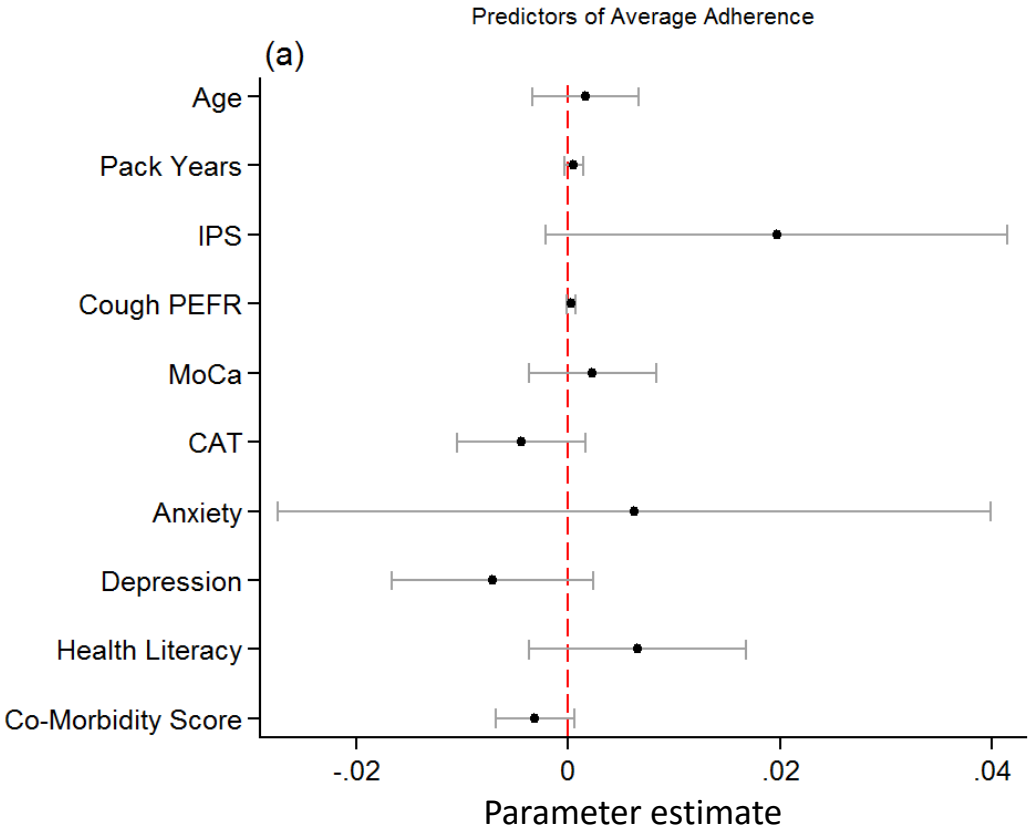
Figures (a) to (c) examine the different measures of adherence for those who had ÁÎ ÅØÁÃÅÒÂÁÔÉÏ Î ÁÆÔÅÒ ÒÅÃÒÕÉÔ Í ÅÎÔ ÁÎÄ ÆÏÒ ÔÈÏÓÅ ÔÈÁÔ ÄÉÄ Î ÔÓÉÇ ÔÈÅ ÄÏÓÅ counter, there was no difference in the Average Adherence. Similarly, there was no significant difference in the Attempted Adherence. However, when accounting for time of use, interval between doses and technique of use, patients who had an exacerbation had a significantly lower Actual Adherence Rate. Figures (d) to (e) examine the different measures of adherence comparing those ÔÈÁÔ ×ÅÒÅ ÁÄ Í ÉÔÔÅÄ ÆÏÒ ÁÎ ÅØÁÃÅÒÂÁÔÉÏ Î ÁÎÄ ÔÈÏÓÅ ×ÈÏ ×ÅÒÅ Î Ô 4ÈÅÒÅ ×ÁÓ Î Ï significant difference in any of the adherence measures calculated.

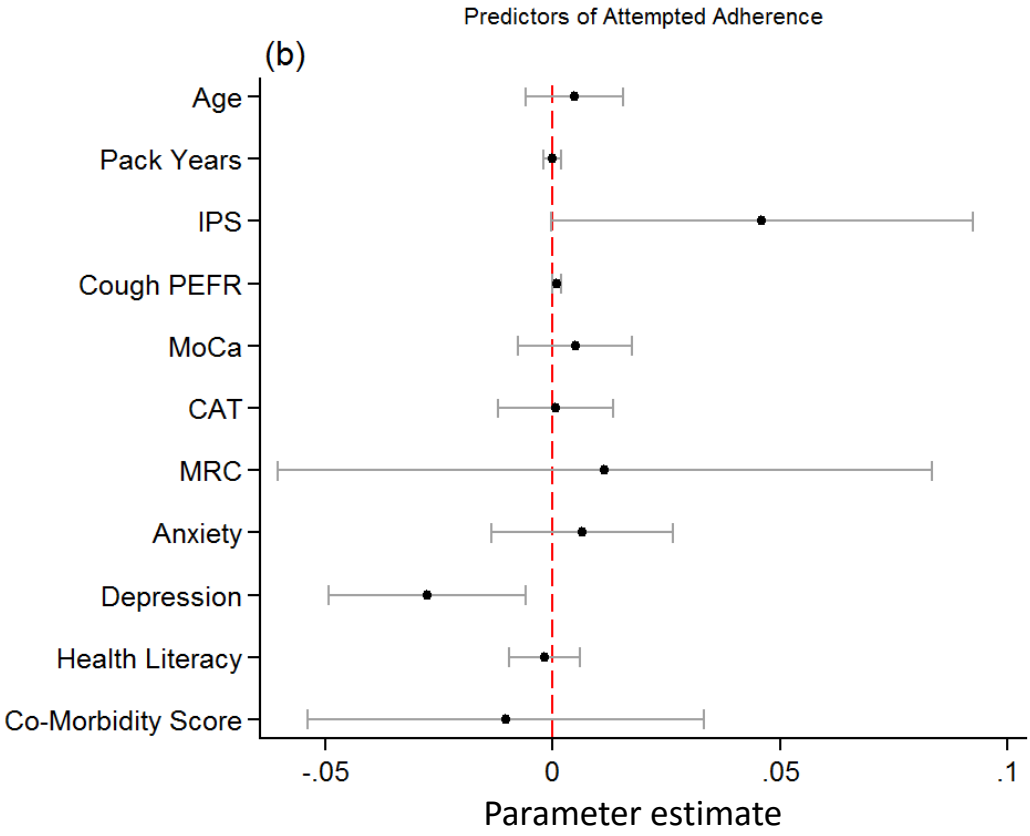
6.4.5 Associations between adherence measures and socioeconomic factors

Social isolation and socio-economic class are important factors related to patients with COPD. When compared to patients who live with other people, isolated patients (patients that live alone) had a significantly lower Average Adherence (76% vs. 64%, $p<0.01$) and Attempted Adherence (62% vs. 51%, $p<0.04$). However, there was no significant difference in the Actual Adherence. As 98% of patients in this patient cohort had government-sponsored health insurance, it was not possible to examine the relationship of cost of medication and inhaler adherence for the different calculations of adherence.

6.4.6 Determinants of Inhaler Adherence

In a multivariate regression model, there were no significant predictors of Average Adherence. There was a significant relationship with Attempted Adherence and depression scores and inhaler proficiency. Patients with low depression scores and high inhaler proficiency, based on the IPS had higher Attempted Adherence ($p=0.01$ and $p=0.03$ respectively). Predictors of higher Actual Adherence included Cough PEFR, MoCA and the Charlson Co-Morbidity Score. In this model, higher Cough PEFR, higher cognition and less co-morbid disease lead to a higher Actual Adherence ($p=0.01$, $p=0.03$ and $p=0.04$ respectively). See Figure 6-6.


Predictors of Average Adherence
(a)
Age
Pack Years
IPS
Cough PEFR
MoCa
CAT
Anxiety
Depression
Health Literacy
Co-Morbidity Score
-.02
0
.02
.04
Parameter estimate


Predictors of Attempted Adherence
(b)
Age
Pack Years
IPS
Cough PEFR
MoCa
CAT
MRC
Anxiety
Depression
Health Literacy
Co-Morbidity Score
-.05
0
.05
.1
Parameter estimate

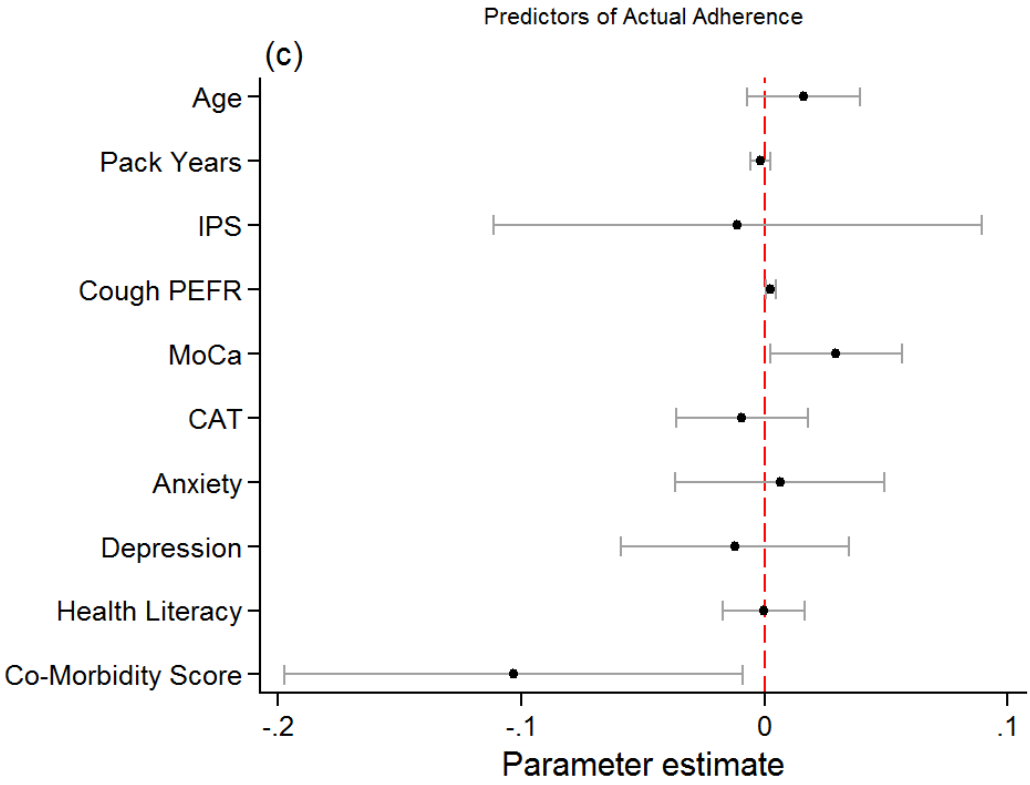

Predictors of Actual Adherence
(c)
Age
Pack Years
IPS
Cough PEFR
MoCa
CAT
Anxiety
Depression
Health Literacy
Co-Morbidity Score
-.2
-.1
0
.1
Parameter estimate

Figure 6-6: Determinants of Inhaler Adherence:

A multivariate regression model with age, sex, current smoking status, pack years, inhaler proficiency score (IPS), Cough PEFR, FEV_1, Montreal Cognitive Assessment (MoCA), COPD Assessment Test (CAT), Medical Research Council Dyspnoea Scale (MRC), anxiety scores, depression scores, Health literacy CharIson Co-Morbidity score, and reason for admission as outcome variables was performed for each of the calculated adherence measures: Average Adherence (a), Attempted Adherence (b) and Actual Adherence (c). In these forest plots, the y axis are the variables used in the regression analysis and the x axis represent the coefficients of this analysis (paramater estimate). Variables ×ÈÏ῀Ό ωυÞ confidence interval (the whisker plots) that cross the zero line have non significant correlations with the adherence measure. Those virables to the left of the zero line have negative correlations and those to the right have positive correlations. For illustrative purposes, reason for admission, current smoking status, FEV_1, MRC and gender were removed, however all of these variables were non significant for each of the adherence measures. For the Average Adherence (a), none of the variables were significant (r^2=0.22). For Attempted Adherence (b), only Inhaler Proficiency score and depression were significant, p=0.03 and p=0.01 respectively (r^2=0.28). For Actual Adherence (c), Cough PEFR (p=0.01), MoCA (p=0.03) and Charlson Co-Morbidity score (p=0.04) were significant (r^2=0.29).

6.4.7 Patterns of inhaler use

I have shown that there is large variability in inhaler use by the participants in other populations (see Chapters 2 and 4); therefore, I sought to characterise inhaler adherence by patterns. Adherence patterns were characterised using clustering of the Attempted Adherence and the technique error rate. Hierarchical clustering found three well-separated clusters of approximately equal size corresponding to distinct patterns of behaviour. The characteristics of the three groups are shown in Table 6-3.

Cluster 1, n=70 (34%), was characterised by low Attempted Adherence (mean=18%), and high error rate (88%). Cluster 2, n=63 (31%), showed high Attempted Adherence (76%), coupled with high error rate (73%), leading to poor Actual Adherence (20%). While Cluster 3, n=61 (30%), contained patients with good overall adherence, characterised by high Attempted Adherence (58%) and low error rate (8%). Ten (5%) patients with 0% Attempted Adherence were excluded from the cluster analysis; see Table 6-4 and Figure 6-7. Interestingly, in this cohort, there were no patients who took their inhaler infrequently but with good technique, suggesting again that time of use and technique of use are linked and should be considered together when measuring adherence.

Table 6-3: Clinical Characteristics of Inhaler Pattern Clusters:

The clinical features of the three clusters include the demographics, COPD features, personal and socio-economic factors. All values are presented as mean (SD) except where indicated. BMI, body mass index; FEV_1, forced expiratory volume; Cough PEFR, cough peak expiratory flow rate; CAT score, COPD assessment test; MoCA, Montréal cognitive assessment; *Isolation Score and ^frailty scores were calculated as described in the methods section.

	CLUSTER 1 *Poor Attempted* *Poor Technique*	**CLUSTER 2** *Good Attempted* *Poor Technique*	**CLUSTER 3** *Good Attempted* *Good Technique*	p value
DEMOGRAPHICS	(n=70)	(n=63)	(n=61)	
Mean Age	71.4 (9.3)	69.2 (8.9)	67.6 (9.8)	0.49
Sex (% Female)	61%	43%	51%	0.10
BMI	27.0 (7.0)	27.6 (7.2)	28.1 (5.4)	0.05
Pack Years smoked	53.9 (43.5)	64.8 (50.5)	50.7 (30.4)	0.75
Currently smoking (%)	29%	23%	15%	0.19
Salmeterol/fluticasone Dose (% 500mcg)	67%	78%	82%	0.14
Inhaler Proficiency Score (range 0-10)	7.2 (1.7)	7.6 (1.7)	8.0 (1.4)	0.20
DISEASE SEVERITY				
FEV_1 (L)	1.3 (0.6)	1.2 (0.7)	1.4 (0.7)	0.35
FEV_1 (%)	54.7 (22.4)	48.3 (20.4)	55.1 (23.6)	0.63
Cough PEFR	121.6 (81.0)	184.8 (111.3)	199.8 (108.8)	<0.01
CAT score (range 0-30)	20.6 (8.1)	18.9 (7.0)	22.4 (7.6)	0.56
Number of COPD admissions in previous year	1.6 (1.7)	1.2 (1.8)	1.3 (1.5)	0.09
Median MRC dyspnoea score (IQR)	3 (1)	4 (1)	4 (1)	0.25

	CLUSTER 1 *Poor Attempted Poor Technique*	**CLUSTER 2** *Good Attempted Poor Technique*	**CLUSTER 3** *Good Attempted Good Technique*	p value
Number in GOLD Grade (%)				
A	0 (0)	1 (2)	0 (0)	0.33
B	14 (20)	10 (15)	12 (20)	0.76
C	1 (2)	1 (2)	0 (0)	0.60
D	55 (78)	51 (81)	48 (80)	0.93
PERSONAL FACTORS				
Charlson Co-Morbidity	6.2 (2.1)	5.9 (1.3)	5.4 (1.8)	0.05
Median No. of Regular Medications (IQR)	12 (6)	12 (7)	11 (9)	0.96
Median No. of Nebulisers used (IQR)	1 (1)	1 (0.5)	1 (1)	0.36
MoCA score (range 0-30)	18.1 (7.0)	22.1 (4.6)	23.1 (4.7)	<0.01
HADS Total score (range 0-42)	13.0 (7.3)	10.9 (6.1)	13.5 (7.6)	0.69
Anxiety component of HADS (range 0-7)	7.0 (4.5)	6.4 (4.3)	7.0 (4.4)	0.69
Depression component of HADS (range 0-7)	5.9 (4.4)	4.6 (2.9)	5.8 (4.1)	0.92
European Health Literacy Score (range 16- 80)	36.8 (11.3)	31.6 (8.0)	32.8 (10.5)	0.61
Mean European Health Literacy Score per Question (range 1-5)	2.3 (0.71)	2.0 (0.50)	2.1 (0.65)	0.46
Beliefs in Medicine Questionnaire (range 18-90)	49.9 (10.3)	53.9 (9.8)	50.5 (11.8)	0.66
MMAS-8 (range 0-2)	1.0 (1.3)	1.0 (1.2)	1.3 (1.5)	0.56
SOCIO-ECONOMIC DETAILS				
Patients Living Alone (%)	26%	26%	19%	0.63
Patients with a Carer (%)	16%	20%	18%	0.80
Number of Floors in Home	1.8 (0.5)	1.9 (0.4)	1.8 (0.5)	0.41
Patients with a Stair Lift (%)	20%	24%	14%	0.55
Patients with Downstairs Bathroom (%)	29%	24%	27%	0.77
Patients with Downstairs Bedroom (%)	52%	41%	47%	0.80

	CLUSTER 1 *Poor Attempted* *Poor Technique*	**CLUSTER 2** *Good Attempted* *Poor Technique*	**CLUSTER 3** *Good Attempted* *Good Technique*	p value
Patients who get Meals Delivered (%)	3%	4%	4%	0.99
Median Isolation Score (IQR)*	2 (1)	2 (1)	2 (0)	<0.01
Patients Isolation Score* >2 (%)	26%	27%	19%	0.59
Patients with Government Sponsored Health Insurance (%)	100%	100%	95%	0.86
Median Frailty Score (IQR)^	2 (1)	2 (3)	2 (2)	0.31
Patients Frailty Score >2 (%)	14%	35%	42%	0.13

Table 6-4: Inhaler Adherence for Different Inhaler Patterns:

Mean (SD) of different adherence measures calculated from the INCA™ device for the three clusters was calculated. p values are obtained from one-way ANOVA of each variable across the three groups. Cluster 1 were patients with poor Attempted Adherence and poor inhaler technique. Cluster 2 were patients with good Attempted Adherence and poor inhaler technique. Cluster 3 were patients with good Attempted Adherence and good inhaler technique.

	CLUSTER 1 *Poor Attempted Poor Technique* n=70	**CLUSTER 2** *Good Attempted Poor Technique* n=63	**CLUSTER 3** *Good Attempted Good Technique* n=61	P
ADHERENCE				
Actual Adherence (%)	1.73 (2.77)	19.5(19.6)	54.6 (28.5)	<0.01
Attempted Adherence (%)	18.1 (13.5)	76.1 (16.7)	58.5 (29.2)	<0.01
Technique Error Rate (%)	88.1 (17.2)	73.2 (24.8)	7.72 (8.63)	<0.01

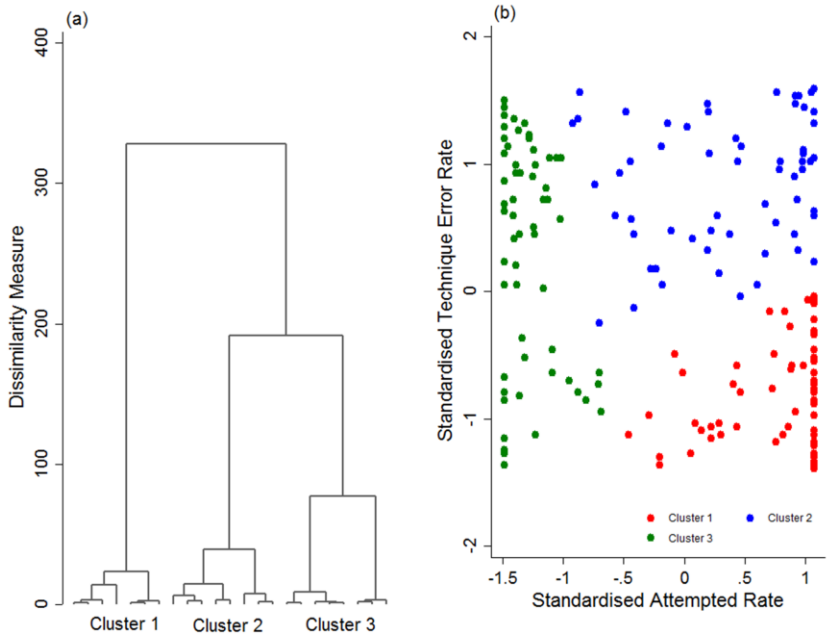


Figure 6-7: Inhaler Use Patterns:

&ÉÇÕÒÅ ¡ÁÇ ÉÓ Á ÄÅÎÄÒÏÇÒÁ Í ÒÅÓÕÌÔÉÇÆÒÏ Í ÔÈÅ ÃÌÕÓÔÅÒ Á Î ÁÌÙÓÉÓ ÕÓÉÎÇ 7 ÁÒÄ¡Ó method in 204 patients with COPD leading to 3 major clusters. Figure (b) is a distribution of the three clusters based on Attempted Adherence and technique error rate. Cluster 1 represents patients with poor Attempted Adherence and high technique error rate, leading to a low Actual Adherence. Cluster 2 represents patients with good Attempted Adherence and high technique error rate. Cluster 3 represents patients with good Attempted Adherence and low technique error rate leading to a high Actual Adherence.

6.4.8 Determinants of Inhaler Pattern Adherence

Demographic and clinical measures predictive of cluster membership were investigated using a multinomial logistic regression, with good adherence (membership of Cluster 3) taken as the base outcome. Co-morbidity was strongly predictive of membership of both Clusters 1 and 2, suggesting a contribution to poor technique, while cough PEFR, age and MoCA were predictive of membership of Cluster 1, corresponding to poor Attempted Adherence and high technique error rate. This all suggests Cluster 3 may be a healthy survivor group. FEV_1 was predictive of membership of cluster 2 (good Attempted Adherence, poor technique), but not cluster 1, suggesting lung function makes a contribution to technique errors in those with good Attempted Adherence. See Table 6-5 for a summary of these results.

Table 6-5: Determinants of Inhaler Patterns:

Multinomial logistic regression of adherence cluster membership against demographic and clinical factors. The reference category is good adherence (cluster 3). All variables have been standardised to unit variance to enable comparison of effect sizes. The coefficients represent the change in log-odds of cluster membership per unit increase in the associated variable. Overall the model fit was highly significant (Likelihood-Ratio Chi-square test, $p < 0.00005$, pseudo-$R^2 = 0.204$).

Adherence Cluster Group	Variable	Relative Risk Ratio	Std. Err.	p value
Cluster 1				
Poor Attempted	MoCA	0.508	0.175	0.049
Poor Technique	Cough PEFR	0.21	0.089	<0.001
	FEV_1	1.263	0.408	0.47
	Co-Morbidity	4.27	2.026	0.002
	Age	0.352	0.155	0.018
	Constant	1.598	0.552	0.174
Cluster 2				
Good Attempted	MoCA	0.786	0.274	0.489
Poor Technique	Cough PEFR	0.728	0.234	0.322
	FEV_1	0.536	0.166	0.045
	Co-Morbidity	3.458	1.609	0.008
	Age	0.604	0.263	0.246
	Constant	1.509	0.51	0.224

6.5 DISCUSSION

Inhaler adherence in Chronic Obstructive Pulmonary Disease (COPD) is a crucial component of disease management with studies reporting relationships with both morbidity and mortality (68). These studies have always used the Average Adherence (from the dose counter) as the method of calculating and reporting inhaler adherence. As previously discussed, this method does not account for inhaler technique or really quantify drug delivery/accumulation which is required for the effective management of respiratory conditions. In Chapter 4, a new method of calculating adherence that incorporates time of use, interval between doses and technique of use in a single metric of drug accumulation, Actual Adherence, was developed. This adherence calculation was more reflective of clinical outcomes than the Average Adherence in a population of asthma patients. As a continuation of Chapters 4 and 5, the aim of this study was to identify determinants of Actual Adherence and different inhaler patterns.

Over a 3-year period data was collected on 265 patients with COPD whose inhaler adherence was monitored for one month. Data on several factors were collected in this large cohort of patients. There were several novel findings in this study. Firstly, I was able to elaborate further from my findings reported in Chapter 4, assessing the relationship Actual Adherence has with clinical outcomes, in comparison to the Average Adherence and in a different patient cohort. Secondly, I identified novel determinants of adherence in this patient cohort. Thirdly, I presented a description of novel patterns of adherence using analysis of data collected to a system that evaluated all aspects of inhaler use.

Compared to Average Adherence, Actual Adherence was more reflective of several factors. At one month, patients who reported worse breathlessness had worse Actual Adherence. Interestingly, patients who had an exacerbation of their COPD within the month after recruitment had significantly lower Actual Adherence than those that did not. In addition, patients with poorer cognition, poorer cough PEFR and more severe COPD (GOLD Stage IV) had worse Actual Adherence. These

relationships were not identified with the Average Adherence suggesting that this method of calculating adherence, which is not reflective of inhaler technique, is missing an important dimension of inhaler adherence.

With regards to inhaler technique, FEV_1 and Cough PEFR were predictive of a high technique error rate. Low cough PEFR could be the result of a number of aspects of severe COPD such as muscle weakness, airflow limitation and or the effect of air trapping. Regardless of the exact mechanism, the low cough PEFR seen in this cohort indicates the severity of the underlying lung condition and the ability of the patient to inhale with sufficient pressure to overcome the internal resistance of the dry powder inhaler. As discussed in Chapter 1, for DPI devices, the balance between device resistance and inspiratory flow are crucial to drug delivery. In this cohort of COPD patients the most common inhaler error was low inspiratory flow; and low cough PEFR was associated with this technique error. It would seem that the combination of low cough PEFR and a high resistance device may lead to poor drug delivery and other inhaler devices, such as nebulisers, may need to be considered.

In this study, 31% of patients used their inhaler regularly but made consistent errors (sometimes termed un-intentional non-adherence) despite repeated instruction in hospital. Another 30% rarely used their inhaler but when they did so, often used it incorrectly (intentional and un-intentional non-adherence). The major factors determining overall adherence (Actual Adherence) were the presence of severely impaired lung function, which affected the inhalation flow, and the patient's cognitive status which affected the patient's ability to remember both when and how to use the inhaler.

The determinants studied were based on the information in the published literature (68,163,230,235-238). One model, the COM B framework of adherence, groups adherence determinants under the themes of comprehension, opportunities and motivation (239). Hence, for COPD patients, their comprehension and capacity to remember and follow instructions, their motivation (which can be affected by the patient's beliefs about medicine and illness), depression, social isolation, frailty and

health status may impact on adherence (163,164,240,241). Lost opportunities for patient learning may also arise either because of poor healthcare professional communication, poor knowledge of inhaler handling leading to poor instruction, or a patient's poor comprehension as a result of lower health literacy (52). I used a variety of validated instruments to evaluate each of these themes and I included information on measures of hyperinflation, as I have previously shown that low inhalation flow is a common error in inhaler handling.

Cluster analysis was used to categorise the patients into groups based on regularity and proficiency of use. Knowledge of these patterns of inhaler use could be used to develop personalised interventions to promote adherence. For example, those who use their inhaler well and on time need encouragement, while those who use the inhaler regularly but with incorrect technique would benefit from an intervention addressing this issue. Patients who are largely forgetful may benefit from a reminder based system (158) or an intervention such as motivational interviewing (148).

The results of this study show that poor cognitive function is an important determinant of adherence. Cognitive impairment is increasingly being recognised in patients with COPD. For example, brain imaging studies have shown significant white matter pathology in the fronto-striatal regions, areas which impact on planning, problem solving, and prospective memory capacity (242,243). Patients with poor executive functioning often display a "knowing-doing discrepancy". While they can report specific instructions they cannot translate these into specific behavioural and motor plans and activity. Hence, abnormalities in the executive and memory domain may influence adherence through poor recall of inhaler technique and not remembering to use their inhaler.

6.5.1 Limitations

There were some limitations to this study. Firstly, the study period was only one month. This short study interval may not be enough time to see changes in clinical outcomes such as quality of life or symptom scores. Additionally, one month may not be enough time to monitor for exacerbations in this patient cohort. However, at one month there were significant reductions in the COPD Assessment Test and the MRC Dyspnoea scale. At follow-up, 77 patients had an exacerbation of their COPD and these patients had a significantly lower Actual Adherence than those that did not have an exacerbation.

Secondly, by providing these patients with a free salmeterol/fluticasone Diskus™ inhaler I only focused on the execution/implementation phase of adherence. In doing so determinants of adherence affecting the initiation or persistence phases of adherence, such as cost and access to pharmacy service to obtain medication, may have not been identified (226).

Thirdly, this study only focused on patients with severe COPD and this must be taken into consideration. However, the patterns of inhaler adherence, poor technique and poor timing, good timing and poor technique, and good technique and good timing are generalizable to any patient cohort using inhaled medication. Additionally, in Chapter 4 I identified a clear relationship between Actual Adherence and clinical outcomes in an asthma cohort, similar to the findings in this Chapter.

6.4 CONCLUSION

As described in Chapter 5, patients with COPD have a very low Actual Adherence. The major determinants of poor adherence in this population are the presence of cognitive impairment, which affected the patient's ability to remember to take the medication and severe hyperinflation, which affected the ability of the individual to generate sufficient inhalation flow and as a consequence resulted in impaired drug delivery.

In Chapter 4 I outlined the development of a new adherence method that accounts for drug accumulation/delivery (as an area under the curve). This new method proved to be more reflective of clinical outcomes than the standard Average Adherence in a group of asthma patients. In this chapter I developed my findings from Chapter 4 in a different patient population and again found that Actual Adherence is more reflective of clinical outcomes than the standard Average Adherence. Actual Adherence had significant correlations with patient characteristics; Cough PEFR and MoCA. These relationships were not present with the Average Adherence, suggesting that inhaler adherence (in regards to drug delivery) are dependent on a good level of cognition and good muscle strength. Overall, this suggests a healthy survivor effect, as proposed by Vestbo et al (68).

In Chapter 4, patients were categorized into groups based on their time of use and technique of us use by physicians assessing their monthly inhaler adherence. In this Chapter, by way of cluster analysis, three distinct groups of inhaler pattern were identified. Patients who infrequently used their inhaler and when used did so with poor technique, patients who used their inhaler regularly but with poor technique and patients who used their inhaler regularly and with good technique.
I have shown that inhaler technique is common, has implications on drug delivery and is an important aspect of inhaler adherence with implications on clinical outcomes in various respiratory diseases. My work so far has been centred around the execution phase of adherence over one month. I have not examined the persistence of adherence and I have not identified how changes in inhaler technique

might affect the calculation of inhaler adherence and clinical outcomes over time. In my next chapter, I will examine a method of modifying inhaler technique and its implications on Actual Adherence and clinical outcomes over a longer period of time.

Chapter 7 :

A RANDOMIZED CONTROLLED TRIAL OF AN ADHERENCE INTERVENTION, AIMED AT INHALER TECHNIQUE, IN PATIENTS WITH SEVERE UNCONTROLLED ASTHMA

7.1 INTRODUCTION

This combined measure of adherence (Actual Adherence) is the only method that incorporates inhaler technique and has proven to be more reflective of changes in clinical outcomes than the current methods of assessing adherence, the Average Adherence both in a population of asthma patients (Chapter 4) and COPD patients (Chapter 5 and 6). These findings all reinforced the idea that inhaler technique is a crucial and integral part of inhaler adherence.

My research in inhaler adherence so far has focused on the execution phase of adherence, particularly with regards to inhaler technique. I have not examined the persistence phase of inhaler adherence using this new method of calculating adherence. Additionally, although it is clear that inhaler technique has an impact on inhaler adherence and clinical outcomes, I have not shown that an improvement in inhaler technique can lead to an improvement in inhaler adherence and potentially clinical outcomes.

7.2 BACKGROUND

For most asthma patients, symptoms can be controlled by the regular use of a combination of inhaled beta agonists and corticosteroids. However, about 10% of asthma patients remain poorly controlled despite the use of these agents (244). For some patients, poor control arises because their condition is truly refractory, for others poor asthma control is due to inadequate adherence to therapy or poor inhaler technique (161,245,246). Therefore, guidelines for management recommend that adherence to therapy and inhaler technique are addressed before stepping up treatment (157,181,194,244). Correctly identifying insufficient adherence is difficult as patient self-reporting is not reliable (72,73,79,161,245,246) and may not address inhaler technique. Furthermore, many healthcare professionals are unfamiliar with correct inhaler technique, so they may not recognize inhaler errors (247). Another method of assessing adherence is through pharmacy refill records. These records indicate that the patient has collected their prescribed

inhaler, but do not assess if patients have used the inhaler correctly and regularly. Currently there are several electronic adherence monitors that can assess inhaler adherence over time (97,101,151,159,162), however none of the current monitors in the market have the facility to address inhaler technique.

To address these challenges with the current methods of monitoring inhaler adherence, the INhaler Compliance Assessment (INCA^{TM}) device, which makes a digital audio recording of the inhaler being used by the patient, was developed. As described previously, analysis of the audio recordings provides an automated, objective, assessment of both when and how the inhaler was used. This detailed information on inhaler use can then be used as visual feedback to the patient instantly (105,107-109,153).

The purpose of this study was to report on the persistence phase of adherence and examine if a strategy to improve inhaler technique will lead to better inhaler adherence and clinical outcomes. An asthma-training program was designed to improve adherence. In this study I tested the hypothesis that a program of repeated monthly training, with visual feedback of the patient's own inhaler use would enhance adherence compared to regular repeated training without visual feedback and better inhaler adherence would lead to improved clinical outcomes.

7.3 METHODS

This was a single blind prospective multicentre randomized controlled clinical trial, conducted between February 2012 and December 2015. The protocol of the study and statistical plan has been published (190) and can be found in Appendix F. The principles of the intervention were the formulation of personal asthma goals and achieving these by developing a regular habit of inhaler use and correct inhaler technique. This study was sponsored by the Royal College of Surgeons in Ireland (RCSI), approved by the local hospitals ethics committees and registered on Clinicaltrials.gov, NCT01529697.

7.3.1 Participants

Patients aged ≥18 years with stage 3-5 asthma according to GINA guidelines were recruited from five specialist asthma clinics within Ireland (see Appendix E for the GINA guidelines). To be eligible patients had to already be prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (157,194) and, in addition, had at least one exacerbation that was treated with systemic glucocorticoids in the previous year. Asthma diagnosis was made using a clinician diagnosis supported by: obstructive spirometry with at least 12% reversibility or a positive bronchial provocation challenge or variability in the diurnal peak expiratory flow of more than 15%.

Exclusion criteria included an unwillingness to participate in a clinical study or prior hypersensitivity to salmeterol/fluticasone. Prior to randomization all patients provided written informed consent.

7.3.2 Randomization

Patients were block randomized by an electronic system and stratified by site. Block sizes varied from 8 to 12 and allocation was 1:1. Patients were enrolled and assigned to the intervention by the research nurse.

7.3.3 Active and Control Group

At recruitment, patients were randomized into active or control groups. Both groups received asthma and inhaler education. All were asked to measure their peak expiratory flow (PEFR) using an electronic monitor (ASMA-1, Vitalograph, Ireland) and to use their salmeterol/fluticasone Diskus™ inhaler one inhalation twice per day. Patients were also asked to list 3 specific goals they would like to achieve through better asthma control.

Over three consecutive months the active group received two further training sessions guided by visual feedback from information recorded to the INCA™ device on the regularity and proficiency of inhaler use and the development of habit of use. This was aligned to their goals and PEFR, so patients could see the relationship. The control group also received repeated inhaler training and asthma education focused on similar principles but without feedback (blinded) from the INCA™ device. All interventions (both active and control) were delivered either by a physician (myself) or a research nurse fully trained in the protocol.

7.3.4 Study design

The study design is summarized in Figure 7-1. The dose of inhaled corticosteroid and long acting beta-agonist (LABA) was not changed during the study although those prescribed formoterol/budesonide at recruitment were changed to a fixed dose salmeterol/fluticasone through a Diskus™ as the validation of the INCA™ device had not been established for the Turbohaler at the time of the study.

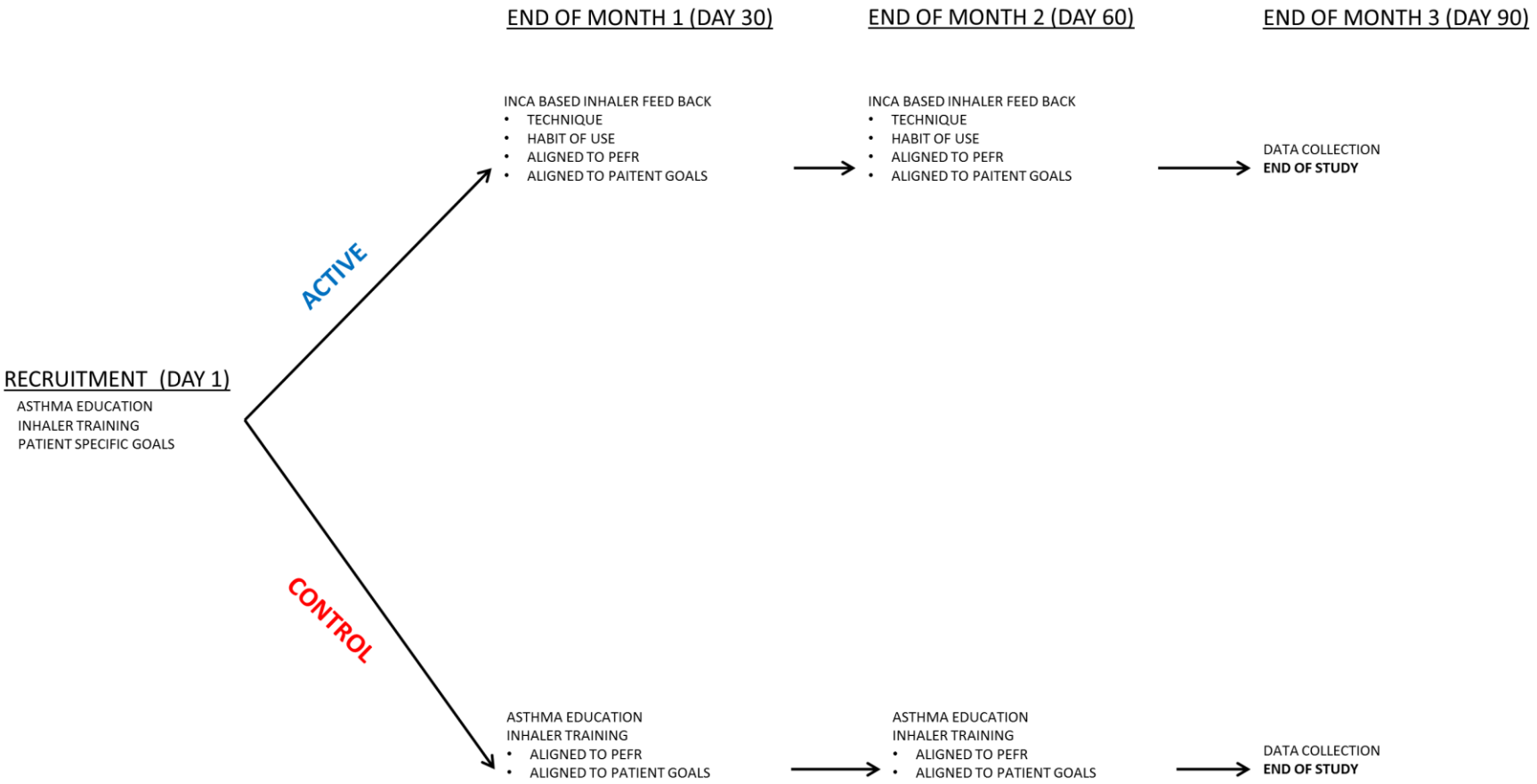

END OF MONTH 1 (DAY 30)
END OF MONTH 2 (DAY 60)
END OF MONTH 3 (DAY 90)
INCA BASED INHALER FEED BACK
• TECHNIQUE
• HABIT OF USE
• ALIGNED TO PEFR
• ALIGNED TO PAITENT GOALS
INCA BASED INHALER FEED BACK
• TECHNIQUE
• HABIT OF USE
• ALIGNED TO PEFR
• ALIGNED TO PAITENT GOALS
DATA COLLECTION
END OF STUDY
ACTIVE
RECRUITMENT (DAY 1)
ASTHMA EDUCATION
INHALER TRAINING
PATIENT SPECIFIC GOALS
CONTROL
ASTHMA EDUCATION
INHALER TRAINING
• ALIGNED TO PEFR
• ALIGNED TO PATIENT GOALS
ASTHMA EDUCATION
INHALER TRAINING
• ALIGNED TO PEFR
• ALIGNED TO PATIENT GOALS
DATA COLLECTION
END OF STUDY

Figure 7-1: Study Design:

OÁÔÉÅÎÔÓ ×ÉÔÈ ÕÎÃÏÎÔÒÏÌÌÅÄ ÐÁÒÔÉÁÌÌÙ ÕÎÃÏÎÔÒÏÌÌÅÄ ÁÓÔÈ Má ÏÎ ') . ! ÓÔÅÐ σ ÔÒÅÁÔ Í ÅÎÔ and at least 1 asthma exacerbation in the previous year were recruited to this study. Patients were randomized in a 1:1 fashion to either the active or control arm. All patients were seen by a nurse on a monthly basis receiving generalized inhaler assessment and training. At each visit patients filled out information on Asthma Quality of Life (AQLQ), Asthma Control Test (ACT), reliever use for the last month and any adverse events (including exacerbation) in the previous month. Each patient was given an INCA™ enabled salmeterol/fluticasone Diskus™ inhaler and an electronic peak flow at each visit. Patients in the active arm had their INCA™ device data downloaded at the ÅÎÄ ÏÆ ÅÁÃÈ Í Ï ÎÔÈ ÁÎÄ ÉÎÈÁÌÅÒ ÁÓÓÅÓÓ Í ÅÎÔ Á ÎÄ ÔÒÁÉÎÉÎÇ ×ÁÓ ÔÁÉÌÏÒÅÄ ÔÏ ÔÈÅ ÉÎÄÉÖÉÄÕÁÌßÓ ÐÒÅÖÉÏÕÓ Í Ï ÎÔÈÓß ÉÎÈÁÌÅÒ ÁÄÈÅÒÅÎÃÅ ¡ÉÎÃÌÕÄÉÎÇ ÔÉ Í Å ÏÆ ÕÓÅ ÁÎÄ ÔÅÃÈÉÑÕÅ ÏÆ ÕÓÅQß

At recruitment (Day 1) the patients received a new inhaler with the INCA^{TM} device attached, they were shown how to use the inhaler and errors were corrected using a 10 point checklist (the inhaler proficiency score, IPS (191-193).

At each subsequent month/visit the patient received a new inhaler with the INCA^{TM} device attached, they were asked to demonstrate their inhaler use, and errors were corrected in the control group using the IPS (191-193) or using visual feedback from the INCA^{TM} device in the active group.

A manual describing the exact steps of this method of inhaler adherence training has been published (190) and can be seen in Appendix F . Other data collected included, Asthma Quality of Life Questionnaire (AQLQ: Ranging from 1-7. A score ≥5 suggests better quality of life & a significant improvement is seen with an increase of ≥0.5) Asthma Control Test (ACT: Ranging from 5 to 25. An ACT>19 indicates well-controlled asthma & a significant improvement is seen with an increase ≥3.0), reliever medication use, PEFR and exacerbations were recorded each month. Due to an omission in the original protocol, the first 60 patients recruited did not have ACT recorded.

7.3.5 Study Endpoints

The primary endpoint in this study was the comparison of the Actual Adherence in month 3 between active and control groups. As described in Chapter 4, this measure of adherence incorporates the time of use, the interval between doses and technique of use, and is calculated as a ratio of expected drug accumulation if adherence had been perfect to what was actually taken.

Secondary endpoints included a comparison between the two groups in achievement of patient goals, change in Actual Adherence, change in AQLQ, change in ACT, change in inhaler reliever use and change in PEFR over the study period.

7.3.6 Sample Size

A sample size of 200 was estimated to have a power of 80% at the 0.05 significance level, with a 10% difference between the two study groups in the Actual Adherence rate and a 0.25 standard deviation assuming that the rate of Actual Adherence was 0.65 in the first month. The sample size baseline rate was based on inhaler adherence reported in primary/pharmacy care (Chapter 2), asthma patients (Chapter 4), COPD patients (Chapter 5) and the relatively modest effect of adherence interventions generally described (179). With an expected dropout rate of 10%, the target sample size to recruit was 220 patients.

7.3.7 Objective measurement of inhaler adherence and technique

The design, validation, and derivation of an automated algorithm and clinical use in a pilot cohort of the INCA^{TM} device have all been reported (106). Briefly, at the end of each month the audio files saved on the INCA^{TM} device are downloaded off the device and uploaded onto a secure webserver. Within the webserver is an automated algorithm then analyses each audio file, firstly identifying the presence of a drug blister (drug priming) and then searching for any inhaler technique errors. Compared to human raters this automated algorithm's accuracy was 83% in determining the correct inhaler technique (106). If an inhalation is present in the audio file the automated system will also analyse the inhalation profile and calculate the Peak Inspiratory Flow Rate (PIFR), as previously published (105,108,109). Proficiency of inhaler use was performed using this automated algorithm. Critical errors, identified in Chapter 3, included whether the drug was not primed, whether the patient exhaled into the inhaler after priming but before inhalation and if they had a low inspiratory flow. Non-critical errors such as not holding the device level, short breath holds or multiple inhalations indicating inadequate breath-holds were recorded and used in the feedback to the patient, to improve their proficiency. The automated process also outputs the date and time of each recorded inhaler use.

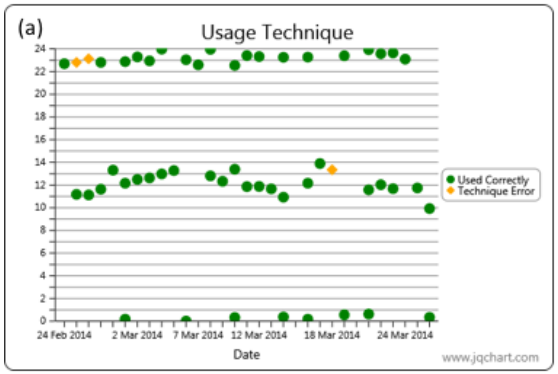
7.3.7.1 Habit of Use

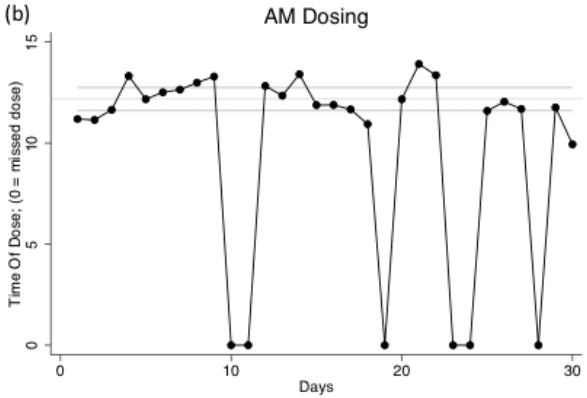
To help educate patients on their time of inhaler use, habit of use was also examined at each visit for patients randomized to the active arm. At each visit graphical representations of an individuals own inhaler use for the previous month was produced, see Figure 7-2 (a) and (c) for examples. To identify a regular habit of use control chart analysis was used to examine an individual's time of use (248-250). Control charts were produced for AM doses and PM doses separately and 3 standard deviations from the mean time was labelled as a violation, see Figure 7-2 (b), (c), (e) and (f). The total number of violations was divided by the number of Attempted Doses in the study period:

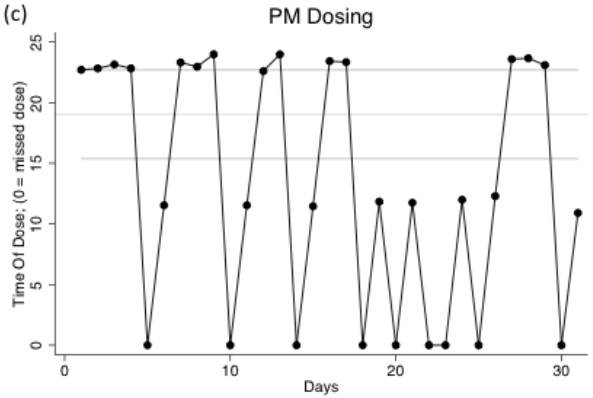
$$\text{AM Violation Rate} = \frac{\text{Number of AM Violations}}{\text{Number of AM Attempted Doses}}$$

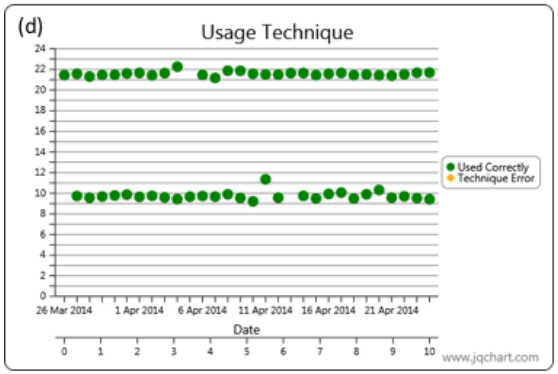
$$\text{PM Violation Rate} = \frac{\text{Number of PM Violations}}{\text{Number of PM Attempted Doses}}$$

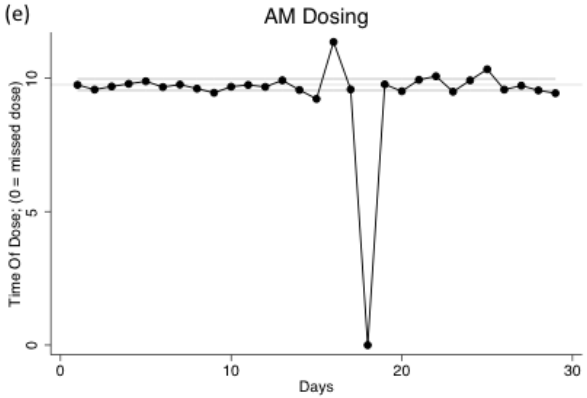
Greater than 20% violations per month in AM or PM were considered significant. Evidence of good habit was defined as a use of medication (Attempted Adherence) ≥80% of the time with a regular pattern of use in the morning or evening or both morning and evening (<20% violations for AM or PM or both).


(a)
Usage Technique
Used Correctly
Technique Error
24 Feb 2014
2 Mar 2014
7 Mar 2014
12 Mar 2014
18 Mar 2014
24 Mar 2014
Date
www.jqchart.com


(b)
AM Dosing
Time Of Dose; (0 = missed dose)
Days


(c)
PM Dosing
Time Of Dose; (0 = missed dose)
Days


(d)
Usage Technique
Used Correctly
Technique Error
26 Mar 2014
1 Apr 2014
6 Apr 2014
11 Apr 2014
16 Apr 2014
21 Apr 2014
Date
www.jqchart.com


(e)
AM Dosing
Time Of Dose; (0 = missed dose)
Days

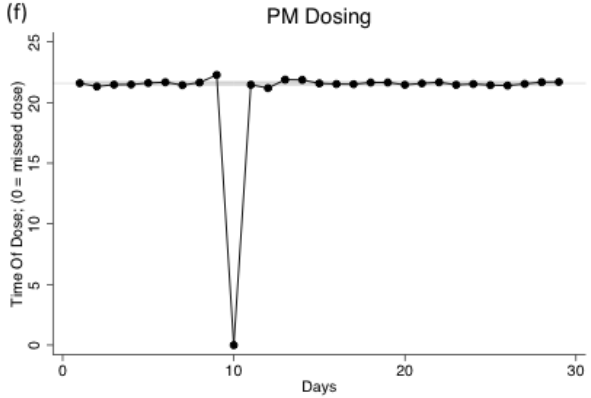

(f)
PM Dosing
Time Of Dose; (0 = missed dose)
Days

Figure 7-2: Control Chart Analysis for Habit of Use:

Figure (a) (b) and (c) are plots of inhaler adherence for a patient at Month 1, while &ÉÇÕÒÅÓ ¡ÄÇ‼ ¡ÅÇ ÁÎÄ ¡ÆÇ ÁÒÅ ÔÈÅ ÓÁÍÅ ÐÁÔÉÅÎÔ‰Ó ÉÎÈÁÌÅÒ ÁÄÈÅÒÅÎÃÅ ÁÔ - ÏÎÔÈ σ& ÏÒ ÁÌÌ figures, the x axis represents the date and the y axis is the time of day. In figures (a) and (d) a green dot indicates correct technique while a yellow diamond indicates poor inhaler technique. Figures (b) and Figures (e) are control charts for AM use of inhaler while Figures (c) and (f) are control charts for PM use of inhaler. In month 1, this patient had several violation points in AM (b) and PM (c) indicating poor inhaler habit ÆÏÒ ÂÏÔÈ ÄÏÓÅÓ‼ Í ÏÒÅ ÓÏ ÉÎ ÔÈÅ 0 - ÄÏÓÅÓ‼)Î Í ÏÎÔÈ σ‼ ÔÈÅ ÐÁÔÉÅÎÔ‰Ó ÈÁÂÉÔ É Í ÐÒÏÖÅÄ dramatically and has very few AM (e) and PM (f) violations suggesting good habit of use for both doses.

7.3.8 Statistical Analysis

All subjects who completed at least one month were included in an intention to treat (ITT) analysis of the primary outcome (n=205), Actual Adherence at month 3. In order to include participants with missing data in the analysis multiple imputation (MI) techniques (251) were used. This was done by imputing multiple complete data sets with Stata's mi command (*StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP*). Each data set was used and, according to the combination rules by Rubin, the obtained individual estimates consolidated into a single set of MI estimates (251). For month 1, 18 values were imputed. For month 2, 14 values were imputed. For month 3, 35 values were imputed. A secondary per protocol analysis was conducted.

Secondary endpoints were comparisons of components of errors in inhaler use, i.e. rates of overuse, underuse, critical errors and habit of use. Further predefined secondary endpoints as mentioned previously included comparison of active and control at month 3 for AQLQ, ACT, reliever use, PEFR and proportions of patients with refractory or difficult to control asthma at the end of the study (190). Post-hoc analysis included changes in Actual Adherence, AQLQ, ACT, reliever use and changes in PEFR. All continuous variables are presented as mean (SD) and categorical variables are presented as proportions (%). Between-group and within group comparisons were made for the mean change between baseline and end of study with the use of unpaired and paired t-tests, respectively and chi^2 analysis where required. In all cases, a 2-sided type I error of 0.05 was used. Additionally, an ordinary least squares (OLS) regression model, adjusted for baseline factors, was used to evaluate factors associated with Actual Adherence at the end of the study (GINA classification, smoking history, previous salmeterol/fluticasone Diskus™ use, and randomization).

7.4 RESULTS

7.4.1 Participants

Between February 2012 and December 2015, 220 patients (the required sample size) were recruited and randomized (111 to active and 109 to control) from five specialist asthma clinics across Ireland. During the study period there were 23-drop outs (10%). There were a total of 47 device failures (7%). There were no study related adverse events during the study period. The flow of patients through the study is shown in Figure 7-3

There were no significant differences in the characteristics between the active and control groups at randomization. The majority of patients were female, never smokers and tended to be overweight. All patients had a mean AQLQ of 3.7 and ACT of 12.1 with a mean use of oral steroids of 3.9 courses in the previous year, suggesting inadequate asthma control (Table 7-1). There was also a high incidence of atopy with a mean IgE level of 461 IU/ml.

I will now describe different adherence calculations for this patient population, comparing the active and control arms.

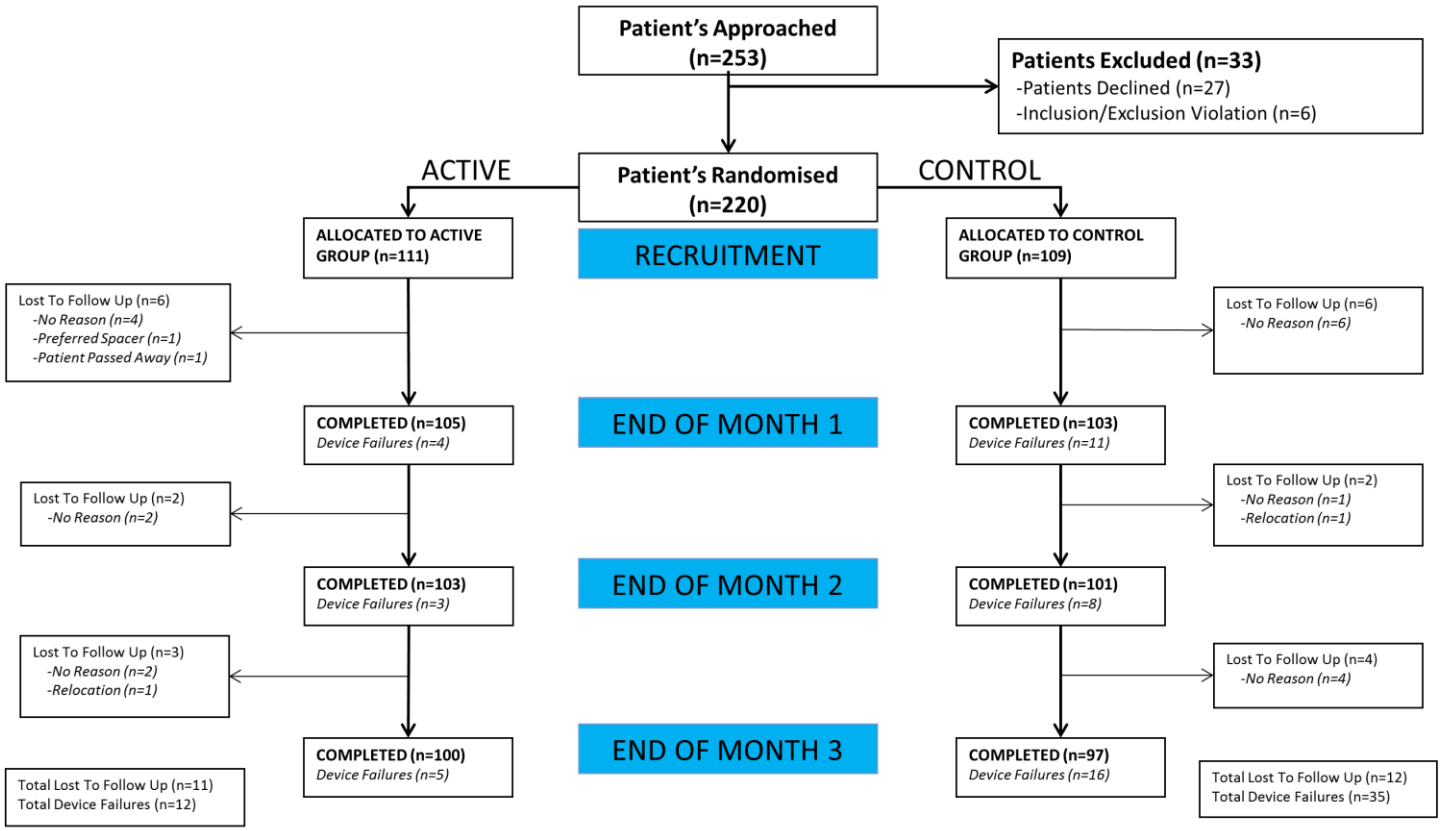


Figure 7-3: Study Flow:

220 patients were randomized to active and control arms. There were a total of 23 patients lost to follow up and 47 device failures over the 3-month study protocol.

Table 7-1: Patient Characteristics:

Baseline patient characteristics for all recruited patients presented as mean (SD) unless stated otherwise. *Atopy status was defined as a positive skin prick test response (wheal 3mm > than negative control) or a positive Radioallergosorbent test (RAST) result to airborne allergens. **Inhaler Proficiency Score is an inhaler technique 10 point checklist, ranging from 0 to 10 and 10 representing perfect inhaler technique. *Body Mass Index (BMI), Forced Expiratory Volume in 1 second (FEV_1), Long Acting Muscarinic Antagonist (LAMA), Global Initiative for Asthma (GINA), Asthma Quality of Life (AQLQ), Asthma Control Test (ACT), Peak Expiratory Flow Rate (PEFR)*

	ALL (N= 220)	ACTIVE (N=111)	CONTROL (N=109)	P VALUE
AGE (YRS)	49.2 (16.4)	48.3 (17.0)	50.1(15.9)	0.42
BMI	29.9 (7.0)	29.7 (7.5)	30.1 (6.4)	0.70
WOMEN (% PATIENTS)	64%	66%	62%	0.57
SMOKING HISTORY (% PATIENTS)	56% Never 36% Ex 8% Current	59% Never 36% Ex 5% Current	53% Never 36% Ex 11% Current	0.29
FEV_1 (L)	2.2 (0.9)	2.2 (0.8)	2.1 (0.9)	0.75
FEV_1 (% PREDICTED)	72.9 (22.0)	74.9 (20.9)	70.9 (23.1)	0.23
IGE (IU/ML)	461.1 (873.1)	428.8 (871.2)	494.3 (880.0)	0.65
SERUM EOSINOPHILS (IU/L)	0.3 (0.4)	0.3 (0.4)	0.4 (0.5)	0.34
*ATOPY (% PATIENTS)	57%	56%	58%	0.76
ORAL STEROID USE IN THE LAST YEAR	3.9 (3.4)	4.0 (3.7)	3.8 (3.2)	0.60
NO. EXACERBATIONS IN THE LAST YEAR	4.4 (3.5)	4.5 (3.8)	4.4 (3.3)	0.94
SALMETEROL/ FLUTICASONE DOSE (% PATIENTS)	36% 500 mcg/day 64% 1000 mcg/day	37% 500 mcg/day 63% 1000 mcg/day	35% 500 mcg/day 65% 1000 mcg/day	0.83
USE OF MONTELUKAST (% PATIENTS)	37%	35%	39%	0.57
USE OF LAMA (% PATIENTS)	16%	16%	17%	0.93
GINA CONTROL (% PATIENTS)	14% Partly Controlled 86% Uncontrolled	12% Partly Controlled 88% Uncontrolled	14% Partly Controlled 86% Uncontrolled	0.64
AQLQ	3.7 (1.2)	3.7 (1.2)	3.6 (1.2)	0.53
ACT	12.1 (4.5)	12.5 (4.6)	11.7 (4.3)	0.25
PEFR (L/MIN)	359.0 (132.1)	348.9 (119.2)	369.6 (144.5)	0.37
PEFR (% EXPECTED)	81.4 (23.5)	82.3 (22.9)	80.5 (24.2)	0.57
INHALER PROFICIENCY SCORE**	7.5 (2.7)	7.6 (2.6)	7.5 (2.8)	0.70

7.4.2 Inhaler adherence and technique

For this study, inhaler adherence was the primary outcome. Including all consented participants who had at least one month of calculated adherence (n=205, 105 active and 100 control), there was a significant difference in the primary outcome, favouring the active treatment group. The rate of Actual Adherence during the third month in the active group was 74% (95% Confidence Interval (C.I.) 69-77) vs. 64% (95% C.I. 59-71) in the control group, p≤0.01, see Figure 7-4(a).

7.4.2.1 Measuring Adherence Persistence

In this study, patients were monitored for 3 months with the INCA™ device. With this longitudinal follow up, the persistence and execution phases of adherence were calculated using the method described in Chapter 4.

Comparing active and control groups in a post-hoc analysis, there was significant difference in the change in Actual Adherence from month 1 to month 3, p=0.03. In the active group, the rate of adherence rose from month 1 to the end of the study by 7.1% (95% C.I. 2.5 - 11.7%), p=0.01 but fell in the control group -1.0% (95% C.I. -6.7-4.7), p=0.77. Over the three months more patients in the active arm (n=53) improved their adherence compared to the control arm (n=38), p=0.10 (Figure 7-4 (b)). By the third month only 14 (14%) patients in the active arm had an adherence rate <50% while 23 (26%) control patients had an Actual Adherence <50% at month 3 (p≤0.05).

Figure 7-4 (c) is an example of an active patient that, with INCA™ driven adherence training, improved their inhaler adherence, which lead to an improvement in PEFR and AQLQ.
In a per protocol analysis, excluding patients with missing data, a significant difference between active and control Actual Adherence at month 3 was still present, 75% vs. 64% respectively, p<0.01. By month 3 there was also a significant difference in the Attempted Adherence between active and control, 87% vs. 81%, p=0.02. This difference in adherence was not appreciated when the Average Adherence (from the dose counter) was used to calculate adherence, p=0.27, see Figure 7-5.

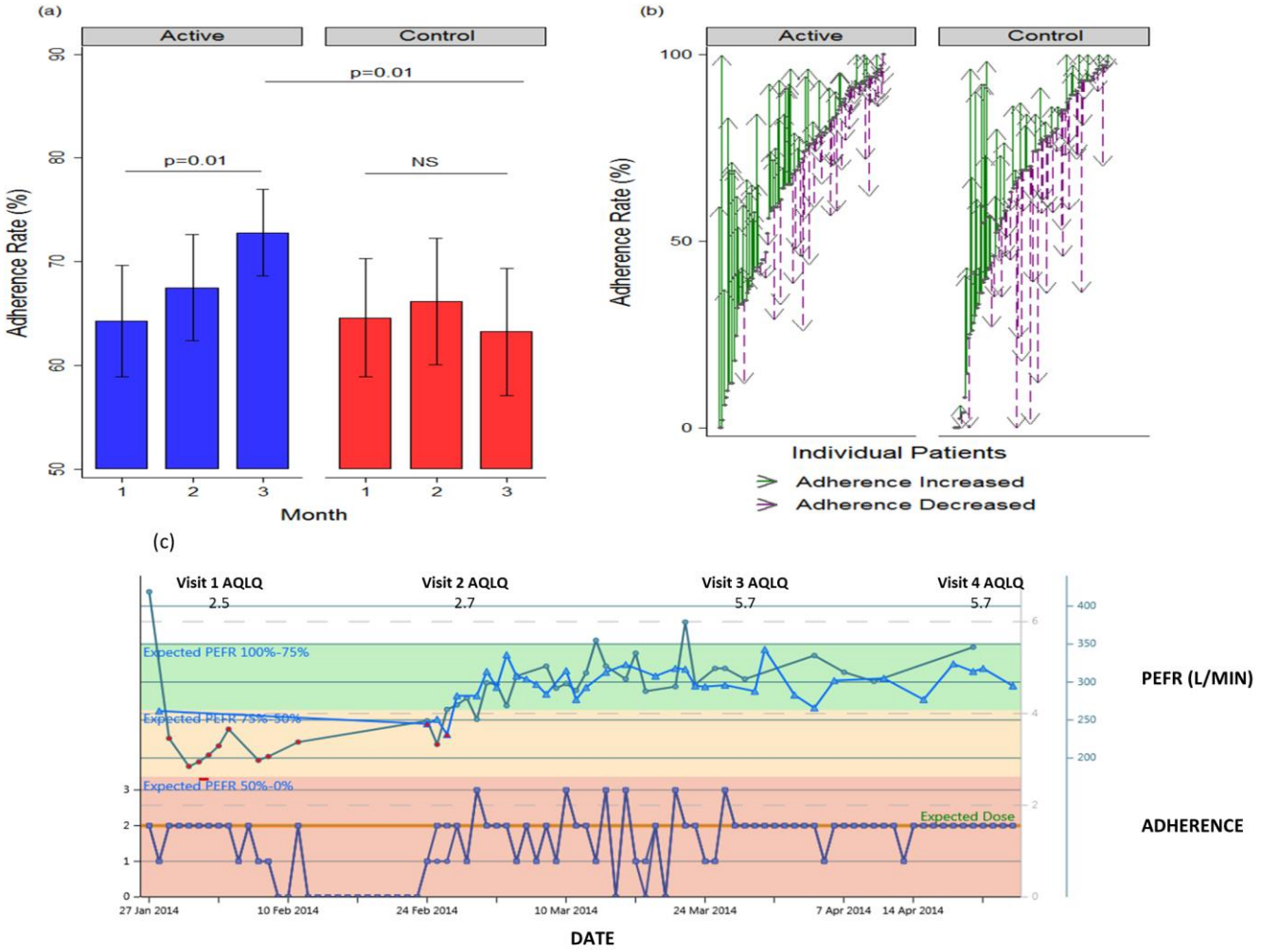

(a)
Active
Control
p=0.01
p=0.01
NS
Adherence Rate (%)
Month
(b)
Active
Control
Adherence Rate (%)
Individual Patients
Adherence Increased
Adherence Decreased
(c)
Visit 1 AQLQ
2.5
Visit 2 AQLQ
2.7
Visit 3 AQLQ
5.7
Visit 4 AQLQ
5.7
Expected PEFR 100%-75%
Expected PEFR 75%-50%
Expected PEFR 50%-0%
Expected Dose
PEFR (L/MIN)
ADHERENCE
27 Jan 2014
10 Feb 2014
24 Feb 2014
10 Mar 2014
24 Mar 2014
7 Apr 2014
14 Apr 2014
DATE

Figure 7-4: Inhaler Use Over 3 Months:

Actual Adherence, accounting for time of use, interval between doses and technique of use was calculated from INCA™ device data for each month. Patients in the active arm ÒÅÃÅÉÖÅÄ ÄÉÒÅÃÔÅÄ ÉÎÈÁÌÅÒ ÅÄÕÃÁÔÉÏ Æ ÏÒ Í ÕÌÁÔÅÄ ÂÙ ÔÈÅ ÐÒÅÖÉÏÕ Í ÏÎÔÈ ÉÎÈÁÌÅÒ adherence while patients in the control arm received monthly visits with a nurse and no review of their previous mÏÎÔÈ ÁÄÈÅÒÅÎÃÅ) Î &ÉÇÕÒÅ ¡ÁÇ ÐÁÔÉÅÎÔ ÉÎ ÔÈÅ ÁÃÔÉÖÅ ÁÒ Í ÈÁd a stepwise increase in their Actual Adherence for each month, there was a significant improvement in Actual Adherence between month 2 and month 3 (p=0.02) and between month 1 and month 3 (p=0.01). In the control arm this improvement was not seen, by month 3 there was a decrease in Actual Adherence, however this was not significant. Figure (b) illustrates the individual Actual Adherence rates of patients from month 1 to month 3. The overall month 3 Actual Adherence rate of control patients was significantly lower than that of the active patients. Figure (c) is an example of an active patient who started with variable adherence, low peak expiratory flow rate (PEFR, ● PM 2ÅÃÏÒÄÉÎÇÓ Ў ! - 2ÅÃÏÒÄings) and poor asthma quality of life (AQLQ). With INCA™ driven education on adherence, by month three this patient had a significant improvement in AQLQ and PEFR with stable adherence.

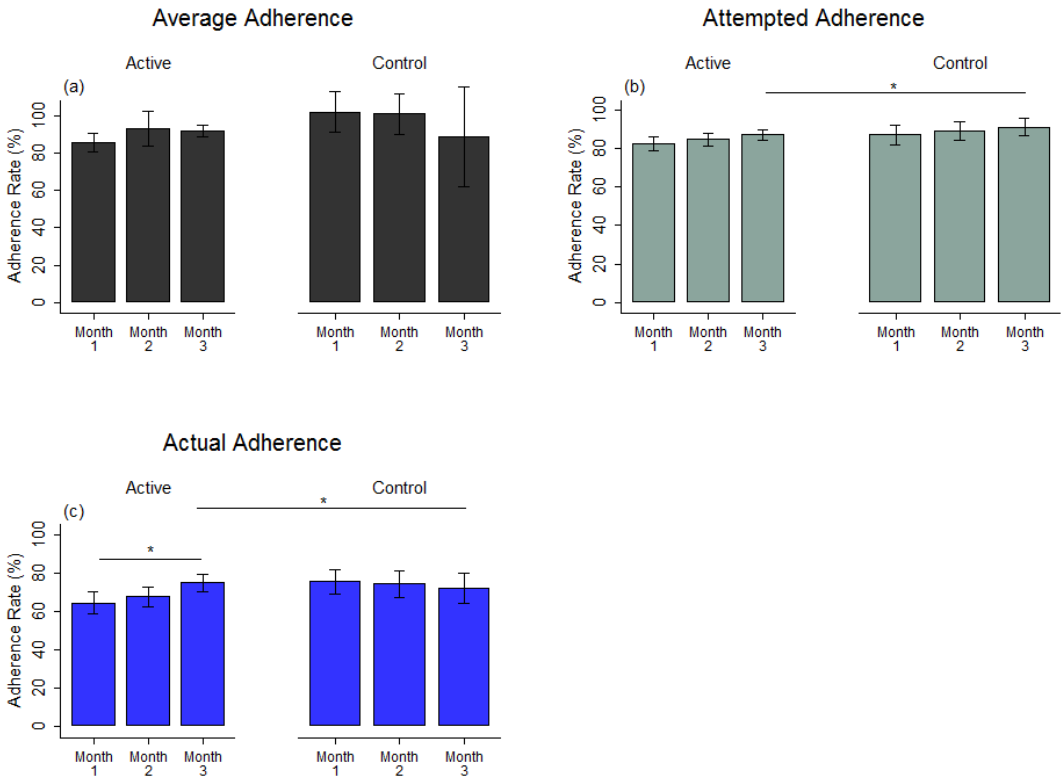


Figure 7-5: Per Protocol Analysis:

These figures compare the different adherence calculations in the per protocol analysis (removing any patients with missing adherence data). Figure (a) is the Average Adherence from the dose counter, using this measure of adherence there was no significant change in adherence over the 3 months and no significant difference between active and control arms. Figure (b) is the Attempted Adherence calculation. There was no significant change in adherence over the three months, but by month 3 the active arm had a significantly higher Attempted Adherence when compared to the control arm. Figure (c) represents the Actual Adherence method of calculating adherence. As described in Chapter 4, this method includes time of use, interval between doses and technique of use as a function of drug accumulation/drug delivery. With this method there was a significant increase in adherence from month 1 to month 3 for the active arm and by month 3 the active arm had a significantly higher adherence rate when compared to the control arm. *$p<0.05$

In an attempt to control for confounding factors an ordinary least squares (OLS) regression model with month 3 Actual Adherence as the dependent variable and age, body mass index (BMI), gender, FEV_1, smoking history, previous salmeterol/fluticasone Diskus™ use, month 1 Actual Adherence, randomisation and GINA classification at recruitment as independent/explanatory variables was completed. This model showed a significant difference in Actual Adherence at month 3, between active and control ($p \leq 0.03$). In this same model there was no significant relationship seen between age ($p=0.54$), BMI ($p=0.05$), gender ($p=0.62$), FEV_1 ($p=0.99$), smoking history ($p=0.94$), GINA classification ($p=0.24$) or previous salmeterol/fluticasone Diskus™ use ($p=0.26$) and Actual Adherence at month 3. There was a significant relationship between Actual Adherence at month 1 and month 3 ($p<0.01$). In an OLS model with the Average Adherence for month 3, there was no significant relationship between active and control.

The rates of technique errors, missed doses, over doses and habit of use were analysed by comparing active and control and the changes from month 1 to month 3, see Table 7-2 and Figure 4. Over the three months of the study period there were a total of 958 inhaler technique errors. The most common technique errors in the two groups were low peak inspiratory flow (PIFR) n=460 (48% of all errors) and exhalation into the Diskus™ before inhalation, n=397 (41% of all errors), both identified as critical technique errors in Chapter 3. Repeated training and feedback led to a reduction in these critical errors in inhaler use, as identified by audio analysis in the active group. At the end of month 3 both the rate of excessive dosing (more than 2 doses in a 24-hour period) and missed doses (less than 2 doses in a 24-hour period) were lower in the active group when compared to the control group, see Table 7-2. There were 14 episodes of dose dumping (more than 10 drug blisters within one audio file) in the control group and none in the active group. The number of patients with regular habitual use, in the evening/morning/both evening and morning, significantly improved in the active group ($p \leq 0.01$), see Figure 4 (d).

Table 7-2: Inhaler Adherence Calculations:

Different measures of adherence calculated over the three-month study period with between group and within group comparisons. Actual Adherence incorporates time of use, interval between doses and technique of use. Average adherence is the conventional method of calculating adherence with the dose counter. Attempted Adherence accounts for the amount of times a patient tried to take their inhaler while over doses and missed doses is the rate of over dose and missed doses for each month. Technique Error Rate is the rate of inhaler errors made per month. Evidence of habit is if a patient has an Attempted Adherence >80% and takes their inhaler at a regular time either in the morning or evening or both.

⁺Unless stated otherwise. *Comparing active and control. ***p<0.05 Comparing Month 1 ôÏ - Ï Î ôÈ χ♂ qÐ Ï τ♀τω # Ï Í ÐÁÒÉÎÇ - Ï Î ôÈ φ ôÏ - Ï Î ôÈ χ♂ dÐ Ï τ♀τω # Ï Í ÐÁÒÉÎÇ - Ï Î ôÈ υ ôÏ Month 2*

	Mean (SD)⁺		
Adherence Measurement	Active	Control	p value*
MONTH 1			
Actual Adherence	64.4 (27.8)	65.5 (27.0)	0.56
Average Adherence (dose counter)	86.8 (24.7)	92.3 (48.1)	0.33
Attempted Adherence	83.1 (18.0)	78.7 (21.7)	0.14
Over Doses	6.4 (9.0)	7.3 (10.6)	0.58
Missed Doses	17.5 (15.8)	19.7 (17.7)	0.38
Technique Error Rate	11.8 (20.4)	8.3 (18.8)	0.25
Evidence of Habit n (%)	5 (5%)	5 (5%)	0.98
MONTH 2			
Actual Adherence	67.5 (24.5)	66.2 (27.8)	0.73
Average Adherence (dose counter)	94.7 (48.2)	91.8 (48.2)	0.70
Attempted Adherence	85.5 (17.0)	81.0 (18.8)	0.10
Over Doses	4.4 (6.5)	6.4 (9.2)	0.11
Missed Doses	14.3 (15.9)	18.1 (17.1)	0.12
Technique Error Rate	12.2 (19.8)	7.7 (16.1)	0.10
Evidence of Habit n (%)	6 (7%)	2 (2%)	0.16
MONTH 3			
Actual Adherence	74.3 (21.6)**	63.6 (28.8)	0.03
Average Adherence (dose counter)	92.4 (15.0)	78.7 (112.8)	0.27
Attempted Adherence	88.1 (11.8)	81.4 (18.3)	0.01
Over Doses	3.4 (5.3)**	6.4 (9.1)	0.01
Missed Doses	11.8 (12.1)**	18.2 (16.9)	0.02
Technique Error Rate	7.4 (11.8)**†	9.0 (16.4)	0.48
Evidence of Habit n (%)	7 (9%) **	2 (3%)	0.11

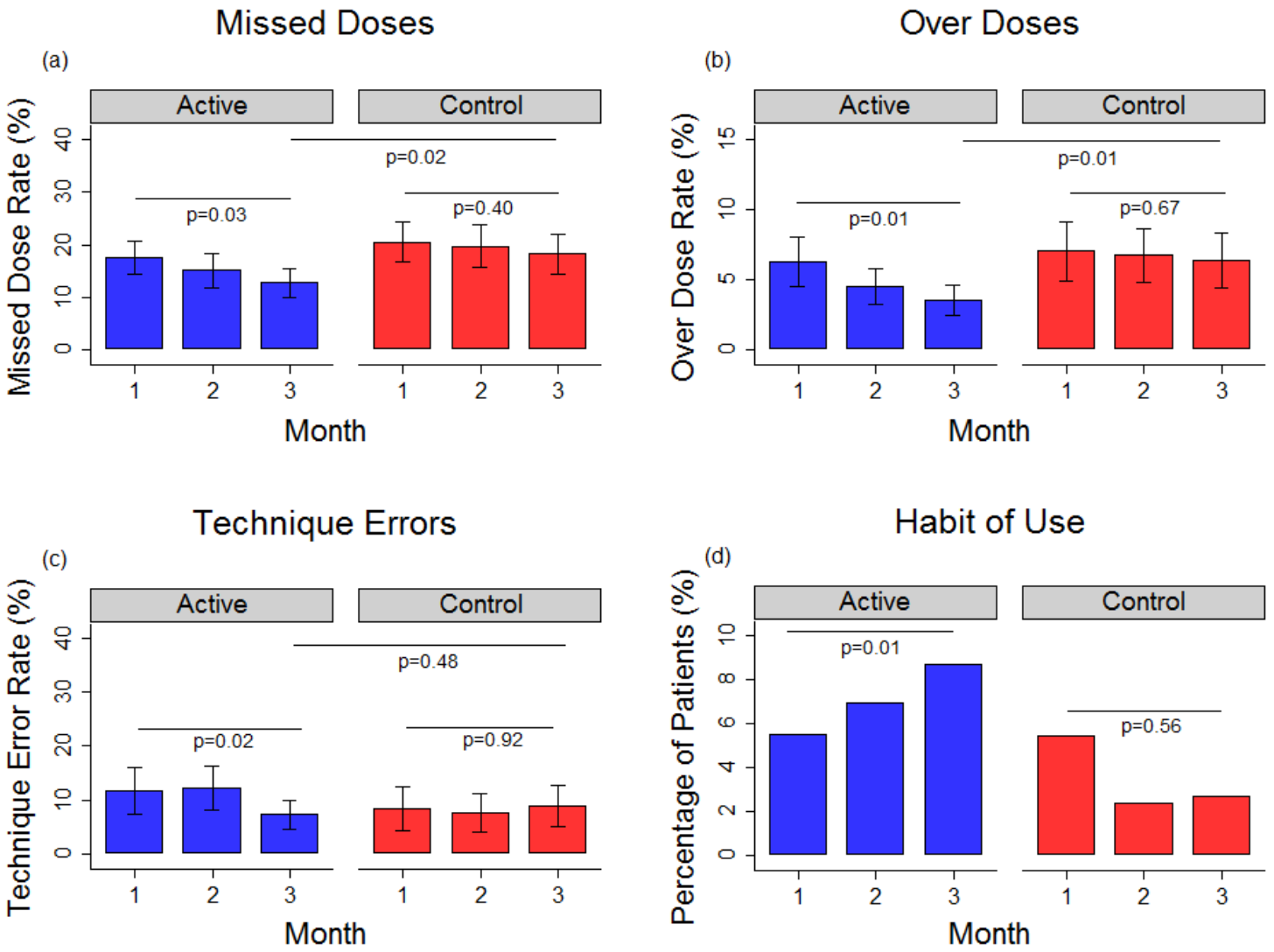

Missed Doses
(a)
Active
Control
p=0.02
p=0.03
p=0.40
Missed Dose Rate (%)
0
10
20
30
40
1
2
3
Month
Over Doses
(b)
p=0.01
p=0.01
p=0.67
Over Dose Rate (%)
0
5
10
15
Technique Errors
(c)
p=0.48
p=0.02
p=0.92
Technique Error Rate (%)
Habit of Use
(d)
p=0.01
p=0.56
Percentage of Patients (%)
0
2
4
6
8
10

Figure 7-6: Missed Doses, Over Doses, Technique Errors and Habit of Use:

In Figure (a) there was a significant reduction in the mean missed doses rate in the active arm. By month 3 there was a lower missed dose rate in the active arm than the control arm, ($p=0.02$). In Figure (b) there was a significant reduction in the over dose rate in the active arm, this was not the case for the control arm. By month 3 there was a lower over dose rate seen in the active arm when compared to the control arm, ($p=0.01$). With inhaler education aided by the INCA™ device, patients in the active arm had a significant fall in their Technique Error Rate, Figure (c). In Figure (d) with the active arm there was a significant increase in the proportion of patients that developed some evidence of a habit (either in the morning or in the evening and attempted to take their medication at least 80% of the time). This improvement was not seen in the control arm of this study.

7.4.3 Clinical Outcomes

In addition to inhaler adherence, clinical outcomes were evaluated in this patient cohort. The measured clinical outcomes, patient stated goals, AQLQ, ACT, GINA defined control, short acting beta-agonist reliever inhaler use and PEFR over time and between group comparisons are shown in Figure 7-7 and Table 7-3. In this section I will describe these clinical outcomes and their relationship with inhaler adherence.

7.4.3.1 Patient Goals

Patient identified goals were divided into 4 broad categories: physical, medical, social and emotional. The most common specific goal was to reduce symptoms (medical), 51% in active and 55% in control. Patient related goals were achieved by 68% in the active group and 61.5% in the control group, not significantly different. There was no significant difference in any of the adherence calculations, comparing those that achieved their goals and those that didn't.

7.4.3.2 Asthma Quality of Life

The asthma quality of life score, AQLQ rose above the minimal clinically important difference (MCID) of 0.5 in both groups (post-hoc), from 3.7 (1.2) at recruitment to 4.8 (1.4) at the end of month 3 in the active group ($p<0.01$) and 3.6 (1.2) to 4.6 (1.5) in the control group ($p<0.01$). In addition, AQLQ rose from the end of month 1 to the end of month 3 in both active ($p<0.01$) and control ($p=0.03$) groups, see Figure 7-1. Comparing active and control groups, there was no significant difference in the change of AQLQ from recruitment to the end of month 3, from the end of month 1 to the end of month 3, or when comparing AQLQ at month 3; $p=0.51$, $p=0.25$ and $p=0.17$ respectively. Sixty-four (65%) active and 62 (67%) control patients achieved a rise above the MCID for AQLQ.

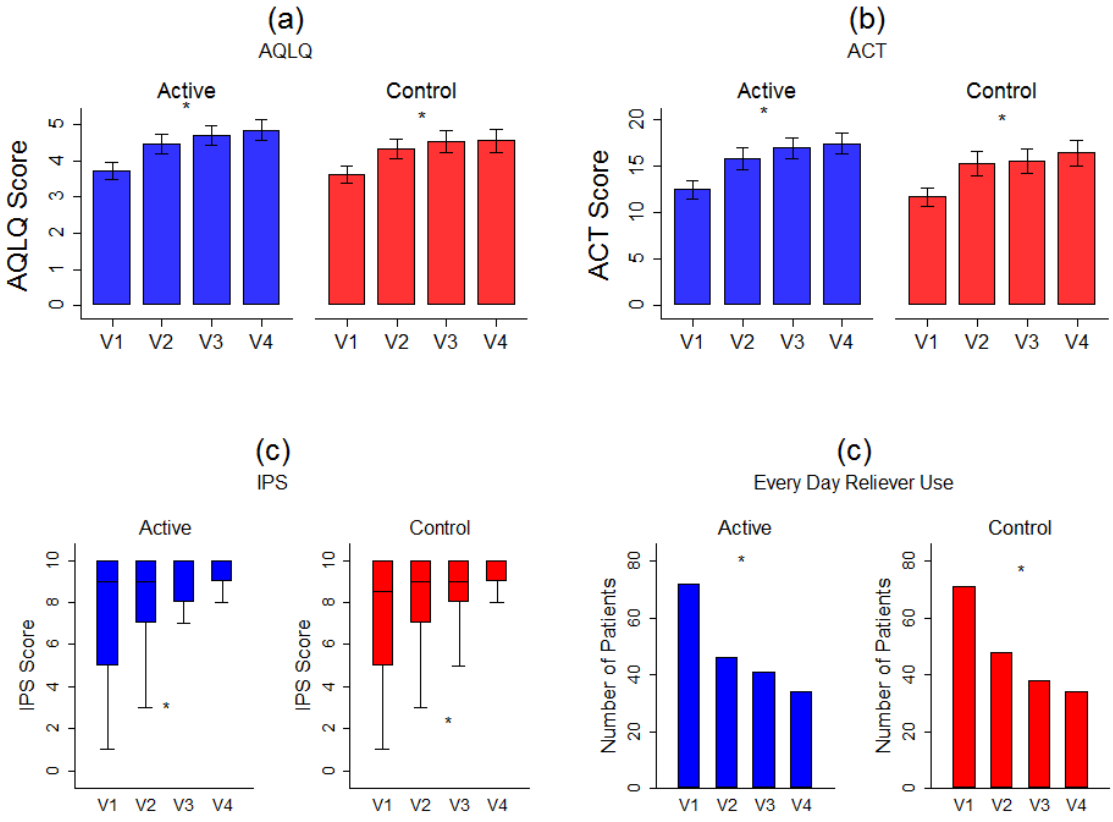


Figure 7-7: Clinical Outcomes:

In Figure (a) there was a significant improvement in Asthma Quality of Life (AQLQ) from recruitment to the end of the study for both active and control arms. In Figure (b) there was a significant improvement in Asthma Control Test (ACT) from recruitment to the end of the study for both active and control arms. In Figure (c) there was a significant improvement in Inhaler Proficiency (IPS) from recruitment to the end of the study for both active and control patients. In Figure (d) there was a significant reduction in the amount of patients that used their reliever salbutamol inhaler on an every day (or more) basis from recruitment to the end of the study for both active and control arms. There was no significant difference between active and control at month 3 for any of the clinical outcomes described. *p<0.01. *V1 = Recruitment, V2= End of Month 1, V3 = End of Month 2, V4 = End of Month 3.*

Table 7-3: Details of Clinical Outcomes over 3 Months:

Clinical outcomes from recruitment to the end of the study protocol. These included patient specific goals, Asthma Quality of Life (AQLQ), Asthma Control Test (ACT), Global Initiative for Asthma (GINA) defined controlled, partially controlled and uncontrolled, reliever use, and Peak Expiratory Flow Rate (PEFR). In this analysis, the reported p value comes from comparing the recruitment and end of month 3 values in active and control arms separately. There were no significant difference between active and control arms at either recruitment or end of Month 3. *Mean (SD).

	ACTIVE			CONTROL		
	Recruitment	End of Month 3	p value	Recruitment	End of Month 3	p value
Goals Achieved	-	67.6%	-	-	61.5%	-
Goals Subunits						
Physical	52%	25%	0.58	55%	30%	0.34
Medical	9%	25%	0.56	8%	22%	0.28
Social	30%	33%	0.16	34%	39%	0.46
Emotional	9%	17%	0.75	3%	9%	0.81
AQLQ*	3.7 (1.2)	4.8 (1.4)	<0.01	3.6 (1.2)	4.6 (1.5)	<0.01
ACT*	12.5 (4.6)	17.4 (5.1)	<0.01	11.7 (4.3)	16.4 (5.9)	<0.01
GINA Controlled	0%	7%		0%	7%	
GINA Partially Controlled	12%	27%	≤0.01	14%	26%	0.19
GINA Uncontrolled	88%	66%	<0.01	86%	67%	<0.01
Reliever Use Every Day	65%	35%	<0.01	67%	37%	<0.01
PEFR* (L/min)	377.3 (128.7)	378.1 (127.1)	0.92	373.5 (142.2)	374.8 (153.5)	0.96
% Expected PEFR*	82.3 (22.9)	83.5 (24.0)%	0.93	80.5 (24.1)	80.3 (27.1)	0.89

7.4.3.4 Asthma Control and GINA Control

Asthma control, assessed by ACT, increased in both groups (post-hoc) from 12.5 (4.6) to 17.4 (5.1) in the active arm ($p<0.01$) and 11.7 (4.3) to 16.4 (5.9) in the control arm ($p<0.01$), see Table 7-3. There was no significant difference in ACT between active and control arms at month 3, $p=0.26$. One hundred and six patients (51 active 55 control) achieved a change in ACT, from recruitment to the end of month 3, greater than or equal to the MCID (≥3), with no significant difference between active and control, see Figure 7-1 (c).

By the end of month 3, the number of partially controlled patients significantly increased only in the active arm [14 (12%) to 27 (27%) patients ($p\leq0.01$) in the active group and 15 (14%) to 24 (26%) patients ($p=0.19$) in the control group]. There was no significant difference in Average Adherence or Attempted Adherence between those who were GINA controlled and those who were partially controlled or uncontrolled. However, patients who were categorized as GINA controlled tended to have a higher Actual Adherence (80.6% vs 68.7%, $p=0.08$).

7.4.3.5 Reliever Use

In the active group, 74 (65%) patients used their short acting beta agonist reliever 1 or more inhalations per day. At the end of the intervention (post-hoc) this was reduced to 34 (35%) patients ($p<0.01$). In the control group short acting beta agonist reliever 1 or more inhalations per day reduced from 73 (67%) to 34 (37%) patients, ($p<0.01$). There was no significant difference comparing active and control, $p=0.75$, see Figure 7-7 (d).

7.4.3.6 Peak Expiratory Flow Rate

By month 3, active patients had a mean (SD) diurnal (AM, PM) variability of 3.5 (3.2), while control patients had a somewhat higher level of variability, 4.7 (4.2). However, this was not significantly different, $p=0.07$. Additionally, the expected PEFR ratio (as a percentage of the recorded value divided by the expected PEFR for age, sex and height of the patient) was slightly higher for active patients (83%) than the control patients (80%), $p=0.40$.

7.4.3.7 Uncontrolled patients

At the end of the 3 months' patients were categorized into 4 disease management groups based on inhaler adherence, asthma control and peak expiratory flow (lung physiology). Patients with adherence levels <80% fell into the group that needed more extensive inhaler training. Patients with good inhaler adherence but still symptomatic and poor lung physiology, fell into the group warranting increased medications or changing medications. Patients who were asymptomatic and had either good or poor adherence, needed to continue or reduce their inhaler medications respectively. Finally, there was a group of patients that remained symptomatic, with good adherence and good lung physiology. These patients suggested a review of diagnosis and co-morbidities (i.e. sinus disease or reflux disease).

At the end of the third month, 65 (32%) patients, (29 active and 36 control), were uncontrolled and had unstable PEFR. These patients could be considered to need further treatment. Of these uncontrolled patients, 24 (11%) patients (9 active, 15 control) patients were adherent >80%, hence required additional therapy. The remaining 41 patients (20%), 20 (49%) active patients and 21 (51%) control patients, had an average Actual Adherence rate of 51.8% and therefore required further intensive adherence counselling. When inhaler adherence was ignored, most patients would fall into the category suggesting increased or changed treatment. Similarly, when the Average Adherence was used to calculate inhaler adherence, most patients were considered adherent but still symptomatic, suggesting the need for increased or different treatment. When the Actual Adherence was calculated, most patients still had poor inhaler adherence and needed longer and more extensive inhaler training, see Figure 7-8.

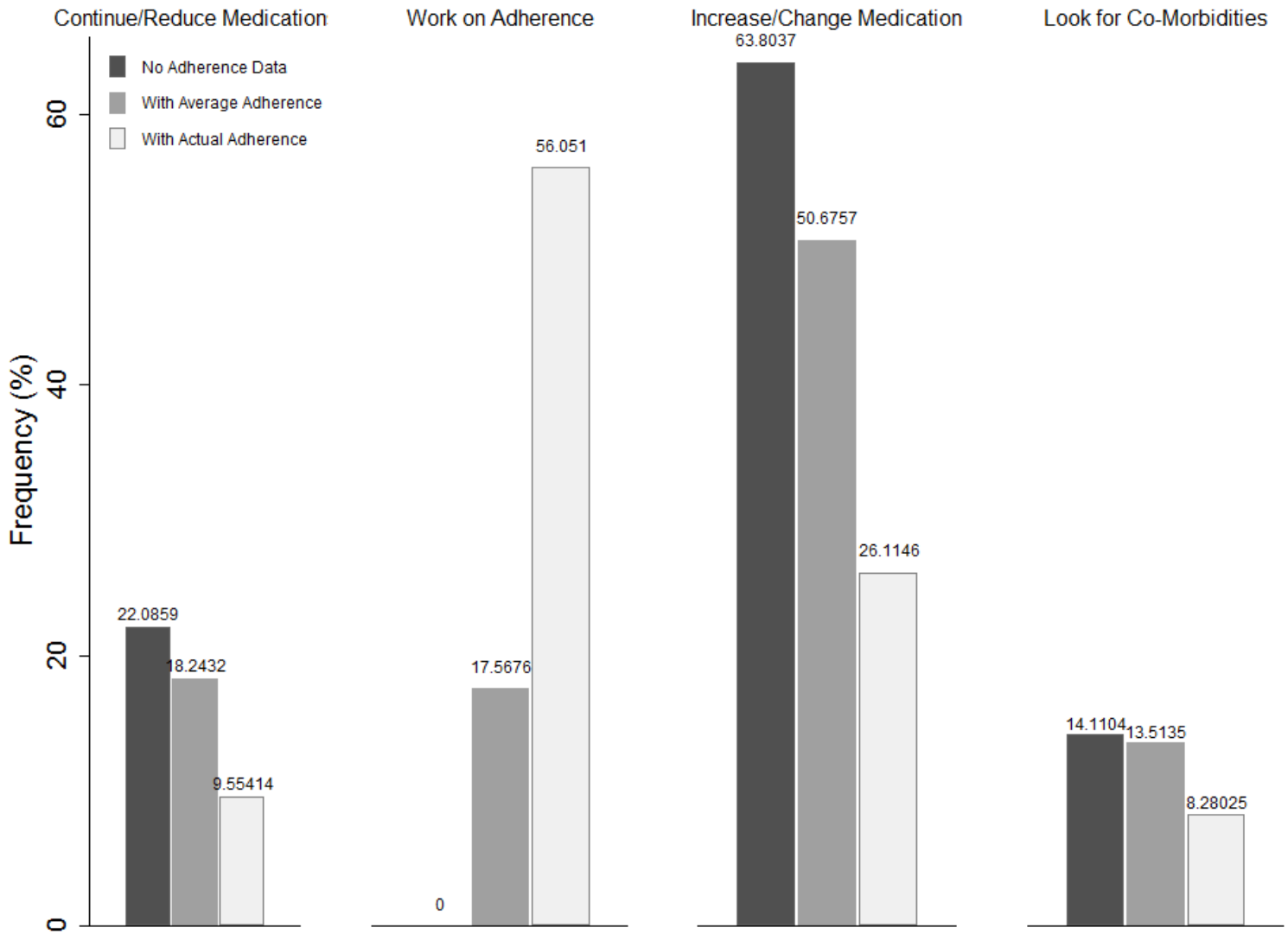

Continue/Reduce Medication
Work on Adherence
Increase/Change Medication
Look for Co-Morbidities
No Adherence Data
With Average Adherence
With Actual Adherence
Frequency (%)
0
20
40
60
22.0859
18.2432
9.55414
0
17.5676
56.051
63.8037
50.6757
26.1146
14.1104
13.5135
8.28025

Figure 7-8: Categorizing Patients:

At the end of this randomized trial, patients could be categorized into four possible groups. Those patients, who were asymptomatic and well controlled, could potentially have their medication continued or possibly reduced. Those patients whose inhaler adherence was poor would need more inhaler adherence education. Those patients who remain symptomatic after the trial but with seemingly good adherence would suggest increasing medication or changing treatment strategy. Finally, there was a group of patients who were symptomatic with seemingly good adherence and good peak expiratory flow; these patients fall into the group where the diagnosis of asthma and co-morbidities need to be reviewed. The majority of patients would have fallen in the category to increase or change medication. When adherence was calculated as the Average Adherence (from the dose counter) the majority of patients again would have fallen into the group where increasing or changing medications might be considered. However, when adherence was calculated as the Actual Adherence (incorporating time of use, interval between doses and technique of use), the majority of patients still had an adherence level <80% therefore requiring more intensive inhaler training rather than changing or increasing medications.

7.5 DISCUSSION

This study has shown that a strategy of repeated goal orientated asthma education focused on achieving these goals with visual feedback to the individual on their inhaler use, technique and habit significantly increased inhaler adherence in patients with uncontrolled asthma. Several clinical outcomes also occurred. Firstly, without changing the dose of their inhaler therapy, over 60% of all patients achieved significant improvements in asthma control. This is a notable feature of this study, as it shows the direct impact of improved adherence on clinical outcomes in patients with severe uncontrolled asthma. Secondly, among those who remained poorly controlled and had persisting airflow limitation 61% were poorly adherent, with a mean adherence of 52%, which may explain why they remained uncontrolled. Of the original cohort only 25 patients (12%) had both persisting airflow limitation and poor control but good adherence suggesting that they might benefit from additional therapy. Hence, incorporating visual feedback of digitally recorded adherence and peak flow is a practical way to direct management of patients with uncontrolled asthma before introducing additional medication(s). These findings provide an evidence base to the recommendations in the GINA strategy for asthma management (157,194,252).

The INCA^{TM} device used in this study is unique because by recording digital audio of the inhaler being used it can objectively assess when and how well the inhaler was used. Currently available electronic monitoring devices used to assess adherence only identify when an inhaler has been used. In prior studies the validity of the device has been tested, proving that audio is a suitable way for assessing critical errors in inhaler use and an automated algorithm to rapidly process this information in the clinic to produce graphical reports for the clinician to use for immediate feedback to patient has been developed (105-109,153,227,228,253). The information recorded to the INCA^{TM} device, including both critical errors in inhaler use, along with missed and significantly delayed inhaler use were combined into a new method of calculating adherence (described in Chapter 4) which is calculated as an area under the curve (AUC). In previous chapters this method of calculating adherence was used to report on the execution phase of adherence (Chapter 4 and Chapter 5) and this method correlates with clinical outcomes (Chapter 4 and Chapter 6), in comparison to the current method of calculating adherence (the Average Adherence). In

this chapter this method was used to describe adherence to therapy over time, inhaler persistence.

A Cochrane review of 109 RCTs in medication adherence found only 5 RCTs that showed any improvement in adherence and at most, limited improvements (179), typically increasing adherence to a level of about 60%. All of these studies used the Average Adherence as the method of calculating adherence. In this study, both active and control groups achieved very high levels of Actual Adherence, over 64% in the control group and 74% in the active group. This change in this persistence phase of adherence was not evident when the Average Adherence was used as the measure of adherence. With inhaler education guided by information on time of use, interval between doses, habit of use and technique of use, patients in the active group increased (absolute improvement) their inhaler adherence by about 10% over 3 months. This is at the higher level of results seen in prior adherence interventions (179). However, prior studies that have achieved similar significant improvements often involved more intensive psychological based interventions, something that is not possible for non-specialists to deliver.

All the literature highlights that education and inhaler training should be given to all patients. Interventions with objective evidence of effectiveness in improving adherence in asthma include those that incorporate feedback on adherence, inhaler training and audio-reminders, but not all have been tested in the setting of specialist clinics caring for patients with severe asthma (247,254-256). However, while adherence strategies are emphasized they do not specify how often education and inhaler training should be given and what behavioural principles best optimize adherence.

The intervention in this trial used a goal orientated method of promoting adherence and addressed three common and important causes of poor adherence (239,257). Firstly, barriers to access to asthma medications were overcome as both groups were given INCA™ adapted salmeterol/fluticasone inhalers each month. Secondly, since inadequate comprehension of key clinical messages is a common cause of poor adherence, the intervention repeatedly reinforced key messages on regular habit formation of inhaler use, inhaler technique and asthma education at the end of each month. Thirdly, at each of these visits the focus was on the patient's own reported goals for asthma outcomes. Having

consecutive visits over three months allowed sufficient time for the medication to achieve clinically meaningful improvements, which was used to show that the patient goals were being achieved. While both groups had a comprehensive intervention the discussion with the active group was supported by visualization of their own data. The feedback given to the active group required relatively little specific training and is feasible to deliver in clinical care without using advanced psychological interventions. Additionally, as the intervention was straightforward and easy to deliver, there was no deviation from the protocol (Appendix F) and the intervention was delivered as intended.

In most clinical trials of patients with severe asthma, as in this study, most patients have improved clinical outcomes, often called the "trial effect", the mechanism of this observation is poorly understood. Both groups in this study did achieve improvements in clinically meaningful outcomes, but this was achieved without changing the dose of the medication prescribed. The strength of this study is that it describes a practical intervention that was effective in achieving good clinical outcomes in the majority of patients, which could be implemented within clinical services. The feedback takes less than 10 minutes to perform, further <10% who were approached to participate in the trial refused to do so because of their concerns that they were having direct monitoring and only 10% of patients dropped out from the study.

Inhaler training tends to be performed only at a patient's first visit. In this study repeated inhaler training, education and feedback led to significant improvements, which suggest that using this approach in future studies may improve participant retention and adherence. Even in this short adherence focused study adherence was not perfect as almost 23% of the control patients had adherence <50% during the third month. This poor adherence was not detected by counting the doses on the dose counter, where only 3% had an average adherence <50%, because a mechanical counter cannot identify inhaler errors or dose dumping. This finding indicates that adherence by patients within clinical trials cannot be assumed to be good. The unintentional inclusion of poorly adherent patients in clinical trials, even if they are randomized equally to both arms, reduces the clinical effect size of the study (258,259), meaning that good treatments may be inappropriately deemed to be infective. Hence, future trials of patients with severe asthma might include an assessment of adherence with electronic devices both during the run-in period and in the intervention

phase of the study.

7.5.1 Limitations

Limitations of the study include the short follow-up, which will be addressed in a currently recruiting follow on study, INCA Sun (NCT02307669). This will incorporate information on the biomarker profile of the patients and a measure of cost effectiveness of the intervention. The longer observation period may aid in observing further improvements in clinical outcomes in patients whose inhaler adherence improves. Another limitation is the regular visits patients in the control arm received. With the monthly visits, patients were seen more frequently when compared to a standard out patient setting, which may have translated into an improvement in clinical outcomes (i.e. AQLQ and ACT) similar to the active arm. To truly see a relationship with improvements in persistence inhaler adherence, not only will a longer trial be needed, but also infrequent visits to cut down the "trial effect." A further limitation of this study was the use of a single inhaler device, which meant that some patients switched from other devices, to the Diskus™ device. All of these people were fully trained in the use of the Diskus™ at the first visit and the rates of adherence and clinical outcomes of these patients were not significantly different than those who did not change over, suggesting that this is not a confounding issue in interpreting the results of this study.

7.6 CONCLUSION

Inhaler technique is an important feature of inhaler adherence that needs to be focused on. I have proven that inhaler technique has a significant impact on drug delivery (Chapter 3) and is therefore integral to the calculation of inhaler adherence (Chapter 4). In this chapter I developed an asthma education program that focuses on inhaler technique in addition to time of use and habit of use. By focusing on these elements of inhaler use, I was able to show a significant improvement in inhaler adherence (a change in persistence). Using the Average Adherence to calculate adherence (where technique of use and habit of use is ignored), there was no significant change in adherence, just a persistently and artificially high level of adherence.

The data in this chapter suggest that without increasing therapy repeated inhaler training, in particular when it incorporates the individuals own inhaler technique of use, leads to significant clinical improvements for patients with uncontrolled asthma on GINA step 3-5 therapy. Clinicians may also benefit from the use of this intervention and this calculation of inhaler adherence in the care of patients with asthma to help them decide whether a patient requires further advanced treatments or interventions to understand and address their patient's barriers to medication adherence.

Chapter 8 **:**

CONCLUSIONS AND FUTURE DIRECTIONS

8.1 INTRODUCTION

There were several aims and intentions of this project focusing on inhaler adherence. The currently used method of calculating inhaler adherence is averaging the number of doses taken (recorded by the inhaler dose counter) divided by the number of doses prescribed. This method has the risk of averaging adherence over time, thus not a true reflection of medication use, and ignores the interval between doses and the technique of inhaler use. My first query was; what inhaler errors do patients make? I then wanted to show how each of these errors impact on drug delivery. My aim was to then use this information in developing a new method of calculating inhaler adherence that incorporates all the crucial components of inhaler adherence (time of use, interval between doses and technique of use). With this method, I then tested its validity and clinical significance in different patient populations. After reporting on inhaler adherence in these populations, another aim of this project was to identify what factors lead to poor inhaler adherence and if there were any particular patterns of inhaler use that would help clinicians develop an intervention to improve inhaler adherence. Lastly, I tested the hypothesis that an education intervention directed at correcting errors in inhaler time and technique of use would lead to improved inhaler adherence and thus clinical outcomes.

8.2 SKILLS AND LEARNING DEVELOPMENT

Durring the three years of this project I was part of a research team. All study design, data collection, data management, data analysis and writing of this thesis was performed by me. I learnt and developed several skills during this process. I have become highly proficient in data managmenet and, with the addition of courses in biostatistics, I am comfortable doing both straightforward and high level data analysis. I am also proficient in data collection for observational studies and running a randomised clinical trial. Through this process I am also comfortable in designing studies and acquiring ethical approval for clinical studies.

8.3 A SUMMARY OF THE FINDINGS AND FUTURE DIRECTIONS

Within this thesis I have reported several interesting findings with the use of a novel electronic inhaler adherence monitor. I initially used this device (INCA^{TM}) to report on

inhaler adherence in a community setting. By doing so I identified several common inhaler technique errors. This has implications for the use of INCA^{TM} technology in both a clinical and reserach setting. As highlighted in Chapter 1 (Section 1.4.3) , the curently available inhaler adherence monitors are unable to provide longitudnal information on inhaler technique. Having identified common inhaler errors I then went on to prove that only two errors significantly impacted on drug delivery. These were exhalation into the device after drug priming and before inhalation and a low peak inspiratory flow rate. These were two of the most common errors identified and these finding have significant clinical implications. In such that, patients who make these errors do not get adequate inhaled drug delivery and may remain symptomatic or may even be treated innapropriately. Highligthed in Chapter 1 (Section 1.2.7), randomised control trials rarely report on adherence and those involving inhalers never report on longitudinal inhaler technique. The findings from this thesis have implications to the findings in these studies, where patients in these studies may be making critical inhaler errors, leading to outcomes that may not hold true for patients who don't make these errors. As expected, missing doses also led to a reduction in drug delivery.

Having identified how imporant inhaler technique is as a component of inhaler adherence, I used these concepts of drug delivery and pharmacokinetics, from Chapter 3, to develop a new method of calculating inhaler adherence that incorporates time of use, interval between doses and technique of use into a function of drug accumulation and drug delivery. This calculation was more reflective of clinical outcomes than the currently used Average Adherence (Section 1.5). In a clinical setting, this method is a good tool for clinicians to use while trying to decide on treatment strategies based on prior adherence as it provides a more comprehensive model of inhaler adherence. As each inhaler technique error has a different impact on drug delivery and therefore inhaler adherence, future work would involve fine tuning this method of calculating adherence to weight each error separately. With the advent of the INCA^{TM} device and the audio recordings, severity of the error could even be measured and incorporated into the adherence calculation. I believe there is more to be done examining the peaks and troughs of drug delivery in relation to time of use and technique of use. These concepts need to be further evaluated and potentially incorporated into this method of calculating inhaler adherence. From a research point of

view, precise knowledge of drug delivery would be useful for research studies and medication assessment of drugs such as inhaled antibiotics.

Nonetheless, this new method of calculating adherence proved to have a stronger relationship with clinical outcomes than the commonly used method of calculating adherence (the Average Adherence) in both severe asthma patients and severe Chronic Obstructive Pulmonary Disease (COPD) patients. Of critical importance, I was able to prove that COPD patients with poor inhaler adherence had a higher incidence of exacerbations in a one month follow up. As I disucssed in Chapter 1 (Section 1.3.4), inhaler adherence in COPD has been poorly published. The relationship of exacerbations and adhernece is an important concept that has implications both for clinical practice and future research. For studies that look at new inhalers to reduce exacerbations, this method of calculating adherence would seem to be the most appropriate method. However, future work would need to be completed, possibly by extending this study up to 90 days to collect more information on exacerbations and examine persistence of inhaler adherence in this patient cohort. The relationship with inhaler adherence and exacerbations would also need to be tested in another population of patients that regularly use inhaled medications, such as asthma. In doing so, the relationship of inhaler technique and inhaler adherence with clinical outcomes becomes even stronger in addition to assessing use.

Incorporating these key components of inhaler adherence into one metric led to a much lower level of adherence than previously thought with the Average Adherence. Interestingly, I identified several factors that predicted good inhaler adherence with this new method of calculating adherence, none of which have been previously identified (Chapter 1, Section 1.6). These included adequate cough peak expiratory flow rate (which may suggest good lung function), good cognition and a low level of co-morbid disease. I also identified 3 different patterns of inhaler use: there are patients who use their inhaler regularly and with good technique, those who use it regularly but with poor technique and those who use their inhaler irregularly and with poor technique. These findings can be used to develop adherence interventions guiding clinicians to the most approriate method for improving adherence. For example, those patients who take their inhaler regularly but incorrectly need more focus on inhaler technique while reminders would not be useful.

These patterns and predictors of inhaler adherence were tested on a group of COPD patients being discharged from a tertiary hospital. Again, it would be important to validate these findings in a different population of patients, such as a cohort of patients with asthma.

I have shown that an education intervention aimed at improving inhaler technique, in a population of severe asthmatics, leads to improved inhaler adherence over a three month follow up and improved clinical outcomes. This education intervention, based on some of the interventions mentioned in Chapter 1 (Section 1.7), was simple to learn and straightforward to deliver. Therfore, this intervention may be a useful tool in a severe asthma clinic, not only to help improve inhaler adherence but also to properly categorise patients before changing therapy. With regards to COPD more research is needed. For example an education intervention aimed at improving inhaler adherence in a severe COPD population would be of interest. With the identification of factors that lead to poor inhaler adherence, as mentioned previously, this intervention can be individualized.

Lastly, all my research has been with the INCA™ device attached to a Diskus™ inhaler. I do believe that my findings are generalizable to any inhaler device, however this will need to tested on all available inhaler devices in future work (identified in Section 1.3).

8.4 CONCLUDING REMARKS

Overall form this research I have answered several questions regarding inhaler adherence and the importance of inhaler technique, leading to the development of a robust method of calculating inhaler adherence that incorporates inhaler time of use, interval between doses and inhaler technique into a single measure that strongly correlates with clinical outcomes in patients with respiratory disease. I have also shown that an intervention geared at improving inhaler technique leads to improved inhaler adherence. The identification of inhaler patters and predictors of inhaler adherence will aid in further development of interventions aimed at improving inhaler adherence.

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Appendix A

The INhaler Compliance Assessment Device (INCA)

In collaboration with the Royal College of Surgeons in Ireland (RCSI) and Trinity College Dublin (TCD) a novel device to longitudinally measure patient inhaler use has been developed. The mechanical development of this device was lead by the Bioengineering department in TCD. The INhaler Compliance Assessment (INCA™) is a plastic device that houses a microphone, a memory card, a battery, a clock and some micro-circuitry. Currently the device is built for the Diskus™ Inhaler and sits directly on top of the inhaler, Figure A-1.

Figure A-1: The INCA Device:

In this image the INCA™ device is sitting on top of a salmeterol/fluticasone Diskus™ inhaler. The Inhaler is closed in this image, once opened the INCA™ is then activated. Device serial number and medication information (i.e. dose) are written on the top label of the device.

The operation of the INCA™ device is as follows: When the Diskus™ inhaler is opened the INCA™ device is activated (to confirm activation a hidden light can be accessed, and will be green if the device is turned on). Once active the INCA™ device begins recording an audio

file through the microphone. This audio file, a mono WAV file (sampling rate of 8000Hz and resolution of 8bits/sample) is saved to the memory card with a specific file name containing the device number, and the date and time of the audio recording. This recording continues up till 90 seconds, or when the Diskus™ inhaler is closed; whichever occurs first.

Once the inhaler has been used for a prescribed time period, the INCA™ device can be removed from the inhaler and by way of a USB cable is connected to a computer (see Figure A-2). Through this process all the audio files saved on the memory card can be downloaded directly to any computer.

Figure A-2: The Back of the INCA Device:

In this image the INCA™ device has been removed from the inhaler and the back of the device is revealed. Here, on the back of the device, there is a serial connection port for a serial to USB cable, allowing all saved audio files to be downloaded directly from the device to a computer for analysis.

Theses audio files provide two valuable pieces of information regarding patient inhaler use. Firstly, with the onboard clock, we know when patients attempted to use their inhalers; therefore, we have information on missed dosing, over dosing and interval between doses. Secondly with a more detailed analysis of the acoustic profile of each audio file we have information on how the patient used their inhaler

Currently analysis of theses audio files follows two methods:

1. The first method involves a human 'over reader' listening to each audio file. In each audio file the first priority is to identify acoustic evidence of drug priming, suggested the patient attempted to take a dose in that audio file. In the files where drug priming is identified the 'over reader' then classifies the technique of use according to pre set rules, see Table A-1. See Appendix B for examples of audio files with technique errors. For this method of analysis, agreement of audio files between two raters is 81%. Disagreements are reconciled by consensus agreement with a third person. Most of the differences observed between raters are due to the classification decision of poor inspiratory flow. In light of this, an automated acoustic analysis algorithm was developed to assess the precise peak inspiratory flow rate achieved by the participant for each event.

2. The second method is an automated signal-processing algorithm developed by the team in TCD (106). For this method all the audio files for one device are fed into an automated algorithm that analyses each audio file looking for specific events: i.e. Drug Blister, Adequate Inhalation, and any inhaler errors. With this automated process a quick output is generated that gives information on doses that that the patient attempted, missed, over dosed and made technique errors in as well as the estimated flow rate of the recorded inhalation.

Table A-1: Over Reading of Audio Files:

Rules for Classification and Error Types. If classification is 2, human over reader or algorithm moves to Error Column and decides on the error type.

	Classification		Error
0	No drug blister or inhalation (i.e. Empty file)		
1	Used Correctly		
2	Drug Blister present, but there is a technique error	→	**1** Multiple Inhalations **2** Multiple Blisters **3** Multiple Blisters & Multiple Inhalations **4** Exhalation into the mouthpiece after Drug Blister and before Inhalation **4.5** Breath Holding after inhalation < 10 seconds **5** Drug Dumping **6** No Blister detected, inhalation present **7** Blister detected, no inhalation present **8** No Blister & No Inhalation present **9** Weak Inhalation (PIFR < 35L/min) **10** Multiple Errors

Appendix B

Acoustic Profiles of Inhaler Use

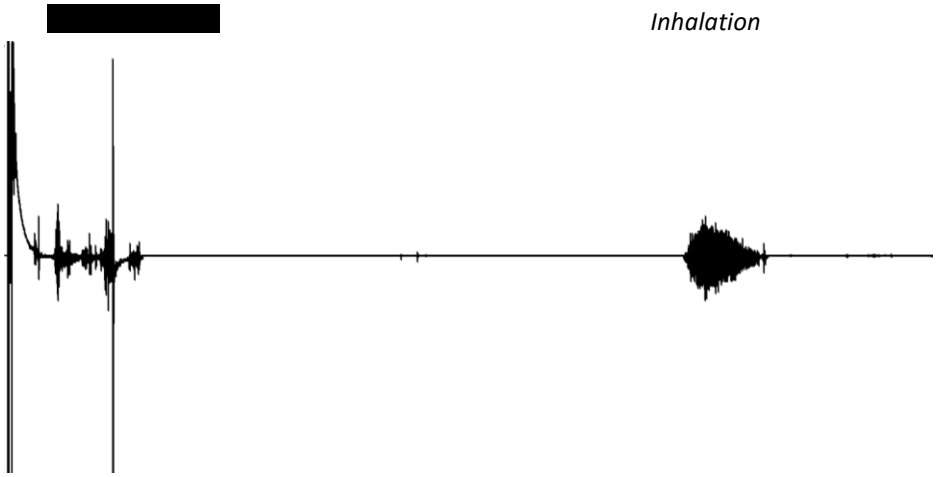


Figure B-1: Good Inhaler Technique:

This is an audio-image of a patient using their inhaler with good inhaler technique. There is a clear drug blister followed by a short but powerful inhalation. An audio example of this error can be heard at:
https://www.dropbox.com/s/isz4rn29yinmesm/GOODUSE.wav?dl=0

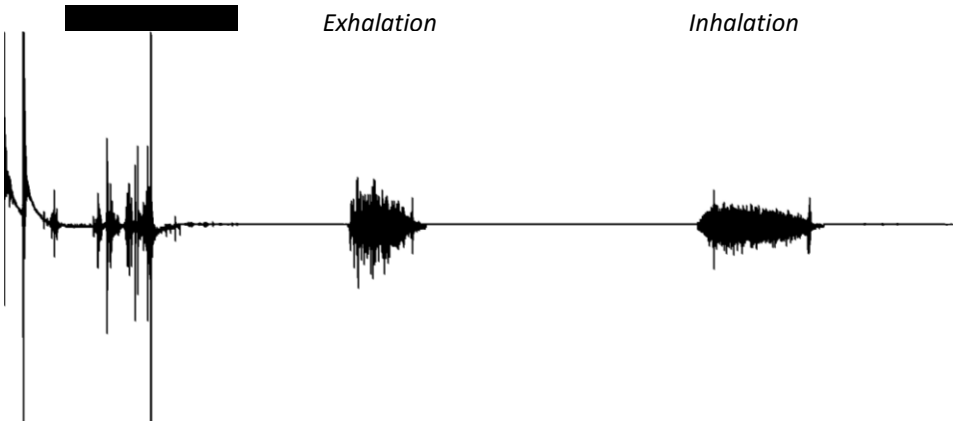


Figure B-2: Exhalation Technique Error:

This is an audio-image of a patient making a critical inhaler error. After blistering the inhaler, which places the dry power near the mouthpiece, the patient exhales into the mouthpiece, therefore removing some of the drug, prior to inhalation, An audio example of this error can be heard at:
https://www.dropbox.com/s/epxknz0bu7vm152/EXHALATION.mp3?dl=0

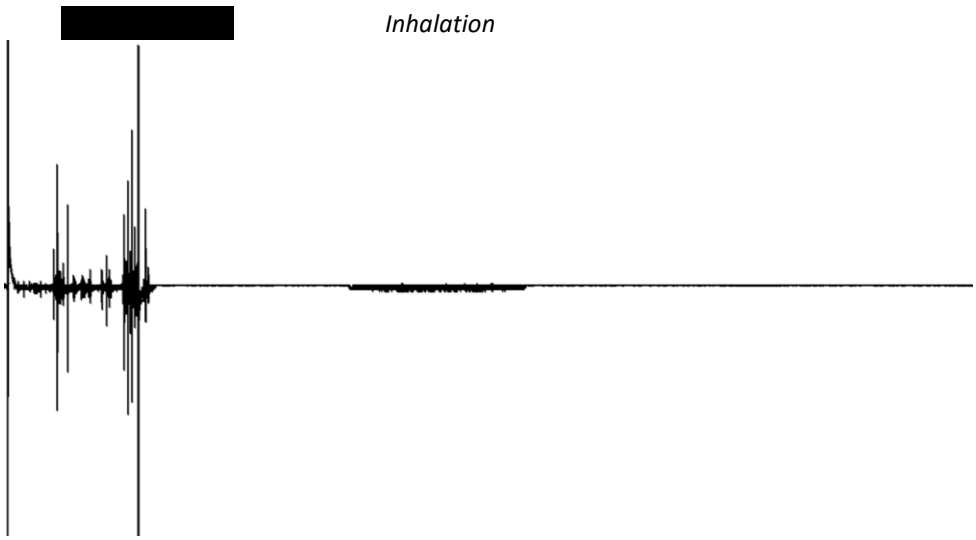


Figure B-3: Poor Inspiratory Flow Rate Technique Error:

This is an audio-image of a patient making a critical inhaler error. In this example the patient blisters the drug and takes a very weak inhalation, compared to the inhalation seen in Figure B-1. An audio example of this error can be heard at: https://www.dropbox.com/s/ofy02y2ilc2nnmr/LOWPIFR.wav?dl=0

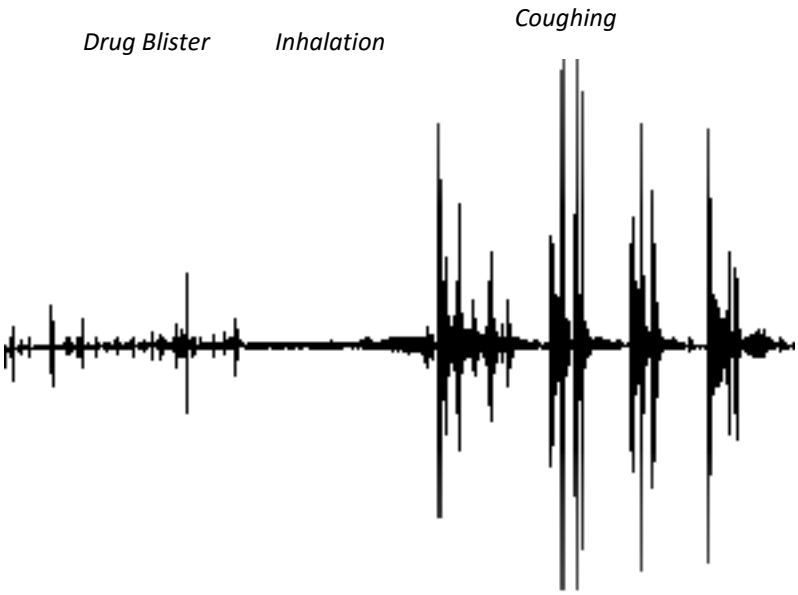


Figure B-4: Poor Breath Hold Technique Error:

This is an audio-image of a patient making an inhaler error. In this example the patient blisters the drug, and takes a short weak inhalation followed immediately by a fit of coughing. An audio example of this error can be heard at: https://www.dropbox.com/s/2jdcl41unv5hpij/Nobreathhold.wav?dl=0

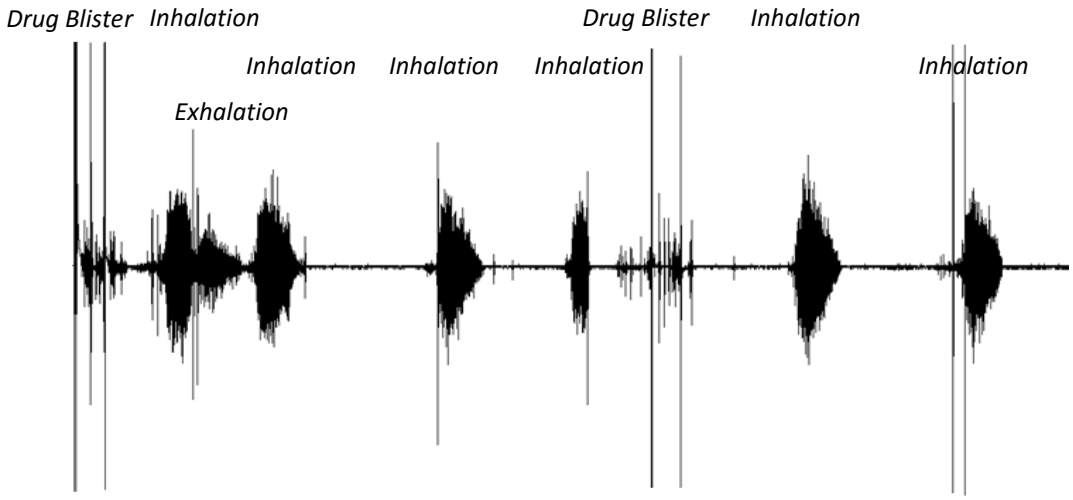


Figure B-5: Multiple Inhalations and Multiple Blisters Technique Error:

This is an audio-image of a patient making an inhaler error. In this example the patient blisters the drug, takes a few inhalations and exhalations, then blisters the drug again and takes another two inhalations. An audio example of a multiple inhalations error can be heard at:
https://www.dropbox.com/s/83qexwsjk39n6ip/Multiple%20Inhalations.wav?dl=0

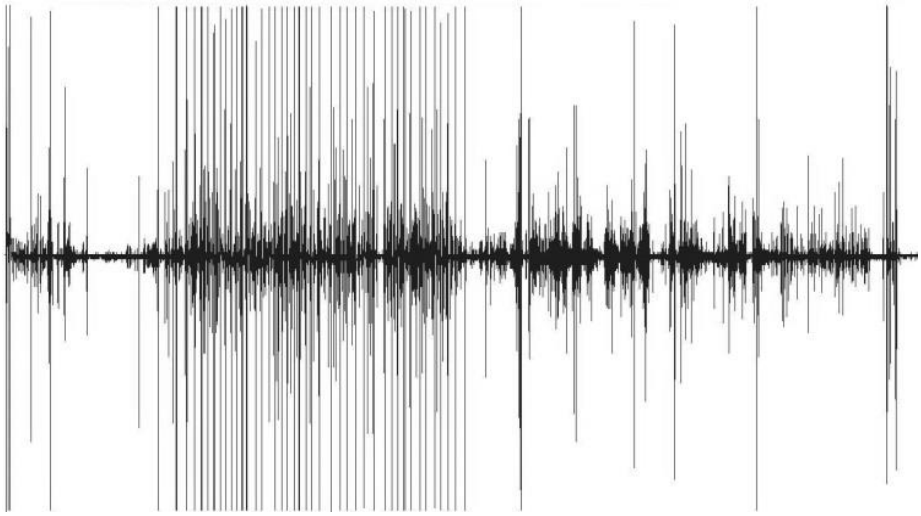


Figure B-6: Multiple Blister (Dose Dumping) Error:

This is an audio-image of a patient making an inhaler error. In this example the patient blisters the drug over 20 times in a single audio file to give the impression that the inhaler was used regularly. An audio example of this error can be heard at:
https://www.dropbox.com/s/e3nyc6x1pgnfxai/MULTIPLE%20BLISTERS.wav?dl=0

Appendix C

Examples of Different Patterns of Inhaler Use (time and technique)

The following figures are bar charts of patients inhaler use, with number of doses on the y-axis and 12-hour intervals on the x-axis. As the medication studied was an inhaler prescribed twice daily there should only be one dose taken for each 12-hour period. Green shading of the bars indicates the patient took their medication with good technique and red indicates poor inhaler technique. These figures show examples of four different patterns of inhaler use with regards to time of use and technique of use.

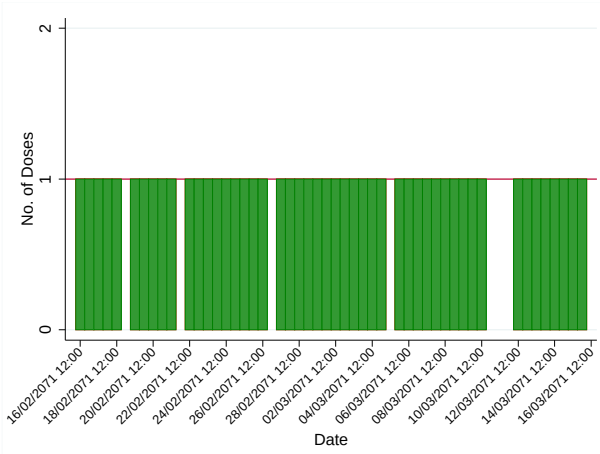


Figure C-1: An example of a patient with good timing and good technique

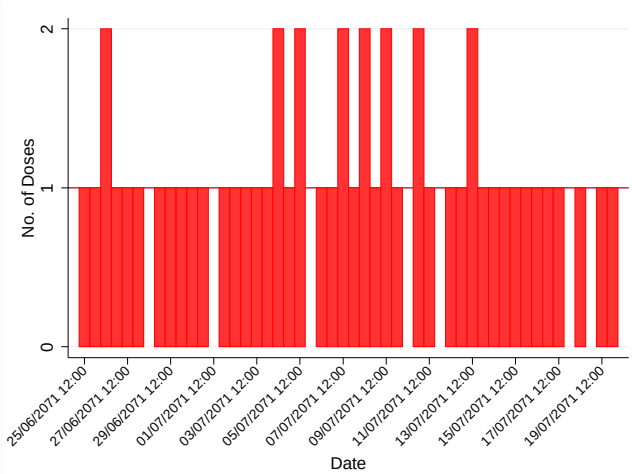


Figure C-2: An example of a patient with good timing and poor technique

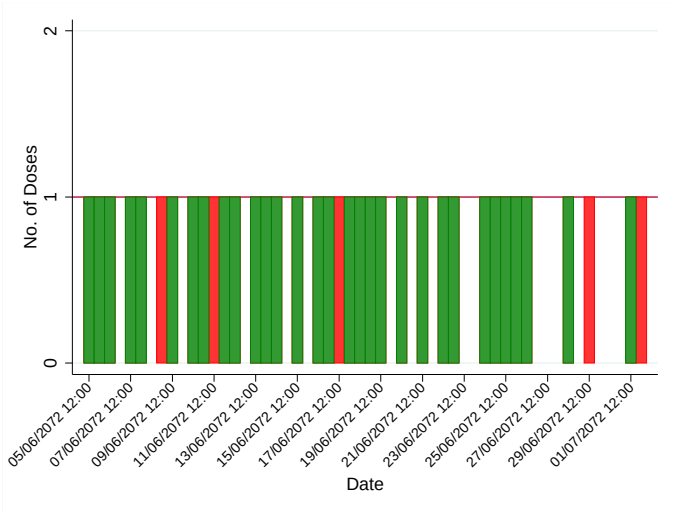


Figure C-3: An example of a patient with good technique and poor timing

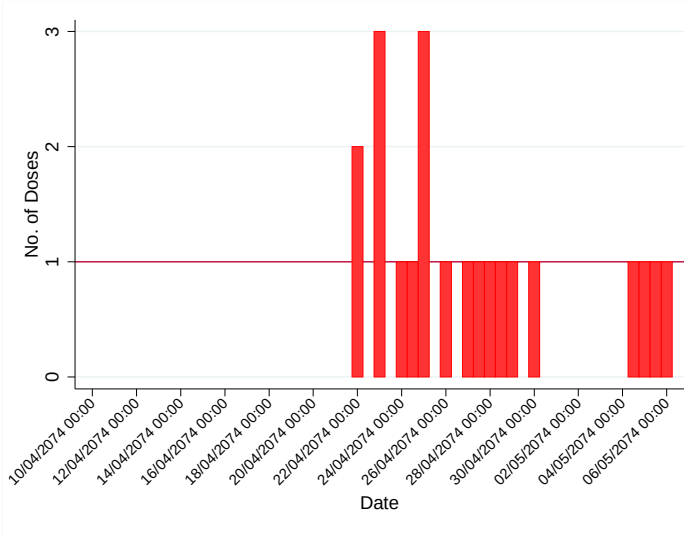


Figure C-4: An example of a patient with poor technique and poor timing.

Appendix D

Procedure for Calculating Adherence Values (used in STATA)

A. Calculating Attempted and Actual Adherence (not including Interval)

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
c. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
d. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
e. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
    ii. combined_doses = 1 whenever ORClass is 1 and not missing
    iii. technique_errors= =1 whenever ORClass is 2
f. Generate a variable that breaks date into weeks of the study period
g. Generate new variable that divides time of device use into AM and PM (TOD)
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
h. Remove any data where date or time are missing
i. Calculate sum of timed_doses, combined_doses, technique_errors for AM and PM of each day
j. Generate new variable that combines date and time (time is AM or PM)
k. Generate new cells for missed doses based on a 12 hour interval between doses
l. Fill new empty cells with dates and time for missing doses
m. Fill new empty cells for timed_doses, combined_doses and technique_errors as 0 (i.e. dose missed)
n. Generate new variable for number of days in each VisitNumber
    i. vdays
o. Generate new variable for number of total days over total study period
    i. day
p. Generate new variable for expected_dose for AM and PM
    i. ==1 dose per time period
q. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
r. The following code calculates the adherence measures for each VisitNumber, as long as there is at least one observation for each VisitNumber

i. Calculate cumulative sum of expected_doses for each Visit
    1. cumulative_expected
ii. Calculate cumulative sum of timed_doses for each Visit
    1. cumulative_doses_attempted
iii. Calculate cumulative sum of combined_doses for each Visit
    1. cumulative_doses_actual
iv. Calculate Area_Attempted for each Visit
    1. Addition of the previous days cumulative_doses_attempted values an todays value for each Visit
    2. Where there is no value (i.e. the first day of each visit) value of Area_Attempted == cumulative_doses_attempted
v. Calculated Area_Expected for each visit
    1. Addition of the previous days cumulative_expected values sand today's values for each Visit
    2. Where there is no value (i.e. the first day of each visit) value of Area_Expected == cumulative_expected
vi. Generate area variables
    1. a=sum of cumulative_doses_attempted
    2. c=sum of cumulative_expected
    3. d= sum of cumulative_doses_attempted/sum of cumulative_expected
vii. Calculate Area_Expected_Attempted
    1. Calculate Area_Expected_Attempted as a percentage of sum of cumulative_doses_attempted/sum of cumulative_expected
        a. Area_Expected_Attempted = Area_Expected * d
viii. Calculated Area_Difference_Attempted
    1. Subtract Area_Attempted from Area_Expected_Attempted
ix. Generate new area variables
    1. f=sum of Area_Difference_Attempted
    2. j=sum of Area_Expected_Attempted
    3. l=sum of Area_Expected
    4. m=sum of Area_Attempted
x. Calculate Final Area_Attempted
    1. If sum of Area_Expected_Attempted is bigger than the sum of Area_Expected
        a. Area_Attempted is the (sum of Area_Expected - (sum of Area_Expected_Attempted – sum of Area_Difference_Attempted –sum of Area_Expected)) divided by sum of Area_Expected then multiplied by 100 to give Percent
            i. Area_Attempted=(l-(j-f-l)/l) * 100
    2. Otherwise
        a. Area_Attempted is (the sum of Area_Expected_Attempted – the sum of Area_Difference_Expected) divided by the sum of Area_Expected then multiplied by 100 to give Percent
            i. Area_Attempted=((j-f)/l) * 100

B. Calculated Attempted and Actual Interval Area Rates

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
    iii. Drop TimeofDeviceUse variable and rename t variable TimeofDeviceUse
c. Generate new variable that combines date and time variables
d. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
e. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
f. Generate new variable that divides time of device use into AM and PM
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
g. Remove any data where date or time are missing
h. Remove any data where file is a book mark/processing file
    i. i.e. ORClass == 0
i. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
j. Generate new variable which is the day number of each day of each visit
    i. i.e. Day 1 to 30 of each Visit
k. Calculate number of hours between doses
    i. Presume first dose of each visit was 12 hours before the previous dose
l. Score Doses based on hours between doses and drug half-life (need combined date and time variable and day of visit variable to do this)
    i. Attempted Interval Dose Score = ATtimediffscore
        1. If ORClass doesn't equal 0
            a. Dose is 1 if time between previous doses is less than 16.5 hours and more than 5.5 hours
            b. Dose is 0.5 if more than 16.5 hours from previous dose
            c. Dose is 0.25 if more than 22 hours from previous dose
            d. Dose is 0.125 if more than 27.5 hours from previous dose
            e. Dose is 0 if more than 33 hours from previous dose
    ii. Actual Interval Dose Score = ACtimediffscore
        1. If ORClass equals 1 and not 0 or 2
            a. Dose is 1 if time between previous doses is less than 16.5 hours and more than 5.5 hours
            b. Dose is 0.5 if more than 16.5 hours from previous dose
            c. Dose is 0.25 if more than 22 hours from previous dose
            d. Dose is 0.125 if more than 27.5 hours from previous dose
            e. Dose is 0 if more than 33 hours from previous dose
            f. Dose is 0 if ORClass is 2

m. Calculate sum of ATtimediffscore, ACtimediffscore, for AM and PM of each day
n. Generate new variable that combines date and time (time is AM or PM)
o. Generate new cells for missed doses based on a 12 hour interval between doses
p. Drop duplicated date and time
q. Fill new empty cells for ATtimediffscore and ACtimediffscore as 0 (i.e. dose missed)
r. Fill new empty cells with dates and time for missing doses
s. Generate new variable for number of days in each VisitNumber
    i. Vdays
    ii. Drop any data that is recorded beyond the 28 days of one Visit
        1. *On the webserver the user needs to enter in the actual start date of each visit, and therefore the adherence will only be calculated for the collected data 28 days after the date entered for each Visit*
t. Generate new variable for expected_dose for AM and PM
    i. ==1 dose per time period
u. New Variable names for ATtimeddiffscore and ACtimediffscore
    i. gen attempted_interval=ATtimediffscore
    ii. gen actual_interval=ACtimediffscore
v. The following code calculates the interval adherence measures for each VisitNumber, as long as there is at least one observation for each VisitNumber
    i. Calculate cumulative sum of expected_doses for each Visit
        1. cumulative_expected
    ii. Calculate cumulative sum of attempted_interval for each Visit
        1. cumulative_doses_attempted
    iii. Calculate cumulative sum of actual_interval for each Visit
        1. cumulative_doses_actual
    iv. Calculate Area_Attempted for each Visit
        1. Addition of the previous days cumulative_doses_attempted values an todays value for each Visit
        2. Where there is no value (i.e. the first day of each visit) value of Area_Attempted == cumulative_doses_attempted
    v. Calculate Area_Actual for each Visit
        1. Addition of the previous days cumulative_doses_actual values an todays value for each Visit
        2. Where there is no value (i.e. the first day of each visit) value of Area_Actual == cumulative_doses_actual
    vi. Calculated Area_Expected for each visit
        1. Addition of the previous days cumulative_expected values sand today's values for each Visit
        2. Where there is no value (i.e. the first day of each visit) value of Area_Expected == cumulative_expected
    vii. Generate area variables
        1. a=sum of cumulative_doses_attempted
        2. b=sum of cumulative_doses_actual
        3. c=sum of cumulative_expected
        4. d= sum of cumulative_doses_attempted/sum of cumulative_expected
        5. e=sum of cumulative_doses_actual/sum of cumulative_expected
    viii. Calculate Area_Expected_Attempted
        1. Calculate Area_Expected_Attempted as a percentage of sum of cumulative_doses_attempted/sum of cumulative_expected
            a. Area_Expected_Attempted = Area_Expected * d

ix. Calculate Area_Expected_Actual
    1. Calculate Area_Expected_Actual as a percentage of sum of cumulative_doses_actual/sum of cumulative_expected
        a. Area_Expected_Actual = Area_Expected * e
x. Calculated Area_Difference_Attempted
    1. Subtract Area_Attempted from Area_Expected_Attempted
xi. Calculated Area_Difference_Actual
    1. Subtract Area_Actual from Area_Expected_Actual
xii. Generate new area variables
    1. f=sum of Area_Difference_Attempted
    2. g=sum of Area_Difference_Actual
    3. j=sum of Area_Expected_Attempted
    4. k=sum of Area_Expected_Actual
    5. l=sum of Area_Expected
    6. m=sum of Area_Attempted
    7. n=sum of Area_Actual
xiii. Calculate Final Adherence Measures
    1. If sum of Area_Expected_Attempted is bigger than the sum of Area_Expected
        a. Area_Attempted_Interval is the (sum of Area_Expected - (sum of Area_Expected_Attempted – sum of Area_Difference_Attempted –sum of Area_Expected)) divided by sum of Area_Expected and multiplied by 100 to give Percent
            i. Area_Attempted_Interval=(l-(j-f-l)/l)*100
        b. Area_Actual_Interval is the (sum of Area_Actual divided by Area_Attempted) multiplied by Area_Attempted_Interval
            i. Area_Actual_Interval=(n/m)*Area_Attempted_Interval
        c. Technique_Error_Rate is Area_Actual_Interval subtracted from the Area_Attempted_Interval
    2. Otherwise
        a. Area_Attempted_Interval is (the sum of Area_Expected_Attempted – the sum of Area_Difference_Expected) divided by the sum of Area_Expected multiplied by 100 to give Percent
            i. Area_Attempted_Interval=((j-f)/l) * 100
        b. Area_Actual_Interval is the (sum of Area_Actual divided by Area_Attempted) multiplied by Area_Attempted_Interval
            i. Area_Actual_Interval=(n/m)*Area_Attempted_Interval
        c. Technique_Error_Rate is Area_Actual_Interval subtracted from the Area_Attempted_Interval

C. Calculate Total Missed Doses and Over Doses

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
c. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
d. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
e. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
f. Generate a variable that breaks date into weeks of the study period
g. Generate new variable that divides time of device use into AM and PM
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
h. Remove any data where date or time are missing
i. Calculate sum of timed_doses for AM and PM of each day
j. Generate new variable that combines date and time (time is AM or PM)
k. Generate new cells for missed doses based on a 12-hour interval between doses
l. Fill new empty cells with dates and time for missing doses
m. Fill new empty cells for timed_doses as 0 (i.e. dose missed)
n. Generate variables to count Missed Doses (MD)
    i. Missed Doses is counted as 1 whenever timed_doses equals 0
o. Generate variable to count Over Doses (OD)
    i. Over Doses is calculated as timed_doses minus what is expected (1) if timed_doses is greater than one
p. Calculate sum of Missed Doses and Over Doses for each VisitNumber
q. Rename variables
    i. MD renamed NumberofMissedDoses
    ii. OD renamed NumberofOverDoses
r. Reshape data into a wide table format for each VisitNumber

D. Calculated Missed Doses, Over Doses and Dose Counter Rate

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
c. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
d. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
e. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
    ii. combined_doses = 1 whenever ORClass is 1 and not missing
    iii. technique_errors= =1 whenever ORClass is 2
f. Generate a variable that breaks date into weeks of the study period
g. Generate new variable that divides time of device use into AM and PM
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
h. Remove any data where date or time are missing
i. Rename DosesRemaining (variable entered manually as the number of doses remaining on Dose Counter) to DoseCounter
j. Calculate sum of timed_doses, combined_doses, technique_errors for AM and PM of each day
k. Generate new variable that combines date and time (time is AM or PM)
l. Generate new cells for missed doses based on a 12 hour interval between doses
m. Fill new empty cells with dates and time for missing doses
n. Fill new empty cells for timed_doses, combined_doses and technique_errors as 0 (i.e. dose missed)
o. Generate new variable for number of days in each VisitNumber
    i. vdays
p. Generate new unique number variable for each data point
    i. day
q. Generate new variable for expected_doses for AM and PM
    i. ==1 dose per time period
r. Calculate Number of Over Doses (OD)
    i. If timed_doses is bigger than expected_doses, overdoses is the expected_doses subtracted from the timed_doses
    ii. Any missing values are equal to 0
s. Calculated Number of Missed Doses (MD)
    i. If the timed_doses is smaller than expected_doses, missed doses is the timed_doses subtracted from the expected_doses
    ii. Any missing values are equal to 0

t. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
u. The following code calculates the Over Dose and Missed Dose Rate for each VisitNumber, as long as there is at least one observation for each VisitNumber
    i. Calculate cumulative sum of expected_doses for each Visit
        1. cumulative_expected
    ii. Calculate cumulative sum of timed_doses for each Visit
        1. cumulative_doses_attempted
    iii. Calculate cumulative sum of Over Doses (OD) for each Visit
        1. cumulative_overdoses
    iv. Calculate cumulative sum of Missed Doses (MD) for each Visit
        1. cumulative_misseddoses
    v. Calculated Area_Expected for each visit
        1. This is equal to the cumulative_expected variable
            a. However the first and last data point of each visit is multiplied by 2
    vi. Calculate Area_Attempted for each Visit
        1. This is equal to the cumulative_doses_attempted variable
            a. However the first and last data point of each visit is multiplied by 2
    vii. Calculated Area_Overdosed for each visit
        1. This is equal to the cumulative_overdoses variable
            a. However the first and last data point of each visit is multiplied by 2
    viii. Calculated Area_Misseddoses for each visit
        1. This is equal to the cumulative_misseddoses variable
            a. However the first and last data point of each visit is multiplied by 2
    ix. Calculate cumulative sum of Area_Expected, Area_Attempted, Area_Overdosed and Area_Misseddoses
        1. Divide all these variables by 2
    x. Calculated Dose Counter Rate (Average Adherence)
        1. Number of Doses Used (60-DoseCounter) divided by the number of doses supplied (number of days * 2) and multiplied by 100 to give a percent
    xi. Calculate Over Doses Rate
        1. This is a ratio of the Area_Overdosed to the Area_Attempted and multiplied by 100 to give a percent
    xii. Calculate Missed Doses Rate
        1. This is a ratio of the Area_Misseddoses to the Area_Expected and multiplied by 100 to give a percent
    xiii. Rename Variables for Output
        1. Rename week to VisitNo
        2. Rename DoseCounter to DC_Rate
        3. Rename Area_Overdosed to OD_Rate
        4. Rename Area_Misseddoses to MD_Rate
    xiv. Output variables For each VistNo

E. Calculate Inhaler Technique Error Data

a. Import data for specific Subject ID
b. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
c. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
d. Generate New Variables for Each Error
    i. Correct is 1 if file is not counted as an error (ORClass==1)
    ii. Error is 1 if file is counted as an error (ORClass==2)
    iii. E0 is 1 if file is counted as Error and Error is 0
        1. ORClass==2 & ORError==0
        2. Book Mark or Processing Error File
    iv. E1 is 1 if file is counted as Error and Error is 1
        1. ORClass==2 & ORError==1
        2. Multiple Inhalations Error
    v. E2 is 1 if file is counted as Error and Error is 2
        1. ORClass==2 & ORError==2
        2. Multiple Blisters Error
    vi. E3 is 1 if file is counted as Error and Error is 3
        1. ORClass==2 & ORError==3
        2. Multiple Inhalations & Multiple Blisters Error
    vii. E4 is 1 if file is counted as Error and Error is 4
        1. ORClass==2 & ORError==4
        2. Exhalation into the Inhaler Error
    viii. E4_5 is 1 if file is counted as Error and Error is 4.5
        1. ORClass==2 & ORError==4.5
        2. Low Breath Hold Error
        3. *This error is currently not classified*
    ix. E5 is 1 if file is counted as Error and Error is 5
        1. ORClass==2 & ORError==5
        2. Dose Dumping Error
    x. E6 is 1 if file is counted as Error and Error is 6
        1. ORClass==2 & ORError==6
        2. No Blister but Inhalation Detected Error
    xi. E7 is 1 if file is counted as Error and Error is 7
        1. ORClass==2 & ORError==7
        2. Blister Present but no Inhalation Detected Error
    xii. E8 is 1 if file is counted as Error and Error is 8
        1. ORClass==2 & ORError==8
        2. No Blister and No Inhalation Detected Error
    xiii. E9 is 1 if file is counted as Error and Error is 9
        1. ORClass==2 & ORError==9

2. Low Inspiratory Flow Rate Error

xiv. E10 is 1 if file is counted as Error and Error is 10
    1. ORClass==2 & ORError==10
    2. Multiple Errors Error
xv. Calculate Total of Each Error for Each Visit Number
xvi. Output Errors for each Visit as a Table

F. Calculate Cluster Over Dose and Missed Dosed Data and Inspiratory Capacity and Peak Inspiratory Flow Rate Data

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
    iii. Drop TimeofDeviceUse variable and rename t variable TimeofDeviceUse
c. Generate new variable that combines date and time variables
d. If the audio files have been over-read then use the over-read classification and error scoring, if not skip this step.
    i. Drop Algorithm calculated adherence variables and rename Final Opinion adherence variables
    ii. ORClass = Algorithm calculated classification of each audio file
    iii. ORError = Algorithm calculated error for each audio file
    iv. FOClass = Final opinion classification of each audio file (overread)
    v. FOError = Final opinion error for each audio file (overread)
    vi. FOClass and FOError get renamed to ORClass and ORError *(this is just done cause I had OR in the rest of my code from previous work so rather than changing it everywhere in the code I just renamed these variables).*
e. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
f. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
    ii. combined_doses = 1 whenever ORClass is 1 and not missing
    iii. technique_errors= =1 whenever ORClass is 2
g. Generate new variable that divides time of device use into AM and PM
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
h. Remove any data where date or time are missing
i. Remove any data where file is a book mark/processing file
    i. i.e. ORClass == 0
j. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
k. Generate new variable which is the day number of each day of each visit
    i. i.e. Day 1 to 30 of each Visit
l. Calculate number of hours between doses
    i. Presume first dose of each visit was 12 hours before the previous dose
m. Generate First Variable for Cluster of Missed Doses
    i. If time between doses is >= 48 hours this is equivalent to missing 4 doses (Cmd)
n. Generate First Variable for Cluster of Over Doses
    i. If time between doses is <12 hours this is equivalent to taking an extra dose within the 12 hour half life of the drug (Cod1)
o. Correct Peak Inspiratory Flow Variable (PeakInspiratoryFlowRatelmi)
    i. When the peak inspiratory flow is too low for the algorithm to calculate it gives it a value of 0
    ii. Anything less than 35L/min is very low
    iii. Replace any PeakInspiratoryFlowRatelmi with a value of 0 to 35
p. Calculate mean Peak Inspiratory Flow and Inspiratory Capacity for each day, AM and PM

q. Calculate sum of timed_doses, Cluster of Missed Doses (Cmd) and Over Doses (Cod1) for each day AM and PM
r. Generate new variable that combines date and time (time is AM or PM)
s. Generate new cells for missed doses based on a 12 hour interval between doses
t. Fill new empty cells with dates and time for missing doses
u. Fill new empty cells for timed_doses as 0 (i.e. dose missed)
v. Generate new variable for number of days in each VisitNumber
    i. day
w. Calculate mean Peak Inspiratory Flow and Inspiratory Capacity for each day
x. Calculate sum of timed_doses, Cluster of Missed Doses (Cmd) and Over Doses (Cod1) for each day
y. Generate Second Variable for Cluster Over Doses
    i. If timed_dose per day is greater than 2 for 2 consecutive days, the patient has taken 6 or more doses over the course of 48 hours (Cod)
z. Calculate mean Peak Inspiratory Flow and Inspiratory Capacity for each Visit
aa. Calculate sum Cluster of Missed Doses (Cmd), first and second variables for Cluster of Over Doses (Cod1 and Cod2) for each Visit
bb. Rename variables
    i. Rename Cmd Cluster_MissedDose
    ii. Rename Cod1 Cluster12_OverDose
    iii. Rename Cod2 Cluster_OverDose
cc. Reshape data so its wide for output as table divided by Visits

G. Calculate Habit Data for AM

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
c. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
d. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
    ii. combined_doses = 1 whenever ORClass is 1 and not missing
    iii. technique_errors= =1 whenever ORClass is 2
e. Generate new Categorical variable that divides time of device use into AM and PM (TOD)
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
f. Generate new variables for time based on TOD classification
    i. one for the AM and
    ii. another for PM
g. The following is to measure Habit in the AM
    i. Generate new continuous variable that divides time of device use into AM and PM (TOD2)
        1. AM is >=3AM and <3PM
        2. PM is >=3PM and < 3AM
    ii. Drop all data for PM time of use
    iii. Remove any data where date or time are missing
    iv. Collapse AM and Timeofdeviceuse for each day and time period (AM)
    v. Generate new variable that combines date and time (time is AM or PM)
    vi. Generate new cells for missed doses based on a 12 hour interval between doses
    vii. Generate new variable for Day number (day)
    viii. Collapse AM data to just the hour (collapsing minutes and seconds to 0)
    ix. For each Visit calculate the mean and standard error for the AM hour
    x. Replace any missed doses (empty cell) as 0 for AM
    xi. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
    xii. For each Visit Generate control chart for AM inhaler use
        1. Mean is calculated above
        2. Upper limit is 2 Standard error above mean
        3. Lower limit is 2 Standard error below mean
        4. Calculate total number of observations
        5. Calculate total number of violations (that is outside the upper or lower limits)
        6. Generate the AMScore variable based on the number of violations divided by the number of observations
        7. Output violations and AMscore for each visit into a Table

H. Calculate Habit Data for PM

a. Import data for specific Subject ID
b. Reformat Date (DateofDeviceUse) and Time (TimeofDeviceUse) Variables
    i. New Date variable date2
    ii. New Time variable t
c. Destring numerical variables *(sometimes ORClass, ORError, FOClass, FOError have string variables in the database)*
d. Generate new variables based on classification and errors
    i. timed_doses = 1 whenever ORClass is not 0 or missing
    ii. combined_doses = 1 whenever ORClass is 1 and not missing
    iii. technique_errors= =1 whenever ORClass is 2
e. Generate new Categorical variable that divides time of device use into AM and PM (TOD)
    i. AM is >=3AM and <3PM
    ii. PM is >=3PM and < 3AM
f. Generate new variables for time based on TOD classification
    i. one for the AM and
    ii. another for PM
g. The following is to measure Habit in the PM
    i. Generate new continuous variable that divides time of device use into AM and PM (TOD2)
        1. AM is >=3AM and <3PM
        2. PM is >=3PM and < 3AM
    ii. Drop all data for AM time of use
    iii. Remove any data where date or time are missing
    iv. Collapse AM and Timeofdeviceuse for each day and time period (PM)
    v. Generate new variable that combines date and time
    vi. Generate new cells for missed doses based on a 12 hour interval between doses
    vii. Generate new variable for Day number (day)
    viii. Collapse PM data to just the hour (collapsing minutes and seconds to 0)
    ix. For each Visit calculate the mean and standard error for the PM hour
    x. Replace any missed doses (empty cell) as 0 for PM
    xi. Rename VisitNumber week *(this is just done because I had used week previously in my code and rather than changing it I just renamed this variable)*
    xii. For each Visit Generate control chart for PM inhaler use
        1. Mean is calculated above
        2. Upper limit is 2 Standard error above mean
        3. Lower limit is 2 Standard error below mean
        4. Calculate total number of observations
        5. Calculate total number of violations (that is outside the upper or lower limits)
        6. Generate the PMScore variable based on the number of violations divided by the number of observations
        7. Output violations and PMscore for each visit into a Table

Appendix E

Questionnaires Used For This Thesis

E.1 Quality of Life

E.1.1 Mini Asthma Quality of Life Questionnaire (AQLQ) (197)

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _____

DATE _____

Page 1 of 2

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1.	Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2.	Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3.	Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4.	Feel bothered by COUGHING?	1	2	3	4	5	6	7
5.	Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6.	Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7.	Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8.	Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9.	Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
10.	Experience a WHEEZE in your chest?	1	2	3	4	5	6	7

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _____

DATE _____

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

DOMAIN CODE:

Symptoms: 1, 4, 6, 8, 10
Activity Limitation: 12, 13, 14, 15
Emotional Function: 3, 5, 9
Environmental Stimuli: 2, 7, 11

E.1.2 COPD Assessment Test (CAT) (215)

Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

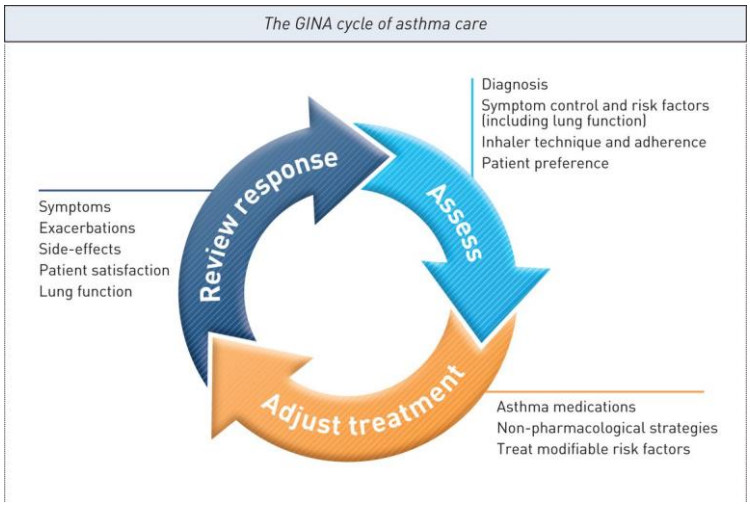
Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

IE/SFC/0016a/11 October 2011

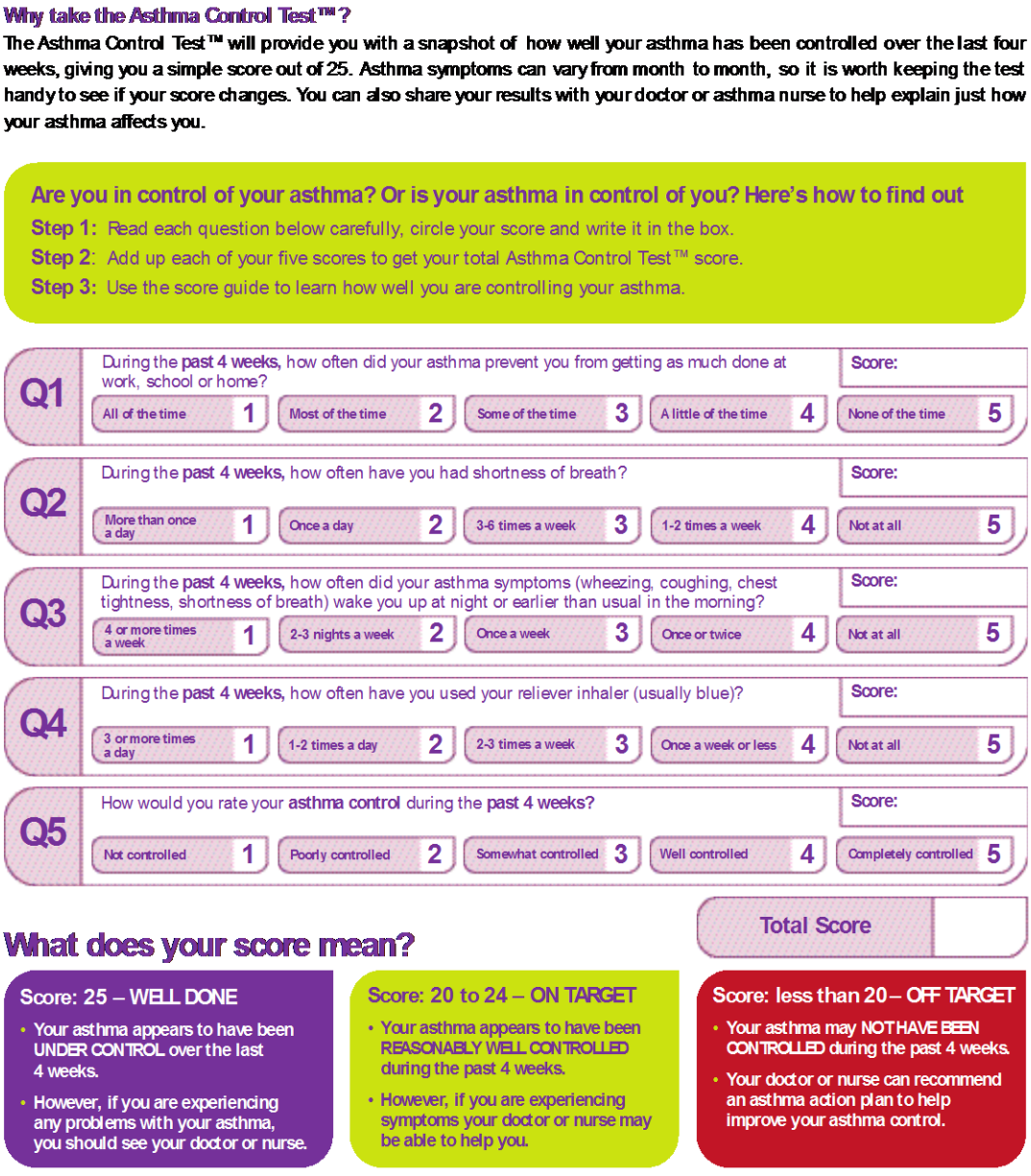
E.2 Disease Factors

E.2.1 Global Initiative for Asthma (GINA) Classification (194,252)



	Current treatment step			
Clinical features	**Step 1** No controller	**Step 2** <500 µg BDP	**Step 3** 200–1,000 µg BDP + LABA	**Step 4** >1,000 BDP µg + LABA ± other
Step 1 Symptoms <1 x week Nocturnal symptoms ≤2 x month Lung function normal between episodes	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Step 2 Symptoms >1 x week Nocturnal symptoms <1 x month Lung function normal between episodes	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Step 3 Symptoms daily Nocturnal symptoms ≥1 x week FEV_1 60–80% predicted	Moderate persistent	Severe persistent	Severe persistent	Severe persistent
Step 4 Symptoms daily Frequent nocturnal symptoms FEV_1 <60% predicted	Severe persistent	Severe persistent	Severe persistent	Severe persistent

E.2.2 Asthma Control Test (ACT) (260)



Why take the Asthma Control Test™?

The Asthma Control Test™ will provide you with a snapshot of how well your asthma has been controlled over the last four weeks, giving you a simple score out of 25. Asthma symptoms can vary from month to month, so it is worth keeping the test handy to see if your score changes. You can also share your results with your doctor or asthma nurse to help explain just how your asthma affects you.

Are you in control of your asthma? Or is your asthma in control of you? Here's how to find out

Step 1: Read each question below carefully, circle your score and write it in the box.
Step 2: Add up each of your five scores to get your total Asthma Control Test™ score.
Step 3: Use the score guide to learn how well you are controlling your asthma.

Q1 During the **past 4 weeks**, how often did your asthma prevent you from getting as much done at work, school or home? — Score:

All of the time 1 | Most of the time 2 | Some of the time 3 | A little of the time 4 | None of the time 5

Q2 During the **past 4 weeks**, how often have you had shortness of breath? — Score:

More than once a day 1 | Once a day 2 | 3-6 times a week 3 | 1-2 times a week 4 | Not at all 5

Q3 During the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning? — Score:

4 or more times a week 1 | 2-3 nights a week 2 | Once a week 3 | Once or twice 4 | Not at all 5

Q4 During the **past 4 weeks**, how often have you used your reliever inhaler (usually blue)? — Score:

3 or more times a day 1 | 1-2 times a day 2 | 2-3 times a week 3 | Once a week or less 4 | Not at all 5

Q5 How would you rate your **asthma control** during the **past 4 weeks**? — Score:

Not controlled 1 | Poorly controlled 2 | Somewhat controlled 3 | Well controlled 4 | Completely controlled 5

Total Score

What does your score mean?

Score: 25 – WELL DONE

- Your asthma appears to have been UNDER CONTROL over the last 4 weeks.
- However, if you are experiencing any problems with your asthma, you should see your doctor or nurse.

Score: 20 to 24 – ON TARGET

- Your asthma appears to have been REASONABLY WELL CONTROLLED during the past 4 weeks.
- However, if you are experiencing symptoms your doctor or nurse may be able to help you.

Score: less than 20 – OFF TARGET

- Your asthma may NOT HAVE BEEN CONTROLLED during the past 4 weeks.
- Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

E.2.3 Modified Medical Research Council Dyspnoea Scale (mMRC) (216)

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

E.2.4 Charlson Co-Morbidity Index (116)

Charlson Comorbidity Index

(http://www.fpnotebook.com/prevent/Exam/ChrlsnCmrbdtyIndx.htm)

Aka: Charlson Comorbidity Index, Comorbidity-Adjusted Life Expectancy

1. Indication
    1. Assess whether a patient will live long enough to benefit from a specific screening measure or medical intervention
2. Scoring: Comorbidity Component (Apply 1 point to each unless otherwise noted)
    1. Myocardial Infarction
    2. Congestive Heart Failure
    3. Peripheral Vascular Disease
    4. Cerebrovascular Disease
    5. Dementia
    6. COPD
    7. Connective Tissue Disease
    8. Peptic Ulcer Disease
    9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)
    10. Moderate to Severe Chronic Kidney Disease (2 points)
    11. Hemiplegia (2 points)
    12. Leukemia (2 points)
    13. Malignant Lymphoma (2 points)
    14. Solid Tumor (2 points, 6 points if metastatic)
    15. Liver Disease (1 point mild, 3 points if moderate to severe)
    16. AIDS (6 points)
3. Scoring: Age
    1. Age <40 years: 0 points
    2. Age 41-50 years: 1 points
    3. Age 51-60 years: 2 points
    4. Age 61-70 years: 3 points
    5. Age 71-80 years: 4 points
4. Interpretation
    1. Calculate Charlson Score or Index (i)
        1. Add Comorbidity score to age score
        2. Total denoted as 'i' below
    2. Calculate Charlson Probablity (10 year mortality)
        1. Calculate Y = e^(i * 0.9)
        2. Calculate Z = 0.983^Y
        3. where Z is the 10 year survival

E.2.5 Hospital Anxiety and Depression Scale (HADS) (219)

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

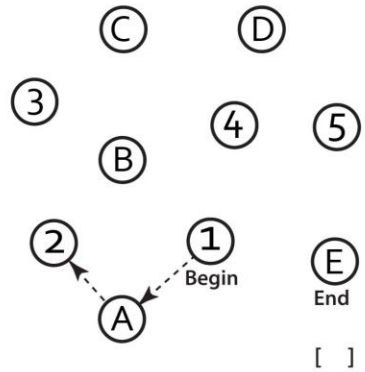
E.3 Cognition and Health Literacy

E.3.1 Montreal Cognitive Assessment (MoCA) (218)

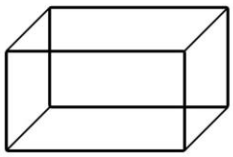
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.2 Alternative Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy rectangle

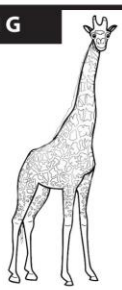


[ ] [ ]

Draw CLOCK (Five past four)
(3 points)

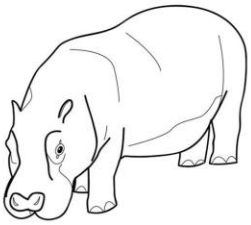
[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



[ ]

[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRUCK	BANANA	VIOLIN	DESK	GREEN
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 3 2 9 6 5
Subject has to repeat them in the backward order [ ] 8 5 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : A bird can fly into closed windows when it's dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle __/2

DELAYED RECALL

	TRUCK	BANANA	VIOLIN	DESK	GREEN	Points for UNCUED recall only
Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional Category cue						
Optional Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Administered by: _____

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

E.3.2 European Health Literacy Questionnaire (EHQL) (220)

European Health Literacy Survey
Questions 1 to 16 of Cure and Care Section Only

All questions are given 5 options and each option is allocated a score:

Option 1: Very easy (1 point given)
Option 2: Fairly easy (2 points given)
Option 3: Fairly difficult (3 points given)
Option 4: Very difficult (4 points given)
Option 5: Don't know {spontaneous} (5 points given)

Question 1: On a scale from very easy to very difficult, how easy would you say it is to: find information about symptoms of illnesses that concern you?

Question 2: On a scale from very easy to very difficult, how easy would you say it is to: find information on treatments of illnesses that concern you?

Question 3: On a scale from very easy to very difficult, how easy would you say it is to: find out what to do in case of a medical emergency?

Question 4: On a scale from very easy to very difficult, how easy would you say it is to: find out where to get professional help when you are ill? (Instructions: such as doctor, pharmacist, psychologist)

Question 5: On a scale from very easy to very difficult, how easy would you say it is to: understand what your doctor says to you?

Question 6: On a scale from very easy to very difficult, how easy would you say it is to: understand the leaflets that come with your medicine?

Question 7: On a scale from very easy to very difficult, how easy would you say it is to: understand what to do in a medical emergency?

Question 8: On a scale from very easy to very difficult, how easy would you say it is to: understand your doctor's or pharmacist's instruction on how to take a prescribed medicine?

Question 9: On a scale from very easy to very difficult, how easy would you say it is to: judge how information from your doctor applies to you?

Question 10: On a scale from very easy to very difficult, how easy would you say it is to: judge the advantages and disadvantages of different treatment options?

Question 11: On a scale from very easy to very difficult, how easy would you say it is to: judge when you may need to get a second opinion from another doctor?

Question 12: On a scale from very easy to very difficult, how easy would you say it is to: judge if the information about illness in the media is reliable? (Instructions: TV, Internet or other media)

Question 13: On a scale from very easy to very difficult, how easy would you say it is to: use information the doctor gives you to make decisions about your illness?

Question 14: On a scale from very easy to very difficult, how easy would you say it is to: follow the instructions on medication?

Question 15: On a scale from very easy to very difficult, how easy would you say it is to: call an ambulance in an emergency?

Question 16: On a scale from very easy to very difficult, how easy would you say it is to: follow instructions from your doctor or pharmacist?

E.4 Medication Adherence/Use

E.4.1 Morisky Adherence Scale (MMAS-4 and MMAS-8) (221)

Morisky Medication Adherence Scales: MMAS-4 and MMAS-8

MMAS-4	MMAS-8
1) Do you ever forget to take your medicine?	1) Do you sometimes forget to take your pills?
2) Are you careless at times about taking your medicine?	2) People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
3) Sometimes if you feel worse when you take the medicine, do you stop taking it?	3) Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?
	4) When you travel or leave home, do you sometimes forget to bring along your medicine?
	5) Did you take all your medicine yesterday?
4) When you feel better do you sometimes stop taking your medicine?	6) When you feel like your symptoms are under control, do you sometimes stop taking your medicine?
	7) Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?
	8) How often do you have difficulty remembering to take all your medicine? ___A. Never/rarely ___B. Once in a while ___C. Sometimes ___D. Usually ___E. All the time

Adherence	MMAS-4 Score	MMAS-8 Score
High Adherence	0	0
Medium Adherence	1-2	1-2
Low Adherence	3-4	3-8

E.4.2 Inhaler Proficiency Score (IPS) for a Dry Powder Inhaler (193)

E.4.3 Beliefs in Medicine Questionnaire (BMQ) General (144)

BMQ-General

- I would like to ask you about your personal views about medicines in general.
- These are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only tick one box per question.

11) Doctors use to many medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

12) People who take medicines should stop their treatment for a while every now and again.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

13) Most medicines are addictive.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

14) Natural remedies are safer than medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

15) Medicines do more harm than good.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

16) All medicines are poisons

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

17) Doctors place too much trust on medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

18) If doctors had more time with patients they would prescribe fewer medicines.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

E.4.4 Beliefs in Medicine Questionnaire (BMQ) Specific for COPD (144)

BMQ –Specific

Your views about medicines prescribed to you.

- I would like to ask you about your personal views about medicines prescribed for your asthma.
- These are statements other people have made about their asthma medication.
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

1) My health at present depends on my COPD medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

2) Having to take COPD medication worries me

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

3) My life would be impossible without my COPD medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

4) Without my COPD medication I would be very ill

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

5) I sometimes worry about the long term effects of my COPD medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

6) My COPD medication is a mystery to me

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

7) My health in the future will depend on my COPD medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

8) My COPD medication disrupts my life

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

9) I sometimes worry about becoming too dependent on my COPD medication

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

10) My COPD medication protects me from becoming worse.

Strongly agree	agree	uncertain	disagree	strongly disagree
☐	☐	☐	☐	☐

Appendix F

Protocol for a Randomised Clinical Trial

Open Access Protocol

BMJ Open

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma

Imran Sulaiman,[1] Elaine Mac Hale,[1] Martin Holmes,[2] Cian Hughes,[2] Shona D'Arcy,[2] Terrence Taylor,[2] Viliam Rapcan,[2] Frank Doyle,[1] Aoife Breathnach,[1] Jansen Seheult,[1] Desmond Murphy,[3] Eoin Hunt,[3] Stephen J Lane,[4] Abhilash Sahadevan,[4] Gloria Crispino,[1] Greg Diette,[5] Isabelle Killane,[2] Richard B Reilly,[2] Richard W Costello[6]

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For numbered affiliations see end of article.

Correspondence to
Dr Imran Sulaiman;
imransulaiman@rcsi.ie

ABSTRACT

Introduction: In clinical practice, it is difficult to distinguish between patients with refractory asthma from those with poorly controlled asthma, where symptoms persist due to poor adherence, inadequate inhaler technique or comorbid diseases. We designed an audio recording device which, when attached to an inhaler, objectively identifies the time and technique of inhaler use, thereby assessing both aspects of adherence. This study will test the hypothesis that feedback on these two aspects of adherence when passed on to patients improves adherence and helps clinicians distinguish refractory from difficult-to-control asthma.

Methods: This is a single, blind, prospective, randomised, clinical trial performed at 5 research centres. Patients with partially controlled or uncontrolled severe asthma who have also had at least one severe asthma exacerbation in the prior year are eligible to participate. The effect of two types of nurse-delivered education interventions to promote adherence and inhaler technique will be assessed. The active group will receive feedback on their inhaler technique and adherence from the new device over a 3-month period. The control group will also receive training in inhaler technique and strategies to promote adherence, but no feedback from the device. The primary outcome is the difference in actual adherence, a measure that incorporates time and technique of inhaler use between groups at the end of the third month. Secondary outcomes include the number of patients who remain refractory despite good adherence, and differences in the components of adherence after the intervention. Data will be analysed on an intention-to-treat and a per-protocol basis. The sample size is 220 subjects (110 in each group), and loss to follow-up is estimated at 10% which will allow results to show a 10% difference (0.8 power) in adherence between group means with a type I error probability of 0.05.

Trial registration number: NCT01529697; Pre-results.

INTRODUCTION

Approximately 10% of patients with asthma remain poorly controlled with persisting symptoms and severe exacerbations despite use of combination therapy with long-acting β agonists and inhaled corticosteroids.[1] This poor control may be due to medication refractory asthma or due to difficult-to-manage asthma from issues such as poor inhaler technique, poor adherence or coexisting comorbid disease.[1–3] In practice, distinguishing refractory from difficult-to-manage asthma is difficult. For example, adherence to medications, a particular problem in patients with severe asthma, is difficult to detect since self-report is unreliable,[4] and pharmacy refill records only identify if the individual has collected a prescription. Some patients may demonstrate a reasonable inhaler technique when directly observed, but may be careless in their inhaler use on a day-to-day basis.[5] Hence, without objective longitudinal information on inhaler adherence and technique it is challenging to distinguish a patient with refractory asthma from one who has difficult-to-manage asthma.[6]

We developed a device, INhaler Compliance Assessment (INCA), which makes a digital audio recording of an inhaler being used.[5 7–13] Analysis of the audio recordings by automated signal processing techniques, provides an objective assessment of both the time and the technique of inhaler use. Validation of the device and the audio recordings have been previously presented.[5 7–13] We hypothesised that this

information could be used both as part of an educational consultation for patients and for clinicians to help distinguish refractory from difficult-to-manage asthma.

The objective of this study is to assess if inhaler use obtained from the INCA device on time and technique of use leads to better inhaler adherence and better clinical information than current best practice.

METHODS

We describe the protocol of a randomised, single blind, nurse-delivered education study. The study will comprise patients with severe asthma attending specialist hospital asthma clinics, who remain uncontrolled and have experienced at least one recent severe asthma exacerbation. Basing on information obtained directly from the INCA acoustic recording device, one group (the active arm) will discuss patterns of adherence and training on technique of inhaler use. The second group (the control arm) will be given generalised strategies to improve adherence, while technique errors will be corrected using checklists.[14] Adherence will be assessed objectively in all participants. Global outcomes will be quantified using the clinical, lung function, adherence and exacerbation data collected during the observation period.

Sponsorship

This is a researcher-initiated study, funded by the Health Research Board of Ireland (Pro/2011/57), and hosted within the Dublin Centre for Clinical Research clinical trials centres. The study sponsor, Royal College of Surgeons, is an independent medical university. The trial was approved by the Beaumont Hospital's Ethics committees. The trial is registered as NCT01529697 on Clinicaltrials.gov and a detailed statistical plan has been approved by an independent statistical team. The INCA device was manufactured and supplied by Vitalograph, Ennis, Ireland, and GlaxoSmithKline provided the salmeterol/fluticasone Diskus inhaler for this study.

Setting

This is a prospective, multicentre, single blind, randomised controlled trial of two nurse-delivered strategies to optimise inhaler technique and adherence of patients with stage 3 to 5 asthma. The study is being conducted at the Clinical Research Centres of five university hospitals within the republic of Ireland (4 in Dublin County, 1 in Cork County). At each centre between one and three nurses have been trained to provide either intervention. The lead clinical nurse was educated by the principal investigator and a respiratory nurse specialist. All other nurses were educated by our lead clinical nurse in a teach-to-goal method with demonstration. The study period is from 2011 with ongoing recruitment.

Participants (n=220)

Prior to study recruitment, an asthma diagnosis is made using a clinician diagnosis supported by one or more of the following: obstructive spirometry with a minimum of 10% reversibility, either spontaneously over time or with inhaled β agonist, or with a minimum 15% peak flow variability over time or through a positive bronchial provocation challenge.

Inclusion criteria

Patients already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (1) for at least 3 months, and who had at least one exacerbation treated with systemic glucocorticoids in the prior year, and who are either uncontrolled or partially controlled by Global Initiative for Asthma (GINA) guidelines are eligible for inclusion.[1] Patients must also be 18 years or older in age.

Exclusion criteria

Patients who are controlled, as defined by the GINA criteria[1] on their current therapy are excluded. Additional exclusion criteria are those who are unwilling to participate in a clinical study, or prior hypersensitivity to salmeterol/fluticasone. There are no other exclusion criteria.

Study design

The study flow is indicated in table 1.

Patients identified at specialist asthma clinics who meet the inclusion and not the exclusion criteria are invited to participate in the study. Once consented, each study visit is performed by a registered nurse.

The dose of inhaled corticosteroid and Long Acting Beta-Agonist (LABA) is not changed at recruitment and during the study procedure, as the main aim of the study is to improve adherence to current asthma treatment.

The audio recording technology has not yet been established for the turbohaler or the pressurised metered dose inhaler (pMDI), hence, for those participants who are currently prescribed formoterol/budesonide/beclomethasone at recruitment, their therapy is changed to an equivalent dose of salmeterol/fluticasone delivered via the Diskus device. This change is made by the physician looking after the patient in the outpatient clinic. Following this, the patient is then referred to the study. The patient may still refuse to enter the study. All other aspects of regular patient care are continued.

At the initial visit, the participant's age, sex, height, weight, duration of asthma, smoking history, number of courses of steroids in the prior year are recorded (self-reported by the participant). The dose of salmeterol/fluticasone and duration of taking this dose, use and dose of other inhaled therapy including short-acting β agonists, long acting muscarinic antagonist, nasal steroid and antihistamines are recorded. The nurse records the peak expiratory flow rate (PEFR) and an Inhaler Proficiency checklist Score (IPS; see online

Table 1 Details of study data collection

Study procedure	Visit 1	Visit 2	Visit 3	Visit 4
Informed consent	X			
Demographics	X			
Medical history	X			
Inclusion and exclusion criteria	X			
Current medications	X			
Physical examination	X			X
	X	X	X	X
AQLQ	X	X	X	X
ACT	X	X	X	X
Randomisation	X			
Dispense adapted Seretide inhaler	X	X	X	
Dispense electronic PEFR monitor	X	X	X	
Download device readings active only		X	X	X
Inhaler use education	X	X	X	X
Adverse events recorded		X	X	X
Concomitant medications recorded		X	X	X

The active group receive a copy of device readings and active feedback about adherence and inhaler technique,
visit 1: screening visit: at time of enrolment (week 0); visit 2: at end of month 1 (week 4); visit 3: at end of month 2 (week 8); visit 4: final visit at the end of month 3 (week 12).
AQLQ, Asthma Quality of Life Questionnaire; ACT, Asthma Control Test; PEFR, peak expiratory flow rate.

supplementary appendix 1), a 10-point checklist score. The Asthma Control Test (ACT) score and Asthma Quality of Life Questionnaire (AQLQ)[15] are completed by the participant. Serum total and specific immunoglobulin E levels and peripheral blood eosinophil levels, prior spirometry and bronchial provocation test are recorded from the clinical notes.

The participants receive a salmeterol/fluticasone Diskus inhaler with an INCA device attached, and they are asked to use the inhaler twice per day and to take reliever salbutamol, as required, for breakthrough symptoms. All participants are informed at recruitment that the device would provide information on how and when they use their inhaler. Participants are asked to record their peak expiratory flow with an electronic monitor (ASMA-1, Vitalograph, Ennis, Ireland) twice daily.

Visits are scheduled 4, 8 and 12 weeks later, summarised in figure 1. At these visits, the participants return their inhaler and electronic peak flow monitor. Additionally, at each of these visits the ACT, AQLQ, PEFR as well as any exacerbations and changes in medications, including new medications are recorded. Owing to an omission in the original study protocol, where ACT was not a measured variable, it was not recorded on the first 60 participants. The training, as per allocation, is then given. Details of the clinical visits are included in the clinical training manual, online supplementary appendix 2.

Interventions

Control group: behavioural intervention and inhaler training

The key points of each of the visit consultations includes: participant-identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan for exacerbations. A checklist

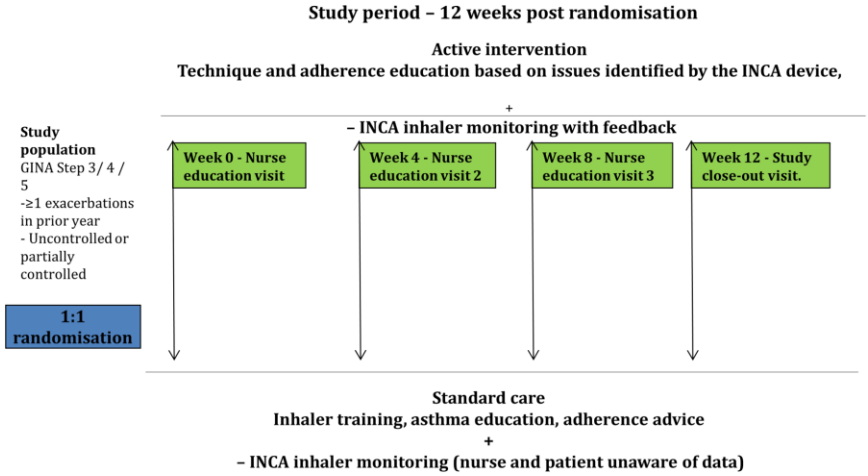

Figure 1 The study participants are patients with a diagnosis of asthma attending a severe asthma clinic who remain uncontrolled or partially controlled and have experienced at least one severe exacerbation of asthma in the prior year. With no medication change, adherence and inhaler technique are re-enforced over the 12-week monitoring period (INCA, INhaler Compliance Assessment).

is used to review and correct errors in inhaler technique (IPS). To promote adherence during the education, emphasis is given on the individual developing a habit in time of use of the inhaler. Four, 8 and 12 weeks later the participants return their inhaler and receive an identical structured consultation as at the first meeting. Participants and nursing staff are unaware of data from the INCA device in the control arm. A video and manual describing the exact steps of usual care is shown as https://www.youtube.com/watch?v=PlTkhVuogaI.

Active group: feedback using recordings from the INCA device

The content of the first visit was the same as for the control group. At 4, 8 and 12 weeks later, the participants together with the nurse review the information recorded on the INCA device and electronic PEFR (ePEFR), in the form of a graph, see figure 2 for an example of graphs produced by the INCA device. This graph leads to a consultation that focuses on the time of use, patterns of inhaler use, attempting to identify barriers to good adherence, development of habit of use as well as remediation of errors in inhaler use, as identified by the analysis of the data.

Figure 2 A screen shot of the data presented to the patient for discussion of their adherence to the salmeterol/fluticasone Diskus inhaler over the prior month. In this example, the patient has good time of use, in particular in the evening, suggesting they are developing a regular habit of use. However, they show intermittent errors in inhaler technique. In this example, they used the inhaler incorrectly on almost half of all occasions in which the inhaler was used.

Data collection

INCA device

The original INCA device was designed at the Department of Bioengineering, Trinity College Dublin, Ireland and Conformité Européenne (CE) marked and manufactured by Vitalograph, Ennis, Ireland.

Analysis of the audio data

Analysis of the digital recordings is performed as previously described.[5] The files are uploaded to a server and analysed using signal processing methods. For patients in the active arm, these audio recordings are uploaded during the visit by the nurse and feedback is given to

the patient based on an automated analysis of the audio files. The sensitivity and specificity details have been published.[7]

At a later date, two independent raters over-read all files from all patients. Their agreed, combined analysis will be used in the calculation of the actual adherence. These raters are unaware of either the patient allocation or any of the patient clinical outcomes and are not involved in any aspect of the patient care during the trial. Critical inhaler errors including whether the drug was primed, whether the patient exhaled after priming but before inhalation, whether an adequate flow rate was achieved, the exact flow rate, whether there were multiple inhalations indicating inadequate breath-holds and correct sequence of events/timing of events were performed. Non-critical errors such as not holding the device vertically (as described by the manufacturer) were not recorded. The sensitivity and agreement within the two raters and between the raters and the algorithm have been published.[9] Any disagreements within raters were reviewed by a third rater who made the final decision on the audio file.

Electronic peak expiratory flow rate

Participants receive an ePEFR device at each visit, which are then collected at the subsequent visit. For participants in the active arm, data from these devices are downloaded during the visit and information on PEFR, in conjunction with adherence data from the INCA device, are feedback to the participant.

Objectives

The objective of this study is to assess if feedback obtained from the INCA device on adherence and technique errors yields better adherence and better clinical information than best practice.

Primary outcome

The actual inhaler adherence, expressed as cumulative drug exposure, is calculated by combining the time of use along with the interval between doses (correct time is twice a day, in a period not <6 h between the last dose and the subsequent doses, or at a time >18 h apart from the previous dose) and incorporating, by audio analysis, if the inhaler was used correctly (ie, no evidence of critical technique errors aforementioned). The rate of actual adherence for the last month of the intervention will be compared between the active and control patients.

Secondary outcome analysis will include

Clinical outcomes, PEFR, ACT, AQLQ, reliever use and exacerbations between active and control arms at the end of the study will be compared. A composite score of these values, the global clinical outcome profile, see table 2 comprising the observed adherence, peak flow data, asthma control, quality of life and reliever use, as well as exacerbations over the study period will be calculated. Exacerbations is defined as an increase in symptoms (ie, shortness of breath, wheeze, cough) requiring a course of systemic glucocorticoids. Healthcare utilisation (ie, unscheduled general practitioner visits, hospitalisation and emergency department visits) will also be compared between active and control arms.

Comparison of the proportion of patients in each group who achieved full adherence at the end of the study (≥80%), as well as changes in patterns of adherence in the two groups, the number progressing to good actual technique will be assessed. A comparison of the morning and evening habits of inhaler use, error rates, overdose rates, interval and attempted rates of adherence in the two groups at the end of the study will be compared. The factors associated with improving adherence will be described.

The relationship between adherence and asthma control, asthma quality of life and PEFR will be assessed by comparing the proportion of patients who are GINA 2011, ACT controlled and no longer require regular β agonist. The ACT, PEFR rate, AQLQ and reliever use between the two groups will also be compared.

The κ score between raters and a sensitivity analysis of the algorithm will be calculated.

Sample size calculation

The usual rate of adherence to inhalers is reported to be calculated from the dose counter, and is expressed as

Table 2 Clinical decision tool

	Non-adherence	Refractory asthma	Controlled asthma	Comorbidity
Actual adherence >80%	No	Yes	Yes or no	Yes
PEFR >80 of area under the curve	Yes or no	No	Yes	Yes
AQLQ >5 and ACT >19	Yes or no	No	Yes	No
Exacerbations	Yes or no	Yes or no	No	Yes or no

The outcome decision tool, at the end of the study the cumulative information on actual adherence. PEFR rate, calculated as the AUC within 80% of normal predicted. ACT and AQLQ considered to be optimal, and exacerbations will be used to describe one of four possible outcomes. Sufficiently non-adherent as the likely reason for failure to progress, asthma that is refractory because despite optimal adherence, both symptoms and lung function and exacerbations occur. Controlled asthma, patients who are no longer impaired nor have exacerbations, and a group of patients who have good adherence and lung function but who continue to have symptoms, therefore suggesting that a significant comorbidity is the likely driver for the ongoing symptoms.
ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; PEFR, peak expiratory flow rate.

an average adherence. Most studies in trials of patients with inhalers report adherence of >0.8. Therefore, we anticipate that there is going to be high adherence in the setting of a clinical trial. However, we also expect that there will be a number of patients with poor inhaler technique which will lead to a lower actual adherence. We shall assume that when this is accounted for then the actual adherence is 0.15 lower, that is, 0.65 adherence at the end of the first month. Our preliminary data in primary care and on the wards indicates an SD of adherence is 0.25.[5] The primary end point is the rate of adherence at the end of the study period, that is, during the last visit at month 3 between active and control groups. We expect the adherence to improve over the study period in the control group, as they are repeatedly educated in inhaler use by 0.05, and we expect the active group to get closer to the physician-reported ideal rate of 0.8, that is, a 0.15 improvement in actual adherence. Hence, with a power of 0.8 at the 0.05 significance level, with a 0.1 difference in the actual adherence rate, then a sample size of 100 in each limb is required. We expect a 10% dropout; hence the target recruitment sample size is 220 in total.

Randomisation and allocation

Randomisation will use a stratified-by-site random block design, with blocks varying in size of 8–12. Allocation ratio is 1:1 with a central computer-generated randomisation. This is a single blind study, the nurse may deliver either intervention and is not blinded to the allocation. The participants are aware which group they are allocated to and aware that data on adherence is being collected for analysis. Patients in the control arm will be blinded to their adherence data from the INCA device.

Statistical methods

Data analysis

Data will be analysed on an intention-to-treat and a per-protocol basis. Data will be presented as means with SDs, and Student t test will be used to compare differences in mean adherence rates between the groups. Significance will be set at the 5% level. Stratification of patients by new versus previous use with respect to use of the Diskus device (ie, if patient's are using the Diskus device for the first time, or if they have previously used the device), stratification based on severity of disease according to GINA guidelines.

DISCUSSION

Most management guidelines suggest that for poorly controlled asthma patients that before changing therapy, issues with adherence and inhaler technique need to be addressed.[1–3] However, this is difficult to achieve in clinical practice. The aim of this study is to see if a nurse-delivered educational intervention with repeated education and monitored adherence can improve both aspects of adherence, the time and the technique of inhaler use. We will record when and how well an individual has used their inhaler over time with a device that makes a digital audio recording of an individual using their inhaler. Analysis of the recorded time of use, the interval between use and technique of use provides a measure termed actual adherence. The study's primary outcome will be a comparison of the actual adherence between the two groups at the end of the third month of participation in the study.

It is expected that over the study period some patients will become fully controlled while others will remain poorly controlled despite being fully adherent over the study period, and others may remain uncontrolled and also poorly adherent. This information may help with clinical decision-making for individual patients, for example, by helping decide who should have their therapy increased, their inhaler device changed or further interventions to promote adherence such as motivational interviewing. Hence, by combining clinical outcomes with the longitudinally collected adherence, asthma control and PEFR data, the composite outcome may assist a clinician in identifying the cause of difficult-to-manage asthma and increase the clinical confidence that the patient has refractory asthma.

This study has several novel features; this is the first study to use a technology that objectively assesses adherence to inhalers both in terms of technique of use as well as time of use. This technology involves not simply the device but also the automated algorithms, the feedback tools and the content of the feedback delivered by the nurse during the consultation.

It could be argued that the results of this clinical research study, performed in a research setting, will lead to greatly improved adherence, which is not reflective of clinical practice. Additionally, both control and active patients will be reviewed on a monthly basis for 3 months. This approach itself will more than likely also lead to an increase in adherence in the active and control group and may not fully reflect 'usual care'. To add to this, patients in both the active and control arms are aware that their inhaler use is being 'monitored', and this may lead to increased inhaler adherence. The authors see no alternative way of performing the study, as practical challenges in a more real-world setting may lead to a significant loss of patient follow-up, and hence, less precise information. The benefits of regular visits and PEFR measurements outweigh the disadvantages. Another limitation of the study is that it has a limited follow-up time frame, hence, the long-term effect on clinical outcomes and persistence of the observed benefits will not be established.

In regard to safety, patients enrolled in this study have to be uncontrolled or partially controlled by GINA guidelines. However, for the duration of the study their regular medical treatment of their asthma will not be changed (ie, their ICS/LABA dose will remain unchanged). The rationale behind this is to see the effect 3 months of adherence training would have on

asthma control, potentially reducing the need to increase patient medication (step-up), and possibly allowing physicians to reduce asthma treatment (step-down). Patients can withdraw at any time during the study without any impact on their clinical care. Additionally, if the clinician feels there is a clinical indication, patients can be removed from the study in the patient's best interest.

In summary, this study proposes to assess the impact of a series of consecutive educational visits on adherence and inhaler use by patients with severe asthma. In addition, by combining objective measurement of lung function, clinical outcomes and objectively assessed adherence, this may also provide clinicians greater precision in decision-making for the future care of this group of patients.

Author affiliations
[1]Clinical Research Centre, Smurfit Building Beaumont Hospital, Royal College of Surgeons Ireland, Dublin, Ireland
[2]Department of Bioengineering, Trinity College, Dublin, Ireland
[3]Department of Respiratory Medicine, University Hospital Cork, Cork, Ireland
[4]Department of Respiratory Medicine, Adelaide and Meath Hospital, Dublin, Ireland
[5]Department of Medicine, Johns Hopkins University Hospital, Baltimore, Maryland, USA
[6]Department of Respiratory Medicine, Royal College of Surgeons Ireland, Dublin, Ireland

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Collaborators Professor D Kelleher, Professor P Murray, Professor Eavan Daly, Professor Cheryl Marron, Professor Frank Keane, Professor Enda Kelly, Professor Deirdre Flynn.

Contributors RBR, CH and RWC conceived the INCA device. RWC conceived and designed the study. EMacH, IS, GD, SDS and MF made substantial contributions to study design; JS, MH, TT, IS, SDS, IK and VR have all been involved in defining the characteristics of the INCA device and the associated acoustic and other analysis. GC provided the statistical support and contributed to the drafting of the manuscript. All authors were involved in the writing of the manuscript and revising it critically for intellectual content; and have given final approval of the version to be published. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Beaumont Hospital Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma

Imran Sulaiman, Elaine Mac Hale, Martin Holmes, Cian Hughes, Shona D'Arcy, Terrence Taylor, Viliam Rapcan, Frank Doyle, Aoife Breathnach, Jansen Seheult, Desmond Murphy, Eoin Hunt, Stephen J Lane, Abhilash Sahadevan, Gloria Crispino, Greg Diette, Isabelle Killane, Richard B Reilly and Richard W Costello

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Appendix G

Strobe and Consort Checklists for Studies in Thesis

G.1 STROBE Checklist for Chapter 2 (Observational Study)

	Item No	Recommendation	PAGE
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	172
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	NA
Introduction			**173-174**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	173-174
Objectives	3	State specific objectives, including any prespecified hypotheses	174
Methods			**175-**
Study design	4	Present key elements of study design early in the paper	175
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	175
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	175
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	175-178
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	175-178
Bias	9	Describe any efforts to address potential sources of bias	175
Study size	10	Explain how the study size was arrived at	175
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	179
		(*b*) Describe any methods used to examine subgroups and interactions	179
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	

Results			**180-196**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	180
		(b) Give reasons for non-participation at each stage	180
		(c) Consider use of a flow diagram	182
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	180-185
		(b) Indicate number of participants with missing data for each variable of interest	180
		(c) *Cohort study*—Summarise follow-up time	180
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	184-185
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	186-195
		(*b*) Report category boundaries when continuous variables were categorized	196
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	196
Discussion			198-200
Key results	18	Summarise key results with reference to study objectives	198
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	199-200
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	200
Generalisability	21	Discuss the generalisability (external validity) of the study results	201-202

G.2 STROBE Checklist for Chapter 5 (Observational Study)

	Item No	Recommendation	PAGE
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	172
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	NA
Introduction			**173-174**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	173-174
Objectives	3	State specific objectives, including any prespecified hypotheses	174
Methods			**175-**
Study design	4	Present key elements of study design early in the paper	175
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	175
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	175
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	175-178
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	175-178
Bias	9	Describe any efforts to address potential sources of bias	175
Study size	10	Explain how the study size was arrived at	175
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	179
		(*b*) Describe any methods used to examine subgroups and interactions	179
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	

Results			**180-196**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	180
		(b) Give reasons for non-participation at each stage	180
		(c) Consider use of a flow diagram	182
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	180-185
		(b) Indicate number of participants with missing data for each variable of interest	180
		(c) *Cohort study*—Summarise follow-up time	180
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	184-185
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	186-195
		(*b*) Report category boundaries when continuous variables were categorized	196
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	196
Discussion			198-200
Key results	18	Summarise key results with reference to study objectives	198
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	199-200
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	200
Generalisability	21	Discuss the generalisability (external validity) of the study results	201-202

G.3 CONSORT Checkilist for Chapter 7 (Randomised Control Trial)

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	240
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	241-242
	2b	Specific objectives or hypotheses	242
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	243
Participants	4a	Eligibility criteria for participants	243
	4b	Settings and locations where the data were collected	243
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	244-247
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	247
Sample size	7a	How sample size was determined	248
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	243
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	243
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	243
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	243
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	244

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	244
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	252
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	252
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	253
	13b	For each group, losses and exclusions after randomisation, together with reasons	253
Recruitment	14a	Dates defining the periods of recruitment and follow-up	253
	14b	Why the trial ended or was stopped	253
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	255
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	256
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	264-270
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	264-270
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	253
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	274
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	272-273
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	271-273
Other information			
Registration	23	Registration number and name of trial registry	243
Protocol	24	Where the full trial protocol can be accessed, if available	243
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Appendix F